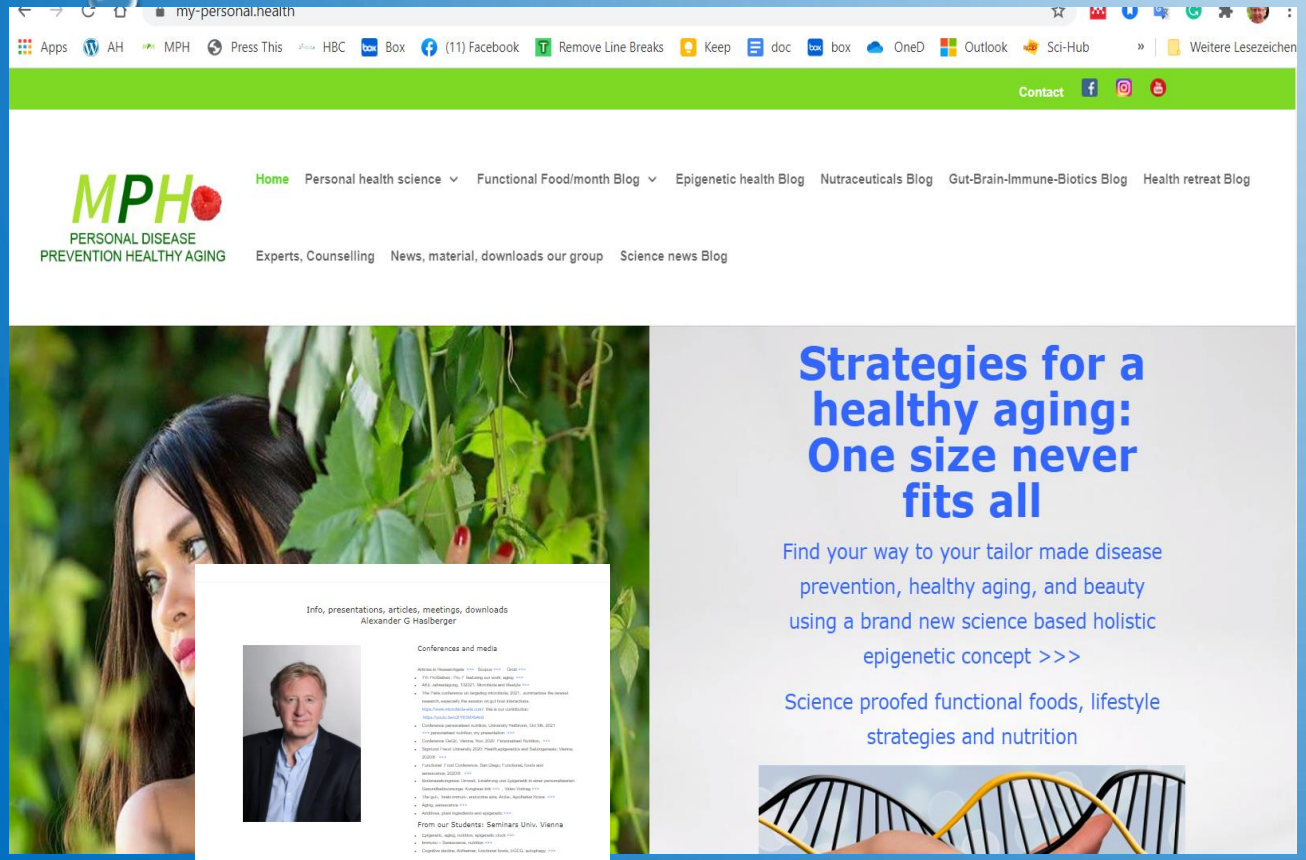
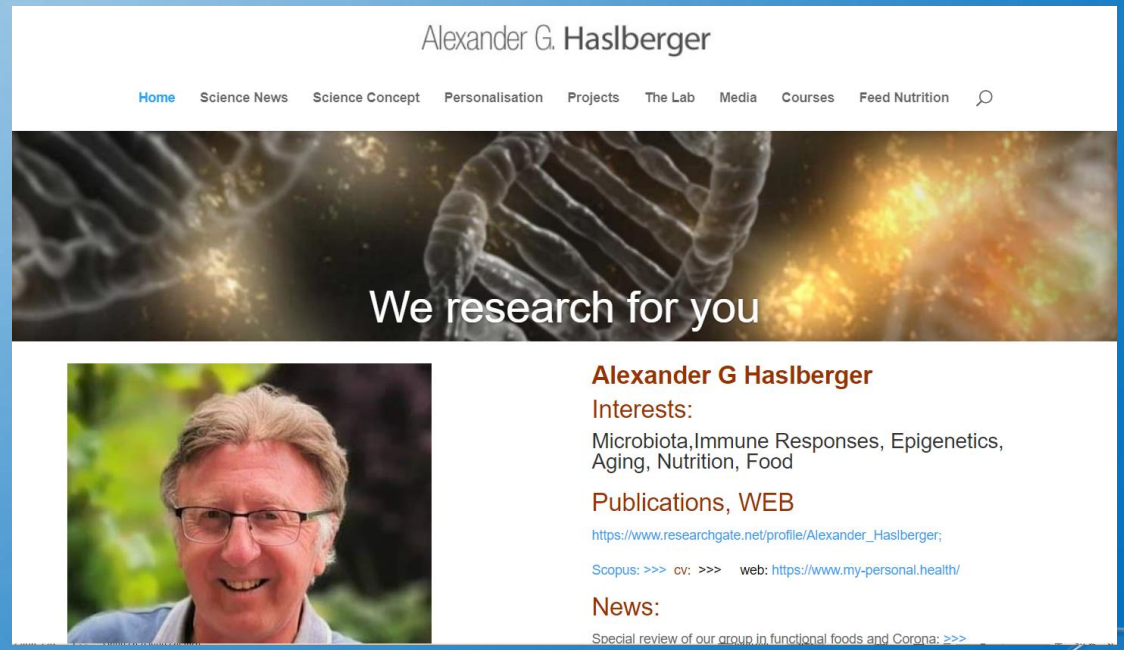
Gesundes Altern, zwischen Epigenetik, Mikrobiota, Immunsystem und ZNS, 2022

Alexander G. Haslberger

Genetik- Epigenetik, System Theorie
Aging, Epigenetik, Nutraceuticals
Fasting, Fasting Mimetics
Mikrobiota, Metabolites, I.S. und gut brain axis
Functional foods, Pro-, Pre, Postbiotics
Personalisation, Prävention, Salutogenesis
Methods, Platforms

MATERIALS





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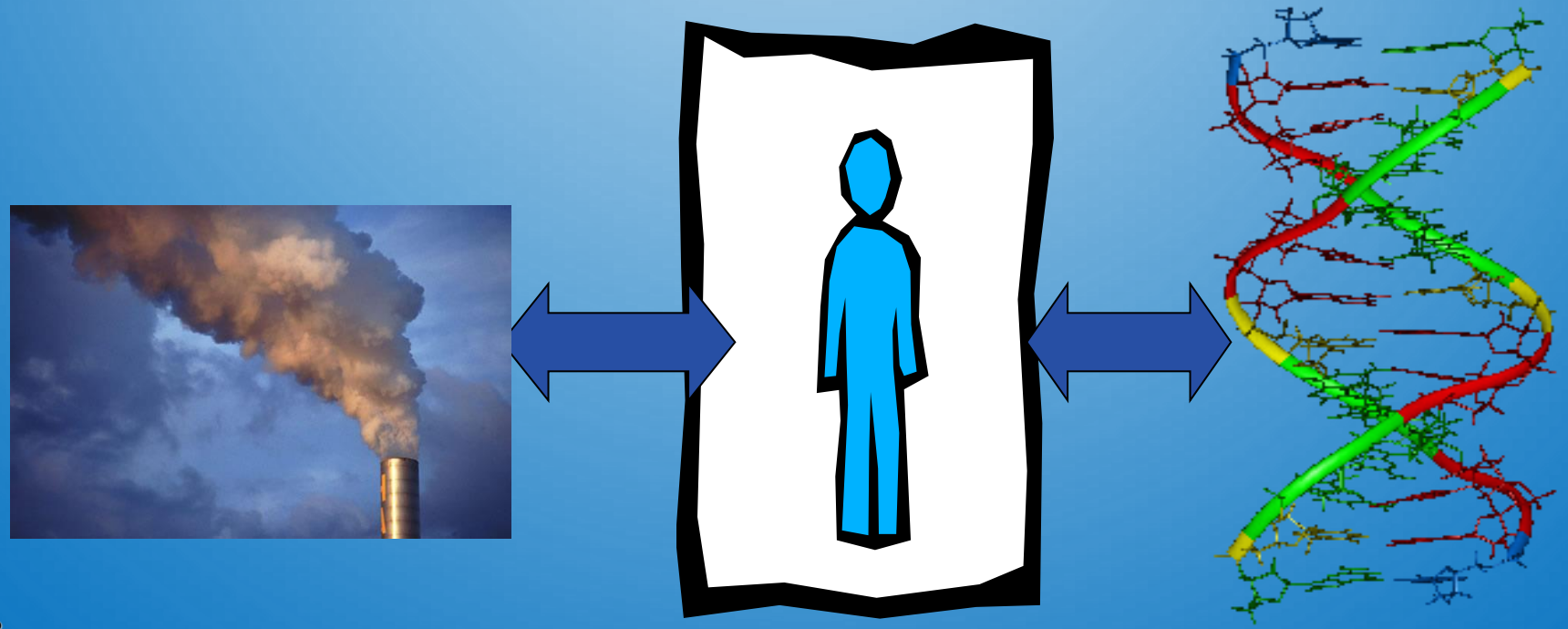
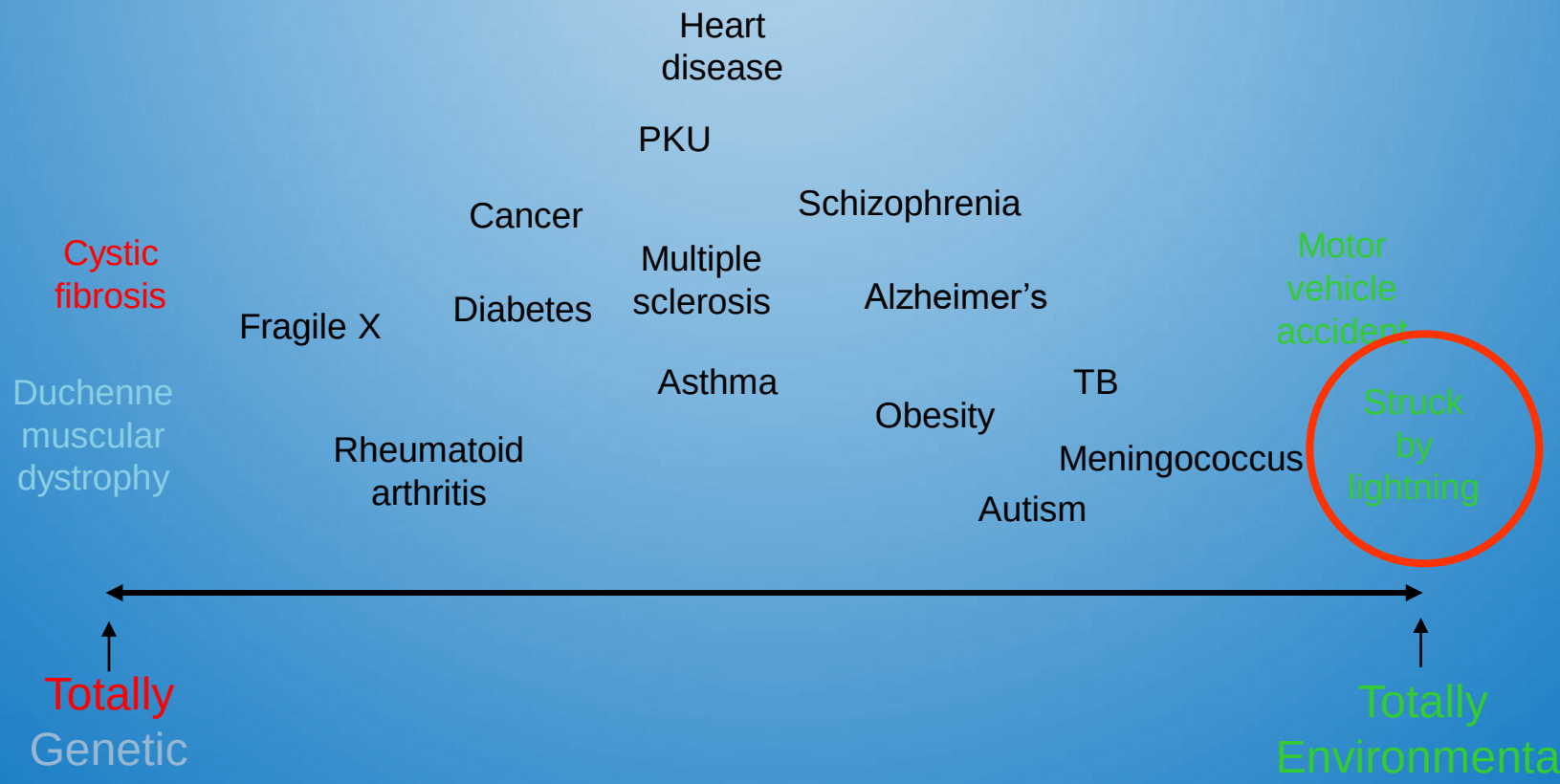
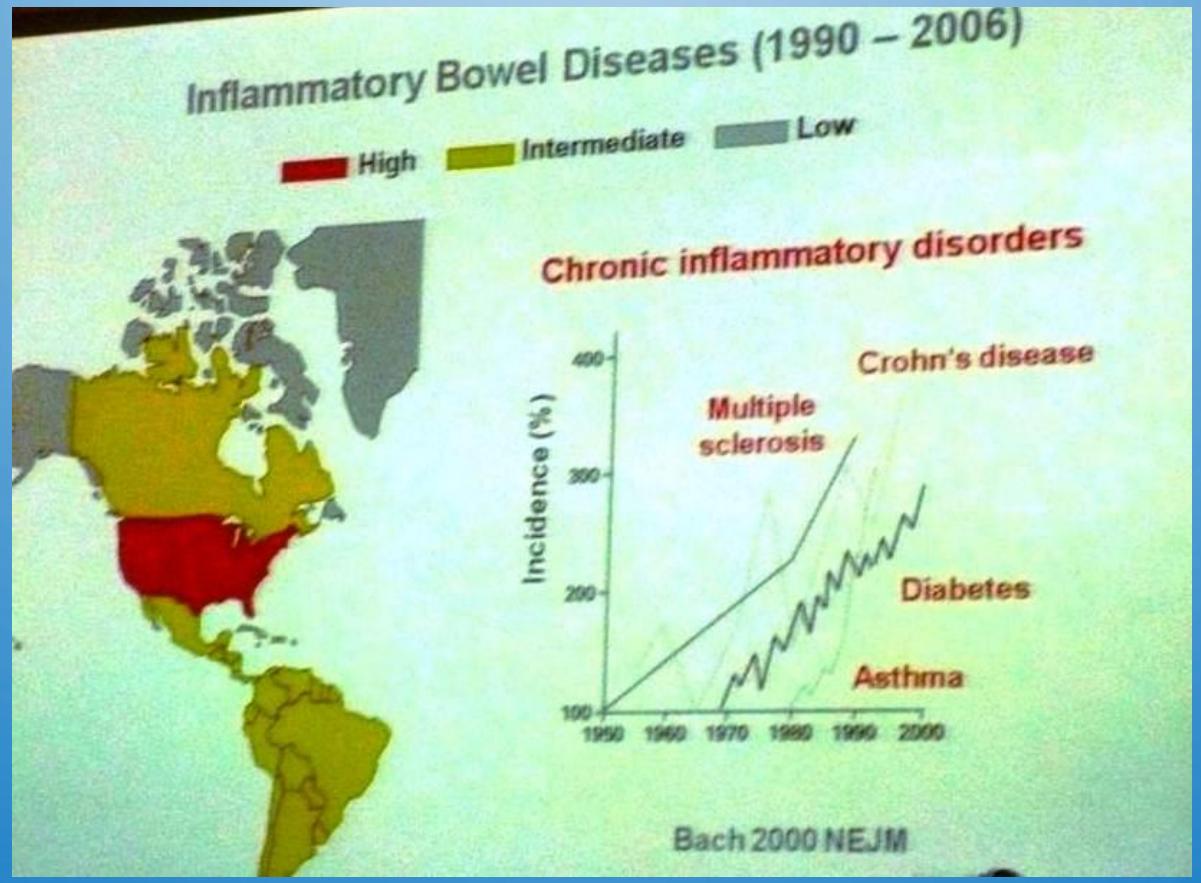
HUMAN: FROM INSIDE OR OUTSIDE HEALTH?



COMPLEX DISEASES: GEN-ENVIRONMENT



COMPLEX DISEASES INCREASE FAST, WHAT CHANGES IN THE ENVIRONMENT ?

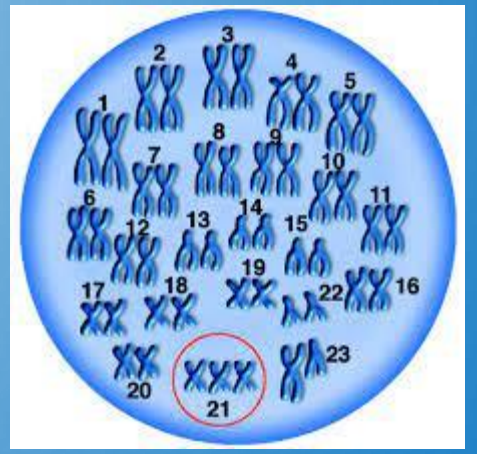


GENETICS

- Human genetics- scientific study of human variation and Heredity
- Medical genetics - study of the hereditary nature of human disease
- Clinical genetics- Care, diagnosis and counseling of patients with congenital malformations or genetic diseases

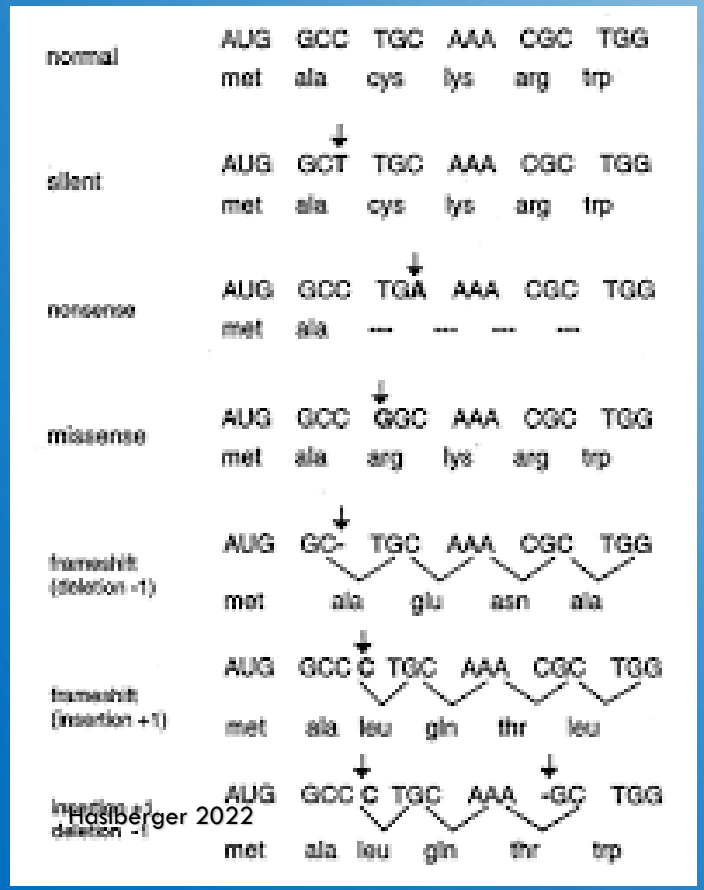
MUTATIONS

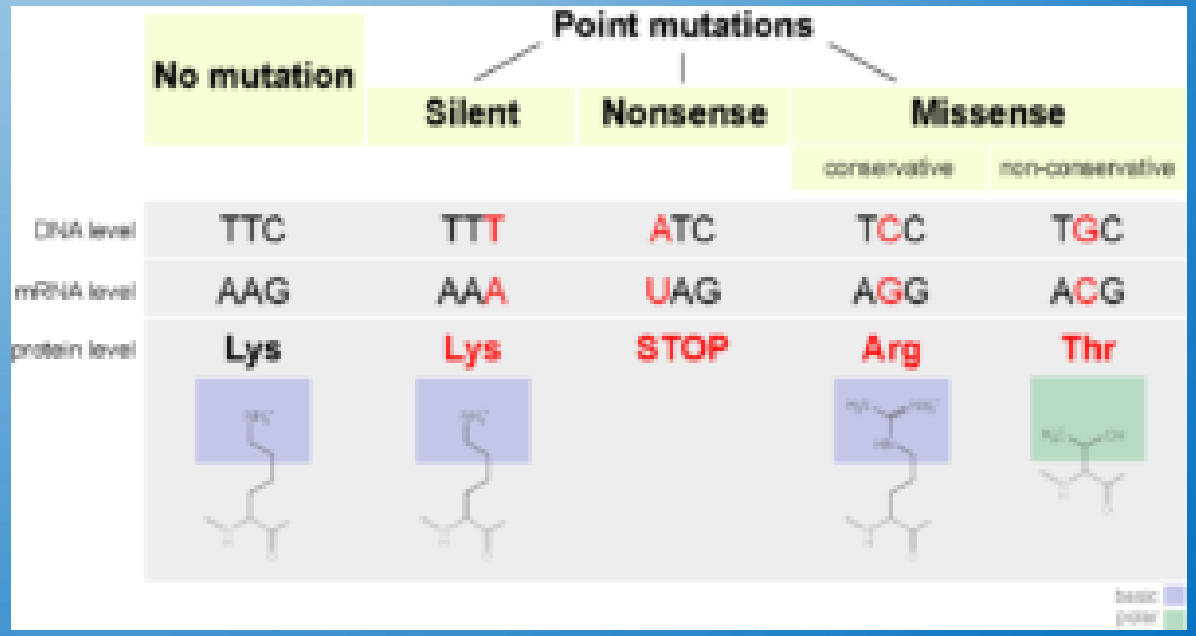
- Deletions- ranging from 1 bp to mega base
- Insertions- including duplications
- Single base substitution-
- Missense mutations, replace one amino acid with another in the gene product
- Nonsense mutations replace one amino acid codon with a stop codon
- Splice site mutations create or destroy signals for exon/intron splicing
- Frame shifts came be produced by deletions, insertions or splice mutations



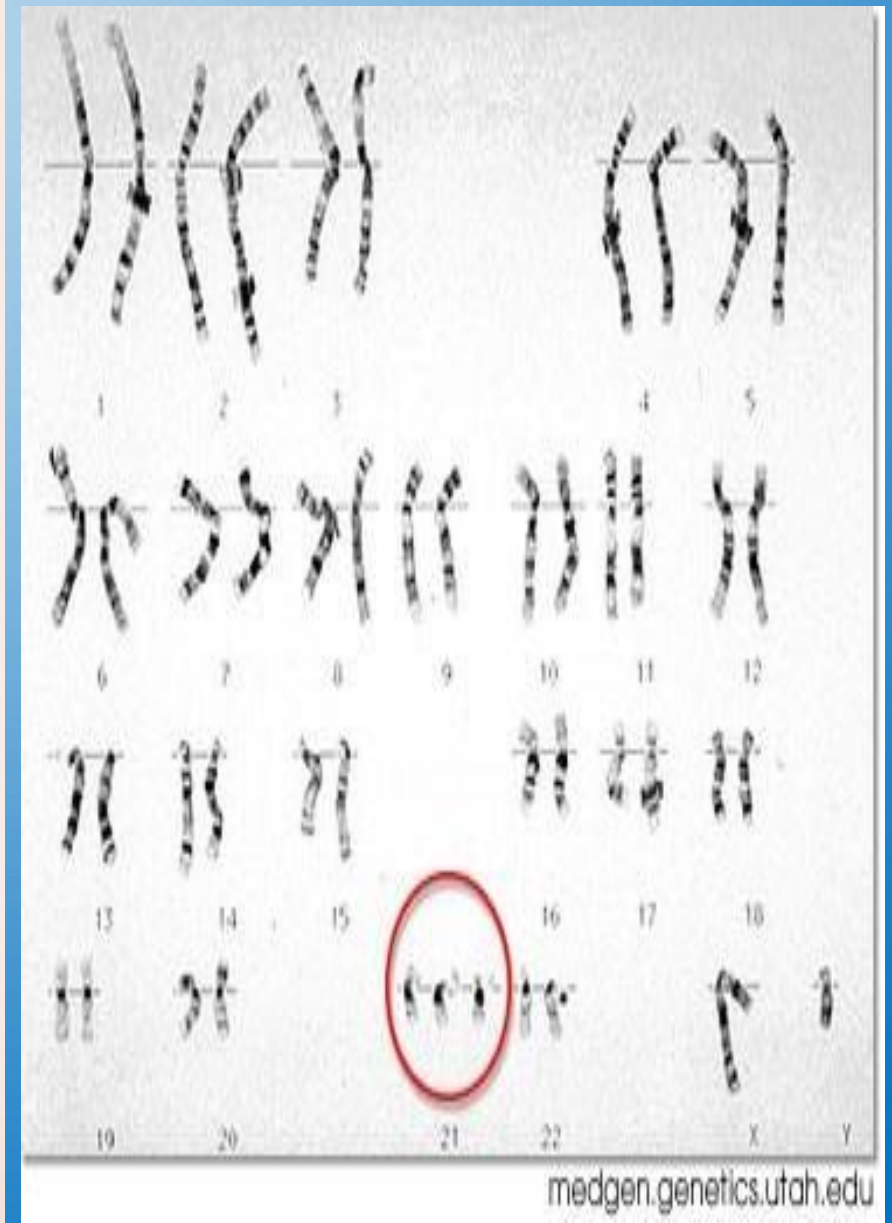
MUTATION- FUNCTIONAL CHANGE

- Loss of function mutations
- Gain of function mutations


normal
AUG GCC TGC AAA CGC TGG
met ala cys lys arg trp
silent
AUG GCT TGC AAA CGC TGG
met ala cys lys arg trp
nonsense
AUG GCC TGA AAA CGC TGG
met ala --- --- --- ---
missense
AUG GCC GGC AAA CGC TGG
met ala arg lys arg trp
frameshift (deletion -1)
AUG GC- TGC AAA CGC TGG
met ala glu asn ala
frameshift (insertion +1)
AUG GCC C TGC AAA CGC TGG
met ala leu gln thr leu
AUG GCC C TGC AAA -GC TGG
met ala leu gln thr trp


No mutation
Point mutations
Silent
Nonsense
Missense
conservative
non-conservative
DNA level
TTC
TTT
ATC
TCC
TGC
mRNA level
AAG
AAA
UAG
AGG
ACG
protein level
Lys
Lys
STOP
Arg
Thr

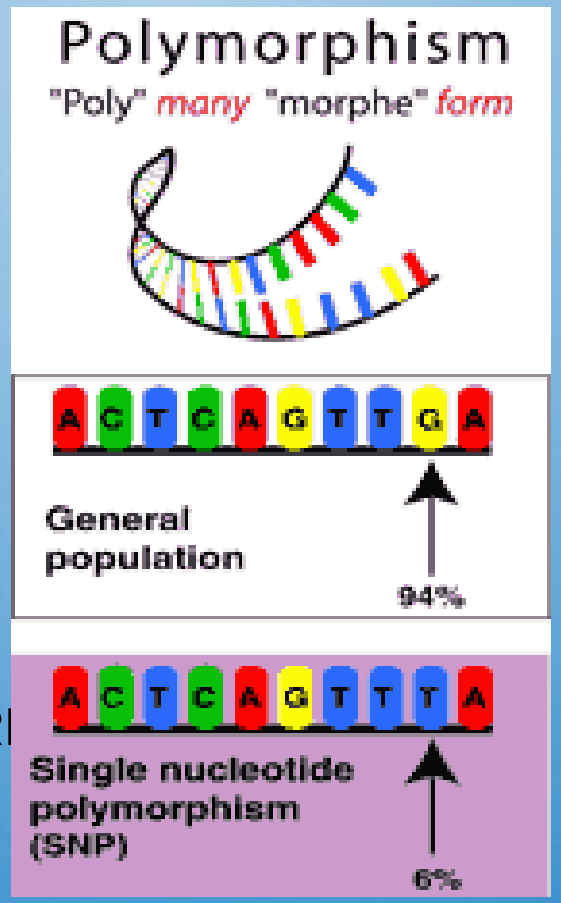
DOWN SYNDROME



SNPS (90 % OF VARIATION)

- NONSENSE
- MIS-SENSE
- FRAMESHIFT
- REGULATORY
- RNA SPLICING
- EXPANDING

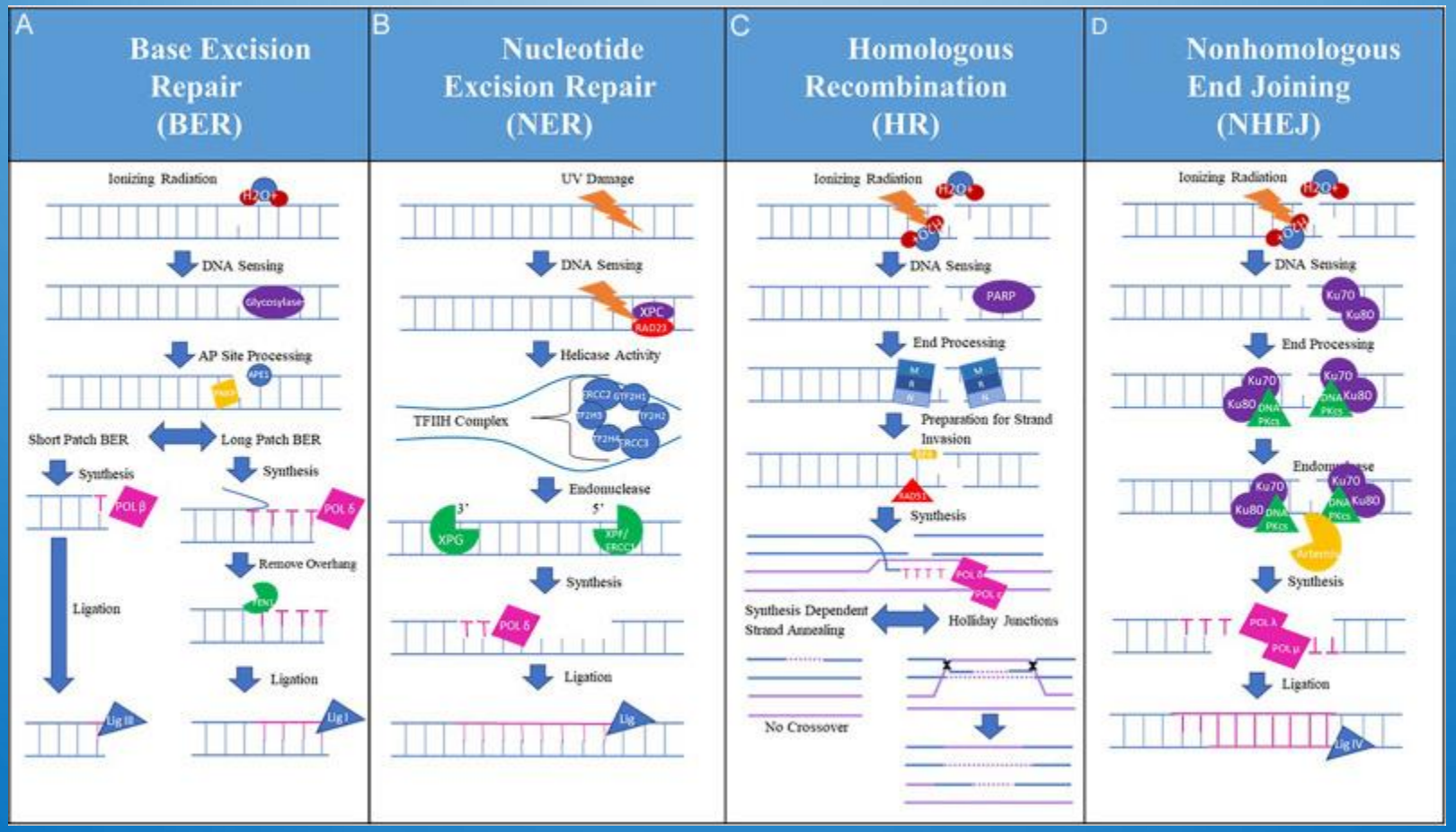
  TRINUCLEOTIDE RI
- OTHERS



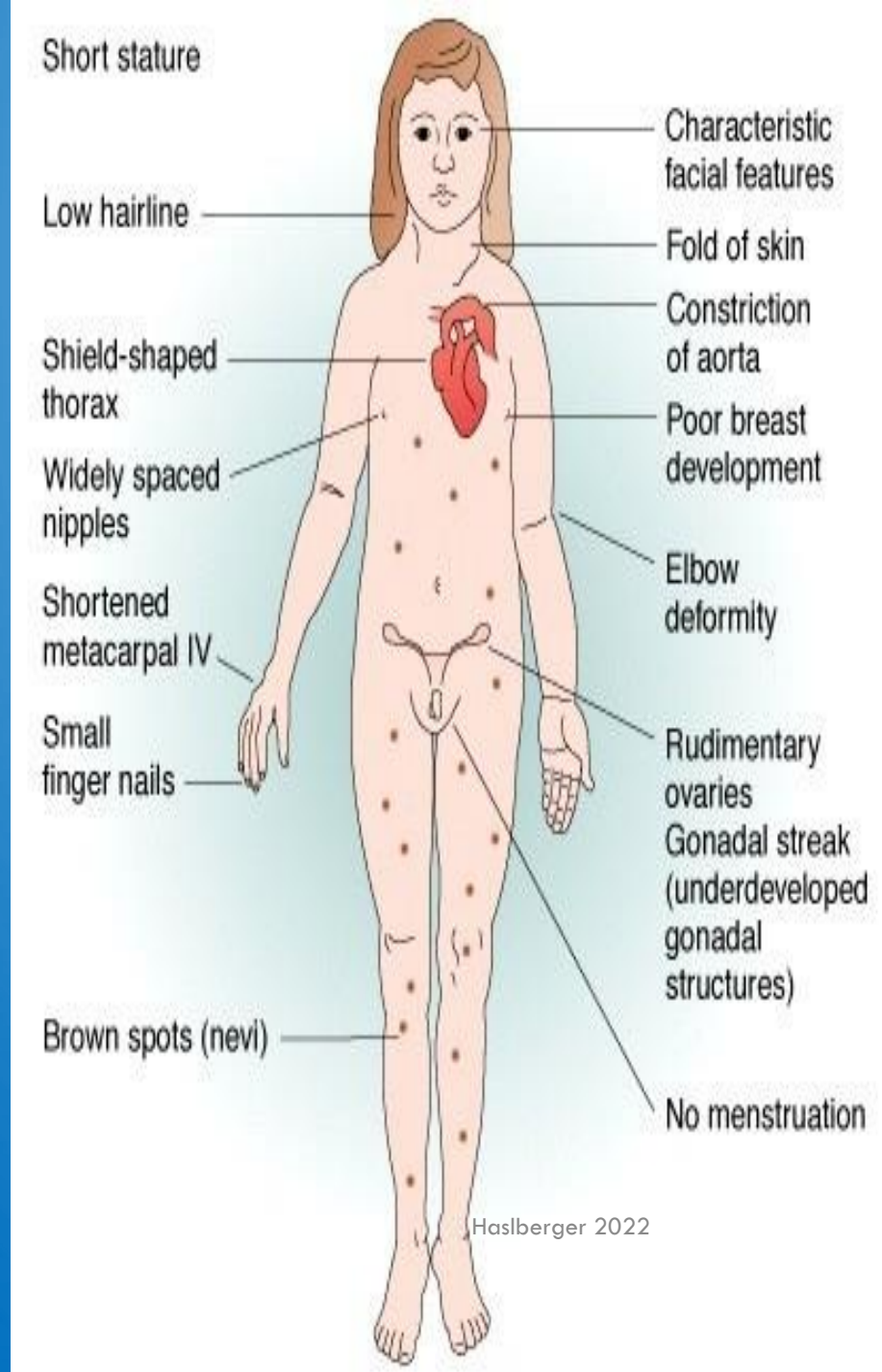
Single nucleotide polymorphisms (SNPs) are common DNA sequence variations among individuals.

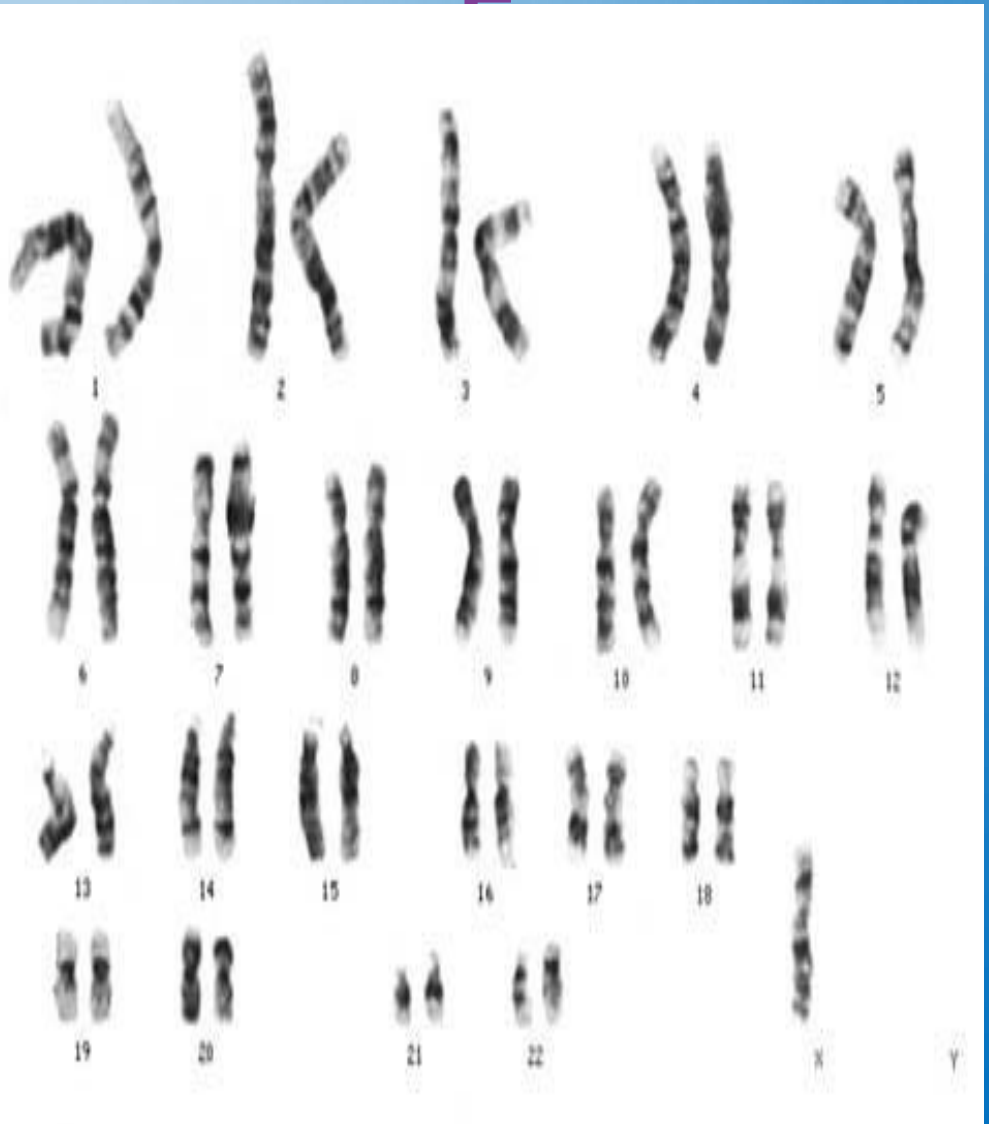
A **tag SNP** is a representative single nucleotide polymorphism (SNP) in a region of the genome with high linkage disequilibrium (the non-random association of alleles at two or more loci)

DNA REPAIR

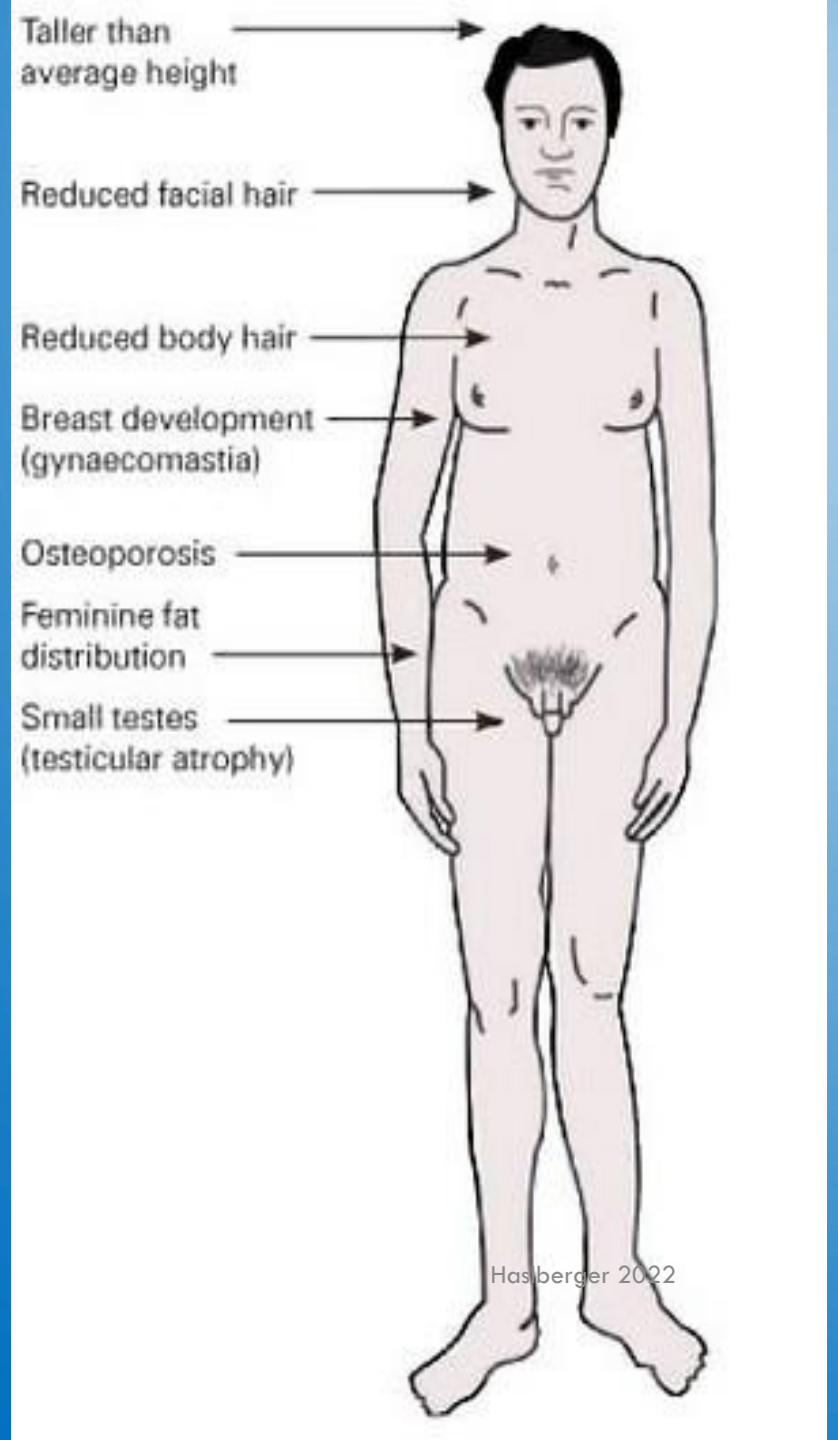

A
Base Excision Repair (BER)
Ionizing Radiation
DNA Sensing
Glycosylase
AP Site Processing
APE1
Short Patch BER
Long Patch BER
Synthesis
Synthesis
POL β
POL δ
Remove Overhang
FEN1
Ligation
Ligation
Lig III
Lig I
B
Nucleotide Excision Repair (NER)
UV Damage
DNA Sensing
XPC
RAD23
Helicase Activity
TFIIH Complex
ERCC2
GTF2H1
GTF2H3
GTF2H2
GTF2H4
ERCC3
Endonuclease
3'
5'
XPG
XPF/ ERCC1
Synthesis
POL δ
Ligation
Lig
C
Homologous Recombination (HR)
Ionizing Radiation
DNA Sensing
PARP
End Processing
MRN
MRN
Preparation for Strand Invasion
RAD51
Synthesis
POL δ
POL ε
Synthesis Dependent Strand Annealing
Holliday Junctions
No Crossover
D
Nonhomologous End Joining (NHEJ)
Ionizing Radiation
DNA Sensing
Ku70
Ku80
End Processing
Ku70
Ku80
DNA PKcs
Endonuclease
Artemis
Synthesis
POL λ
POL μ
Ligation
Lig IV

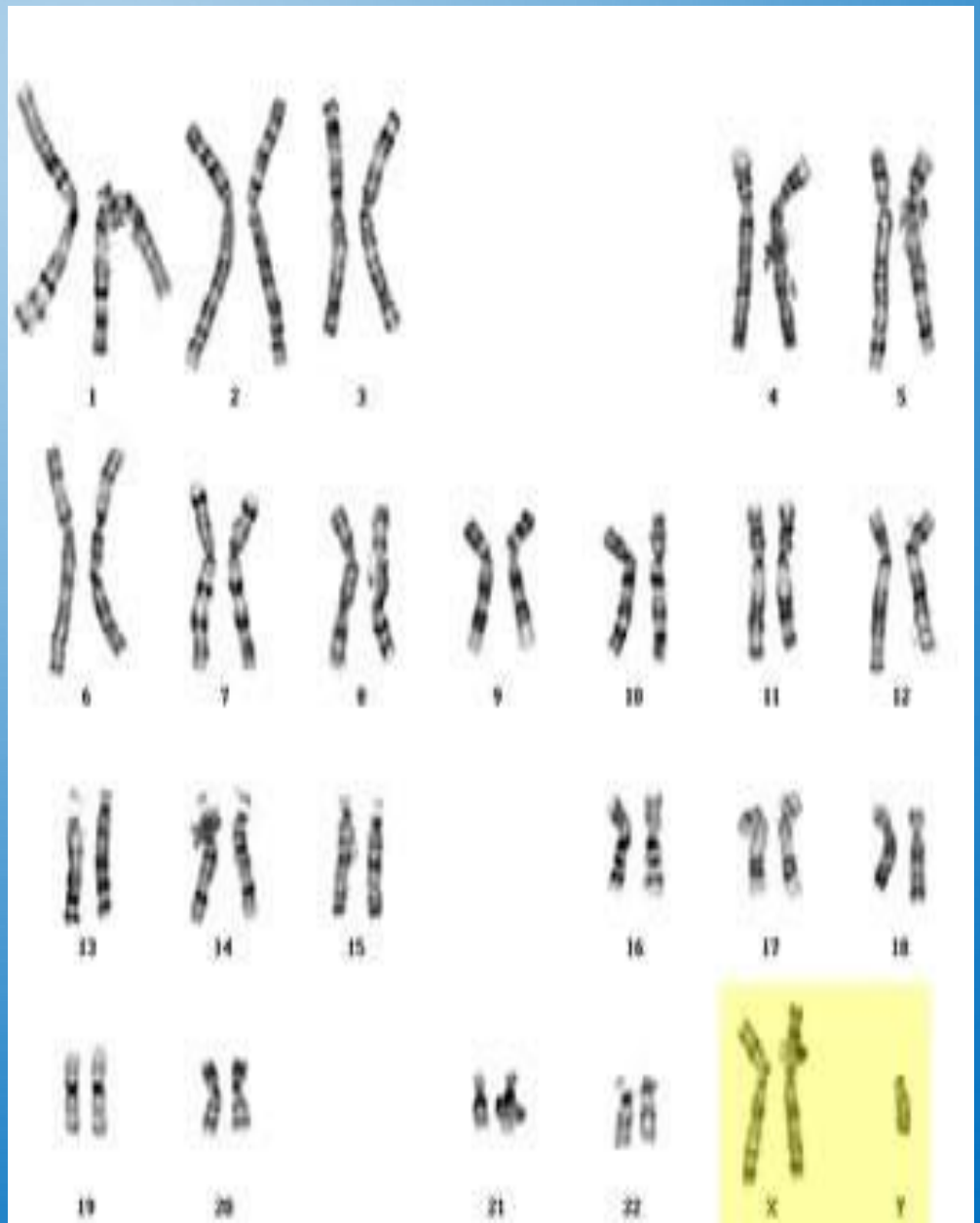
TURNER SYNDROME



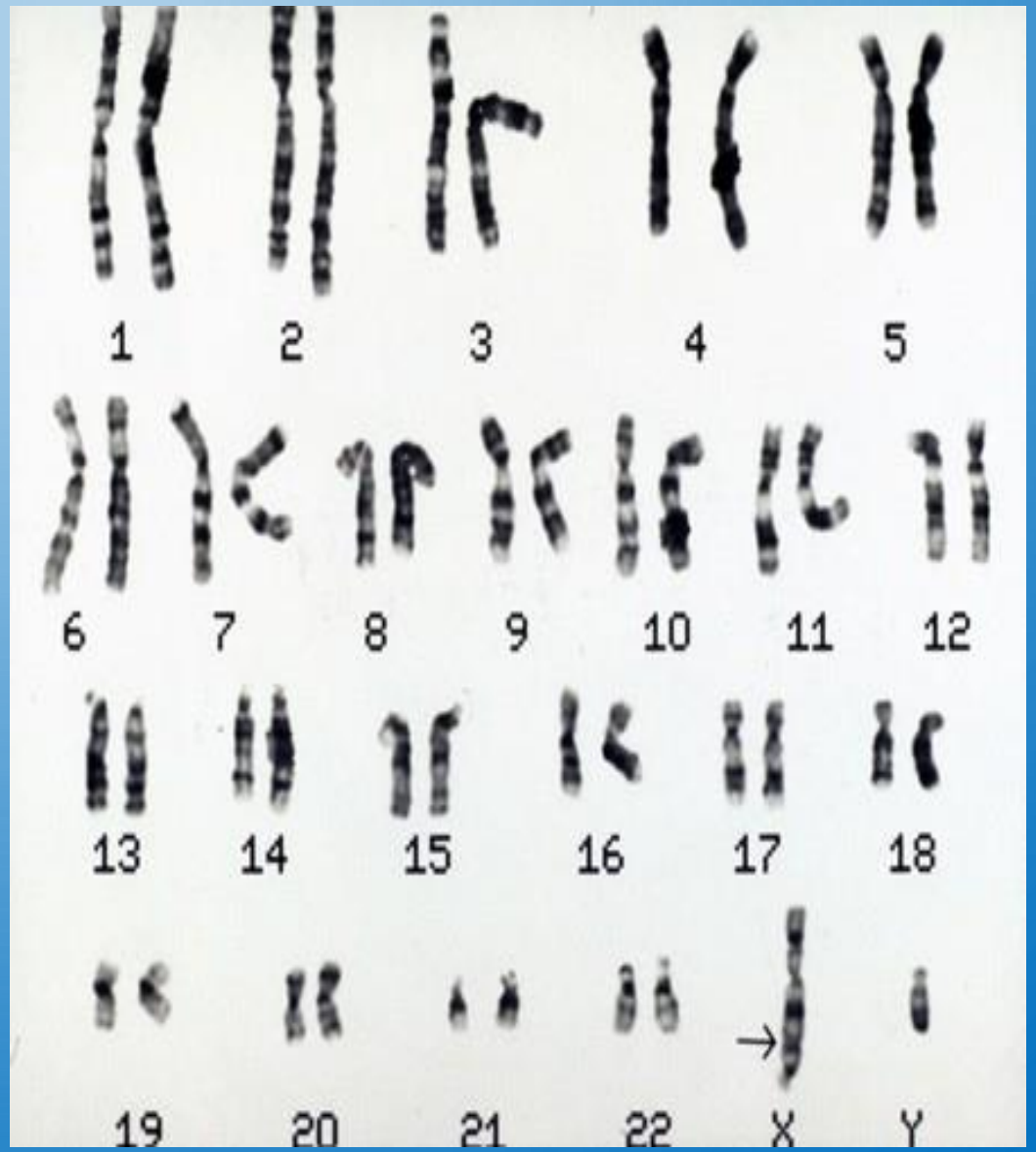


KLINEFELTER SYNDROME





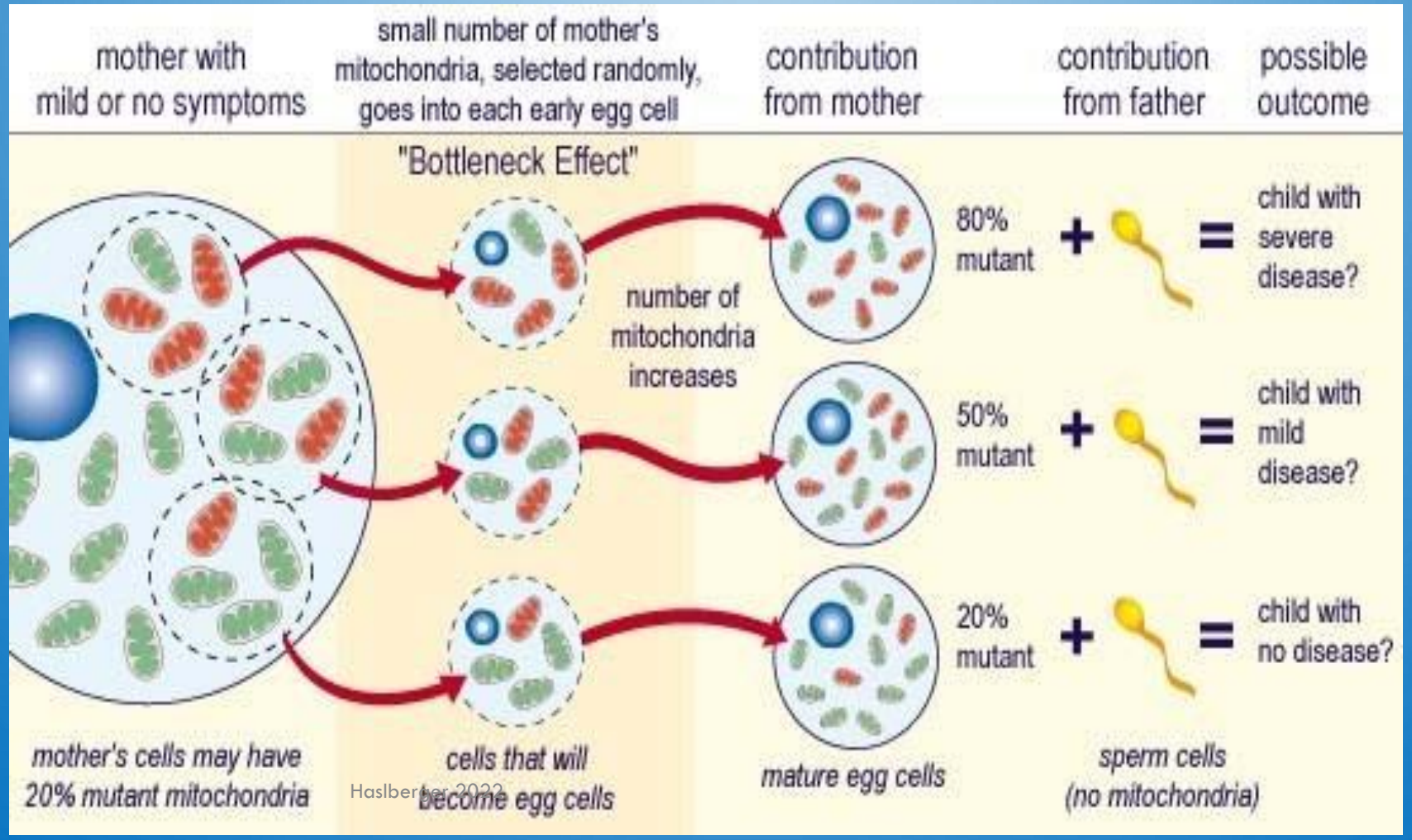
FRAGILE X SYNDROME



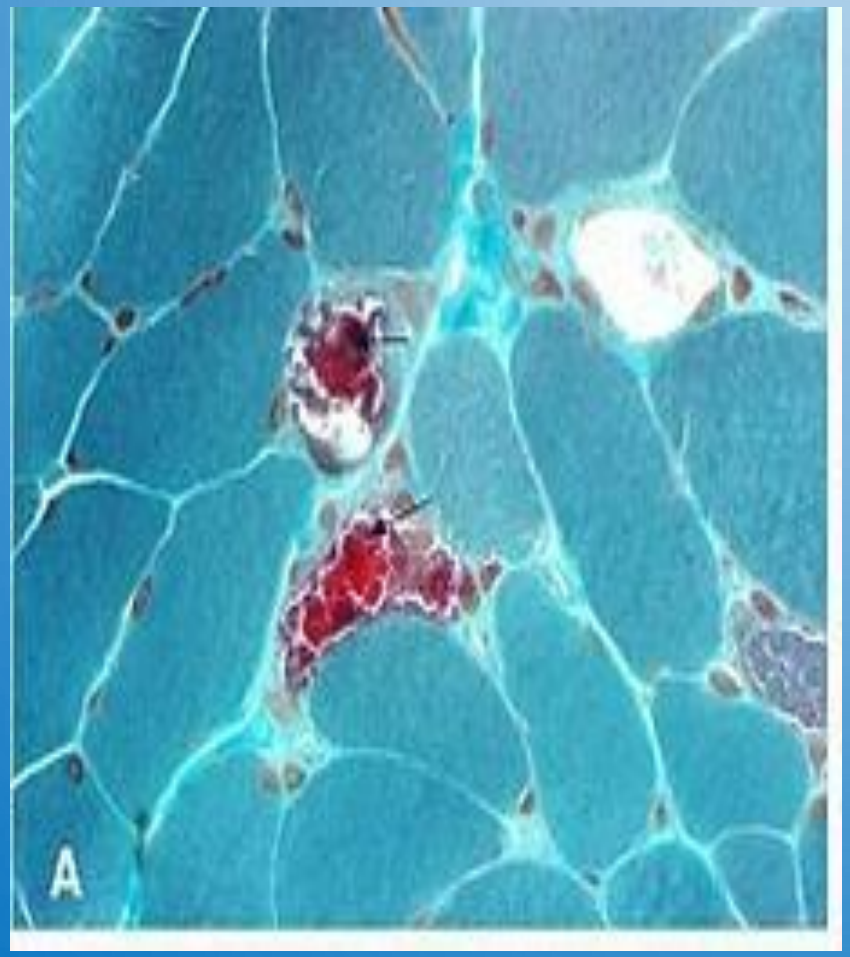
MITOCHONDRIAL INHERITANCE

- Matrineal inheritance
- Variable clinical manifestation due to heteroplasmy

MITOCHONDRIAL INHERITANCE



MITOCHONDRIAL DISEASE

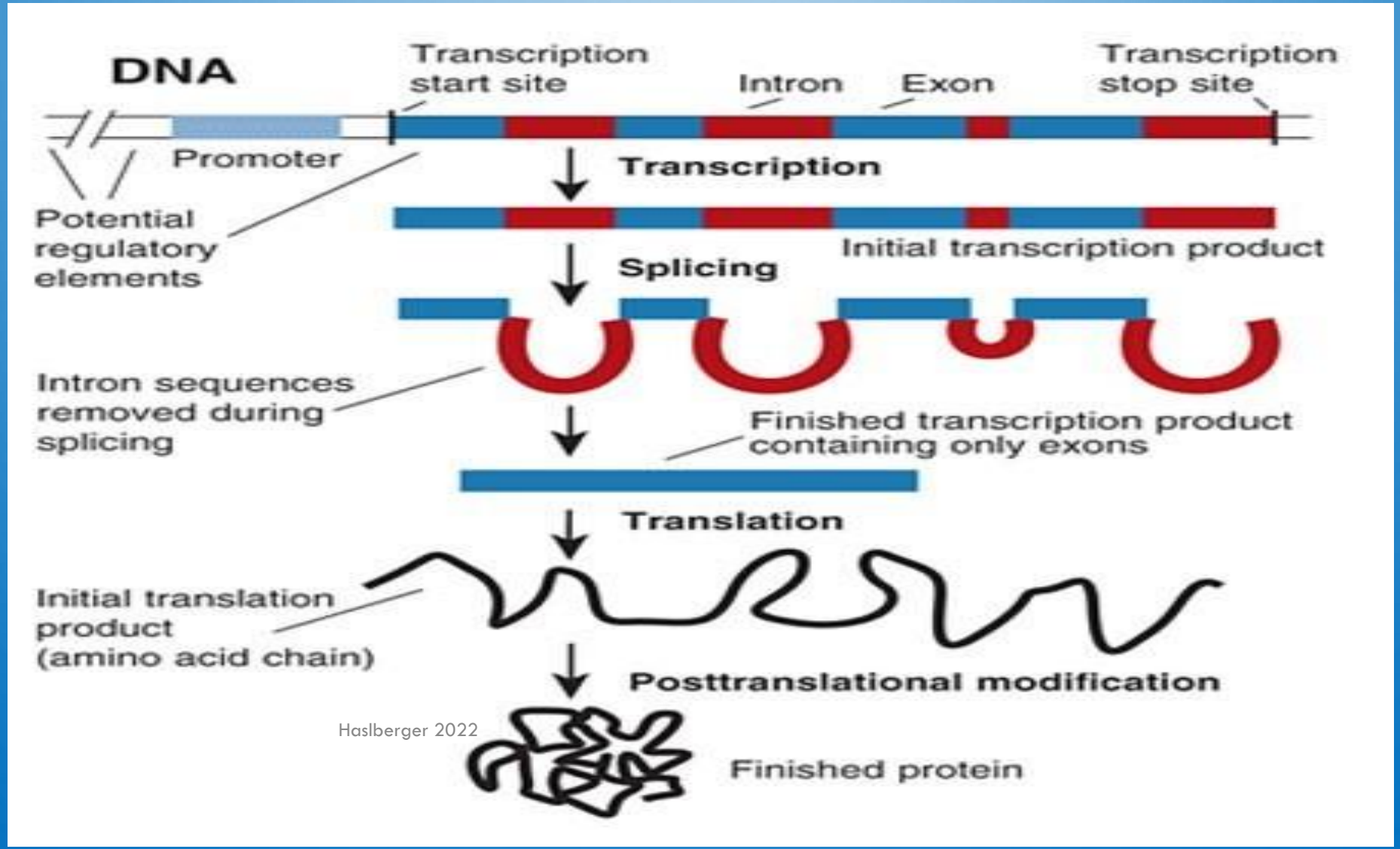


- *RAGGED RED FIBERS*" - CLUMPS OF DISEASED MITOCHONDRIA ACCUMULATE IN THE SUBSARCOLEMMAL REGION OF THE MUSCLE FIBER AND APPEAR AS "RAGGED RED FIBERS" WHEN MUSCLE IS STAINED WITH MODIFIED GÖMÖRI TRICHROME STAIN

Complex traits

- DIABETES MELLITUS, HYPERTENSION, MENTAL DISORDERS ETC
  - Gene and environment interaction
  - Population studies
  - Family studies
  - Twin studies

GENES STRUCTURE AND PROTEIN SYNTHESIS



INTRODUCTION TO HGP

- The **Human Genome Project (HGP)** was an international scientific research project that aimed to determine the **complete sequence of nucleotide base pairs** that make up human DNA and all the genes it contains.
- It remains the world's largest collaborative biological project.
- The idea was picked up in 1984 by the **US government** when the planning started, the project was formally launched in **1990** and was declared complete in **2003**.

INTRODUCTION TO HGP

- The Human Genome Project originally aimed to map the nucleotides contained in a **human haploid reference genome.**
- The "genome" of any given individual is unique; mapping the "human genome" involved **sequencing** the genomes of a small number of individuals and then **assembling** these together to get a complete sequence for each chromosome.
- The finished human genome is thus a **mosaic**, not representing any one individual.

GOALS OF HGP

- To identify and map all the **20,000-25,000 genes** (approx) in the human DNA from a physical and functional standpoint.
- To determine the sequences of the **3 billion chemical base pairs** that make up the human DNA.
- To store these informations in **databases.**
- To discover more **efficient technologies** for data analysis.
- Allow the private sector **access to the informations** and technologies that arise from this project.
- Also to **sequence the genomes of other organisms** that are important in medical research such as mouse, Drosophila etc,.
- To address ethical, legal and social issues.

PIONEERS IN HGP

- **Robert Sinsheimer** proposed the idea of sequencing the human genome in the year 1985.
- **Charles DeLisi** and **David Smith** proposed the budget for Human Genome Project.
- HGP act was passed in the US congress under **President Regan** in 1988.
- **James Watson** headed the NIH Genome Program.
- **Francis Collins** succeeded James Watson in 1993 as the overall Project Head and the Director of the NIH (which later become the National Human Genome Research Institute **NHGRI**) and was in power until the completion of HGP in 2003.

TIMELINE OF HGP

- **1970** – FREDRICK SANGER DEVELOPED A TECHNIQUE FOR DNA SEQUENCING, KNOWN AS THE SANGER'S METHOD OF DNA SEQUENCING.
- **1985** - ROBERT SINSHEIMER AT UCSC PROPOSED THE IDEA OF SEQUENCING THE HUMAN GENOME.
- **1986** -THE U.S. DEPT OF ENERGY AND THE NATIONAL INSTITUTE OF HEALTH CAME FORWARD TO FUND THE HUMAN GENOME PROJECT.

1989 - U.K's medical research council (MRC) joined the Human Genome Project.

TIMELINE OF HGP

1990 – HGP was officially launched with James Watson as its Project Director.
the 1st gene to be mapped was BRCA1, which is the gene for breast cancer.

1993 - 1st 5 year plan for HGP was published.
Sanger Institute(UK) joins HGP.

1994 – HGP's Human genetic mapping goal was achieved.

1995 - Genetic privacy act was passed.
1st bacterial genome was sequenced (Hemophilus influenzae)

1996 – 1st Human Gene map was published.
Yeast genome was sequenced.
HGP's mouse genetic mapping goal was achieved.

TIMELINE OF HGP

1997 - NIH becomes NHGRI.
E.coli genome sequenced.
Genoscope, French National Genome Sequencing Centre was established.

1998 - 2nd 5 year plan for HGP was published.
Japan's RIKEN Genomic Services Centre was established.
Genome of the roundworm Caenorhabditis elegans was sequenced.
SNP sequencing was initiated.
the Chinese National Human Genome Centres were established in Beijing and Shanghai.

1999 - sequencing of human chromosome 22 was completed and was published in "The Nature."

TIMELINE OF HGP

2000 - working draft of human genome completed.
US president Clinton & UK's PM Blair
support free access to genome information.
Genomes of D.melanogaster and A.thaliana
were sequenced & published in "The Nature".

2001 – working draft of human genome sequence was
published in "The Nature" & "Science".

2002 – working draft of mouse genome sequence was
completed & published.

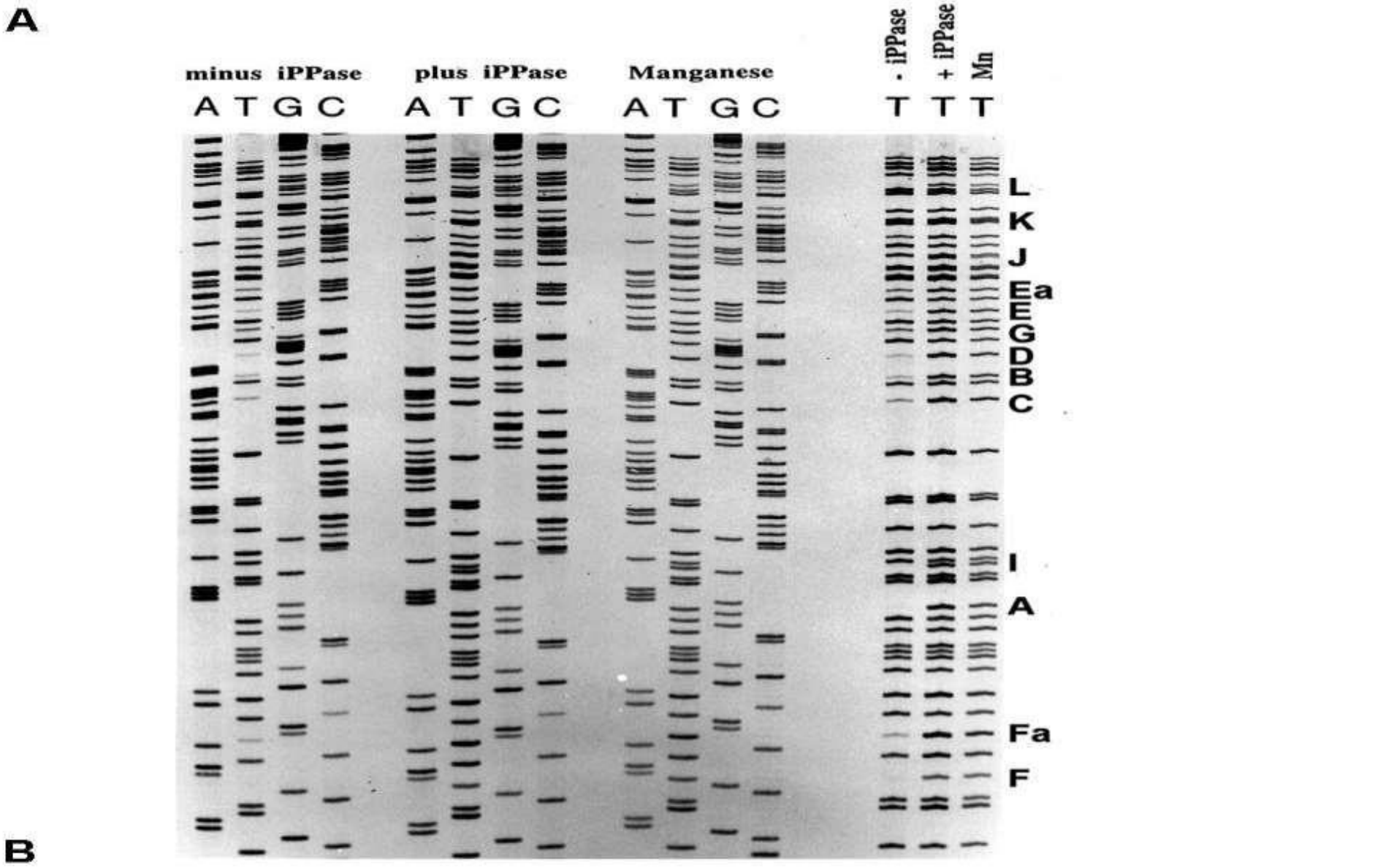
2003 - finished version of human genome sequence
was completed.
HGP ended with all the goals achieved.

TECHNICAL ASPECTS IN HGP

- The process of determining the human genome first involves **genome mapping**, or characterizing the chromosomes. This is called a **genetic map.**
- The next step is **DNA sequencing** ,or determining the order of DNA bases on a chromosome. These are **physical maps.**

MAPPING STRATEGIES

- **Genetic markers** are invaluable for genome mapping.
- Markers are any inherited physical or molecular characteristics that are different among individuals of a population (polymorphic)
- A **genetic map** shows the relative locations of these specific markers on the chromosomes.
- An example of a marker includes restriction fragment length polymorphisms **(RFLP).**
- Used in RFLP markers are restriction enzymes. These enzymes recognize short sequences of DNA and cut them at specific sites, therefore, DNA can be cut into many different fragments. These fragments are the DNA pieces used in physical maps
- RFLPs reflect sequence differences in DNA sites which are cleaved by restriction enzymes.


A
minus iPPase
plus iPPase
Manganese
- iPPase
+ iPPase
Mn
A T G C
A T G C
A T G C
T T T
L
K
J
Ea
E
G
D
B
C
I
A
Fa
F
B
5′ TCGAATTCGTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATT
1 2,3 F 3a Ea 4 5 6 (7) 8 8a A 9,10 I 11 12 13 14,15
CCACACAACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAG
16 C 17 B D 18 G 19 E
CTAACTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTG
20 Ea 21,22 22a,b J 30 23 23a 24 K 25 26 27 28 L

OUTCOMES OF HGP

- There are approximately **22,300** protein-coding genes in human beings, the same range as in other mammals. Mouse – 23,000 genes (approx)
- **Drosophila – 17,000 genes (approx),**
  C.elegans - < 22,000 genes
- we share many homologous genes (called "orthologs") with both these animals. But:-
- many of our protein-encoding genes produce more than one protein product (e.g., by alternative splicing of the primary transcript of the gene). On average, each of our ORFs produces 2 to 3 different proteins.
- So the human "proteome" (our total number of proteins) may be 10 or more times larger than that of the fruit fly and roundworm.

- A larger proportion of our genome :-
  encodes transcription factors
  is dedicated to control elements (e.g., enhancers) to which these transcription factors bind
  The combinatorial use of these elements provides much greater flexibility of gene expression than is found in Drosophila and C.elegans.

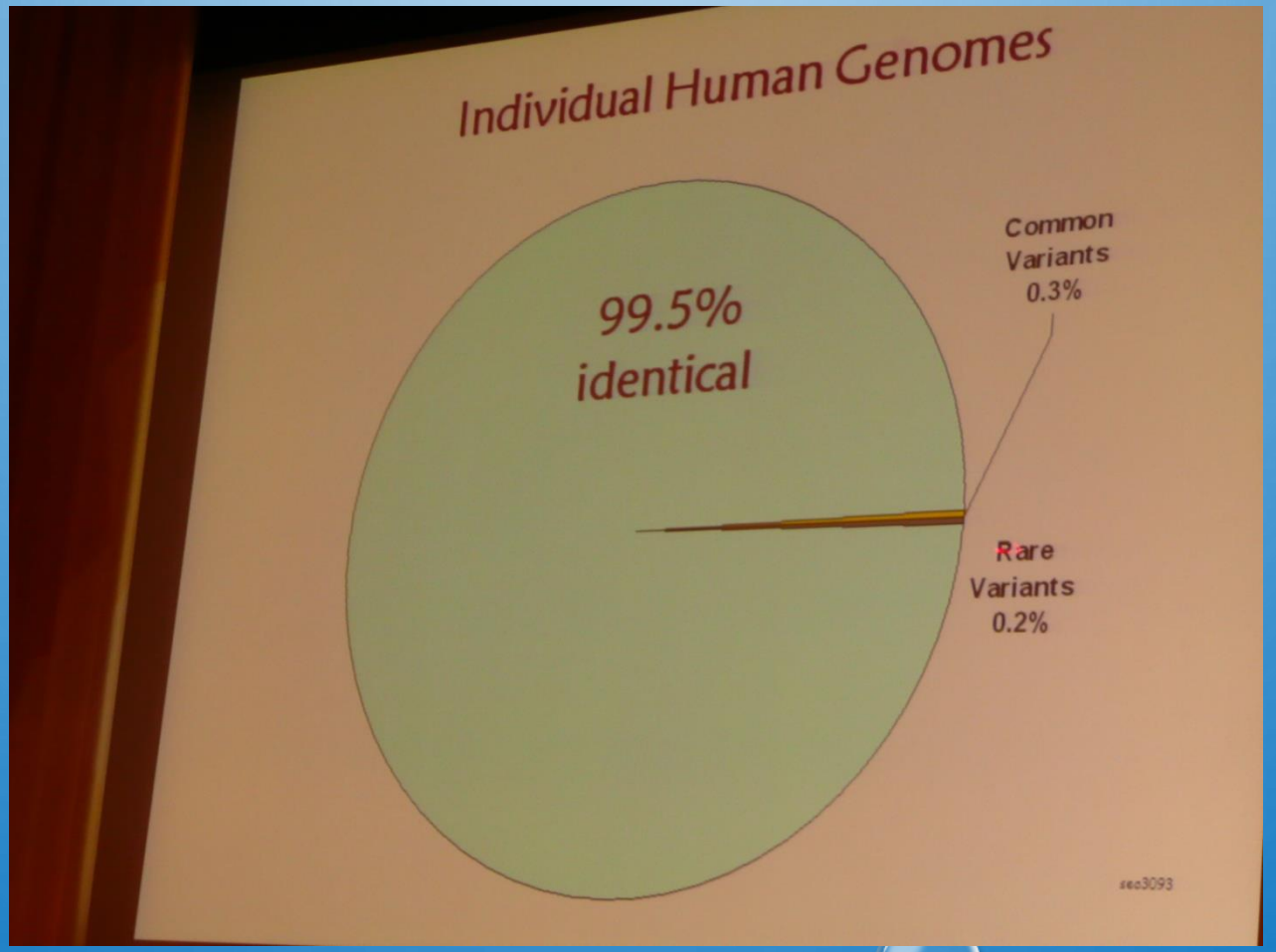
OUTCOMES OF HGP

- **Gene density :-**
  - 23 genes per million base pairs on chromosome 19
  - 5 genes per million base pairs on chromosome 13.
- Humans, and presumably most vertebrates, have genes not found in invertebrate animals like Drosophila and C. elegans. Few of those genes are :-
  - antibodies and T cell receptors for antigen (TCRs)
  - the transplantation antigens of the major histocompatibility complex (MHC) & human leucocyte antigen (HLA).
  - cell-signaling molecules including the many types of cytokines
  - the molecules that participate in blood clotting.
- Human genome comprises of 2% of exons (coding regions) and 98% of introns (non-coding regions).

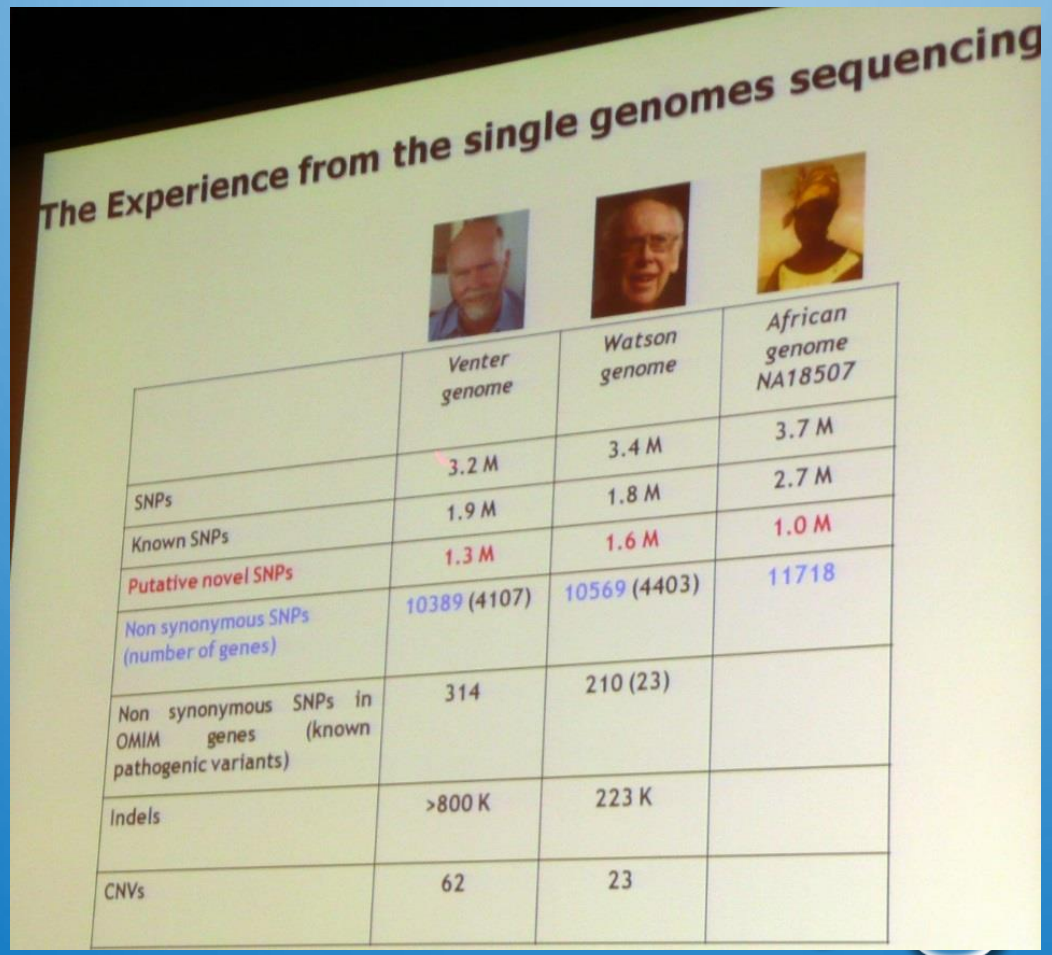
APPLICATIONS OF HGP

- The sequencing of the human genome holds benefits for many fields, from **molecular medicine** to human evolution.
- Helps in identifying **disease causing gene**.
- identification of **mutations** linked to different forms of cancer.
- The sequence of the DNA is stored in **databases** available to anyone on the Internet.
- The U.S. National Center for Biotechnology Information (and sister organizations in Europe and Japan) house the gene sequence in a database known as **GenBank**, along with sequences of known and hypothetical genes and proteins.
- will allow for advances in agriculture through **genetic modification** to yield healthier, more disease-resistant crops.
- Benefitted the advancement of **forensic science**.

INDIVIDUAL VARIATIONS

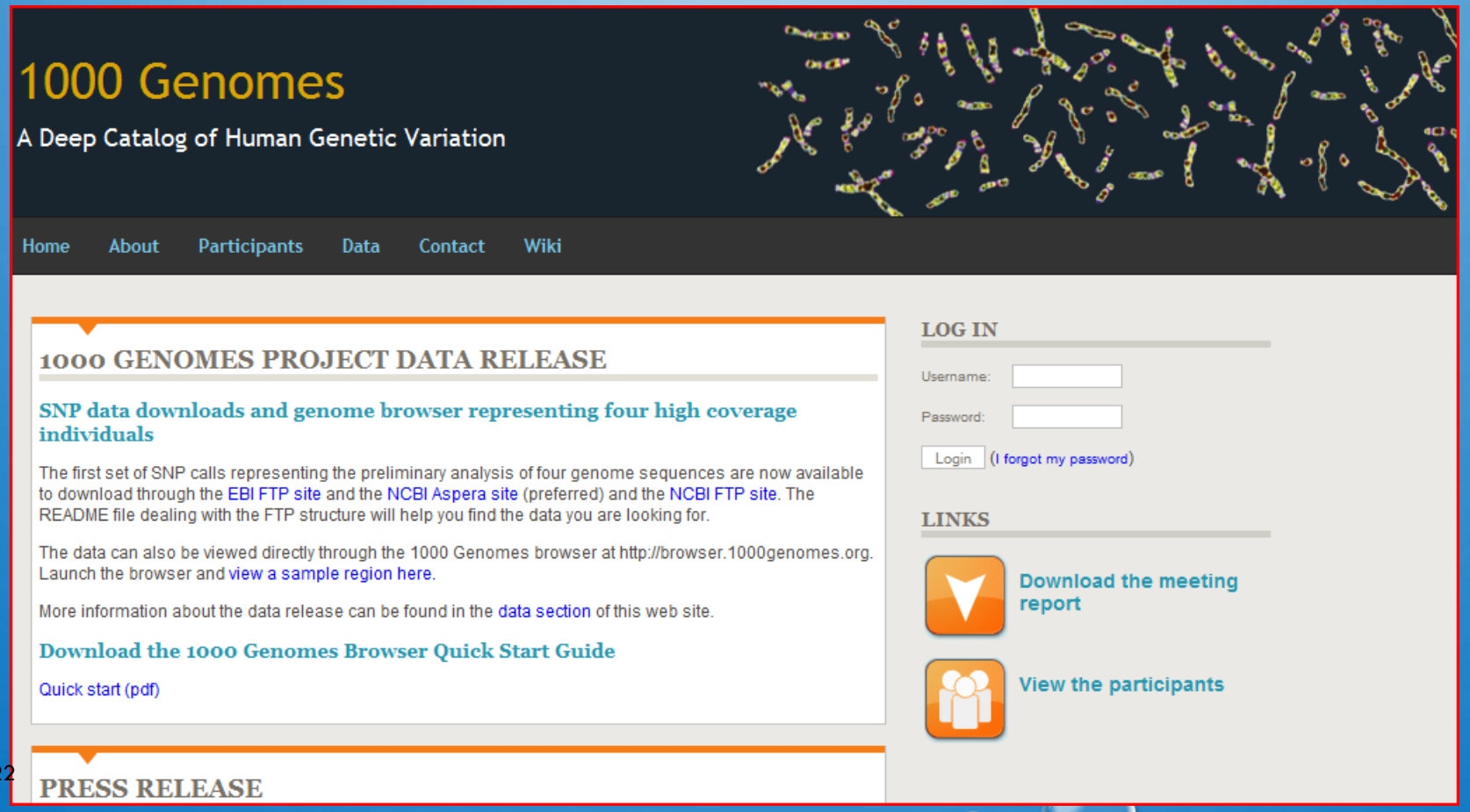


FROM HUMAN GENOME PROJECT TO SINGLE GENOME SEQUENCING; SNPS



	Venter genome	Watson genome	African genome NA18507
SNPs	3.2 M	3.4 M	3.7 M
Known SNPs	1.9 M	1.8 M	2.7 M
Putative novel SNPs	1.3 M	1.6 M	1.0 M
Non synonymous SNPs (number of genes)	10389 (4107)	10569 (4403)	11718
Non synonymous SNPs in OMIM genes (known pathogenic variants)	314	210 (23)	
Indels	>800 K	223 K	
CNVs	62	23	

THE 1000 GENOME PROJECT



SNPS (90 % OF VARIATION)

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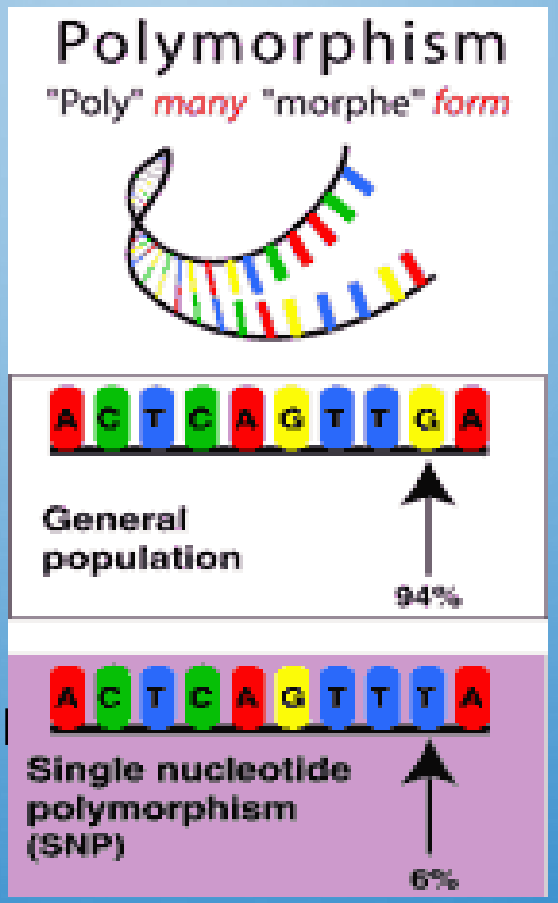

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POLYGENETIC DISEASES, GENOME WIDE ASSOCIATION STUDIES

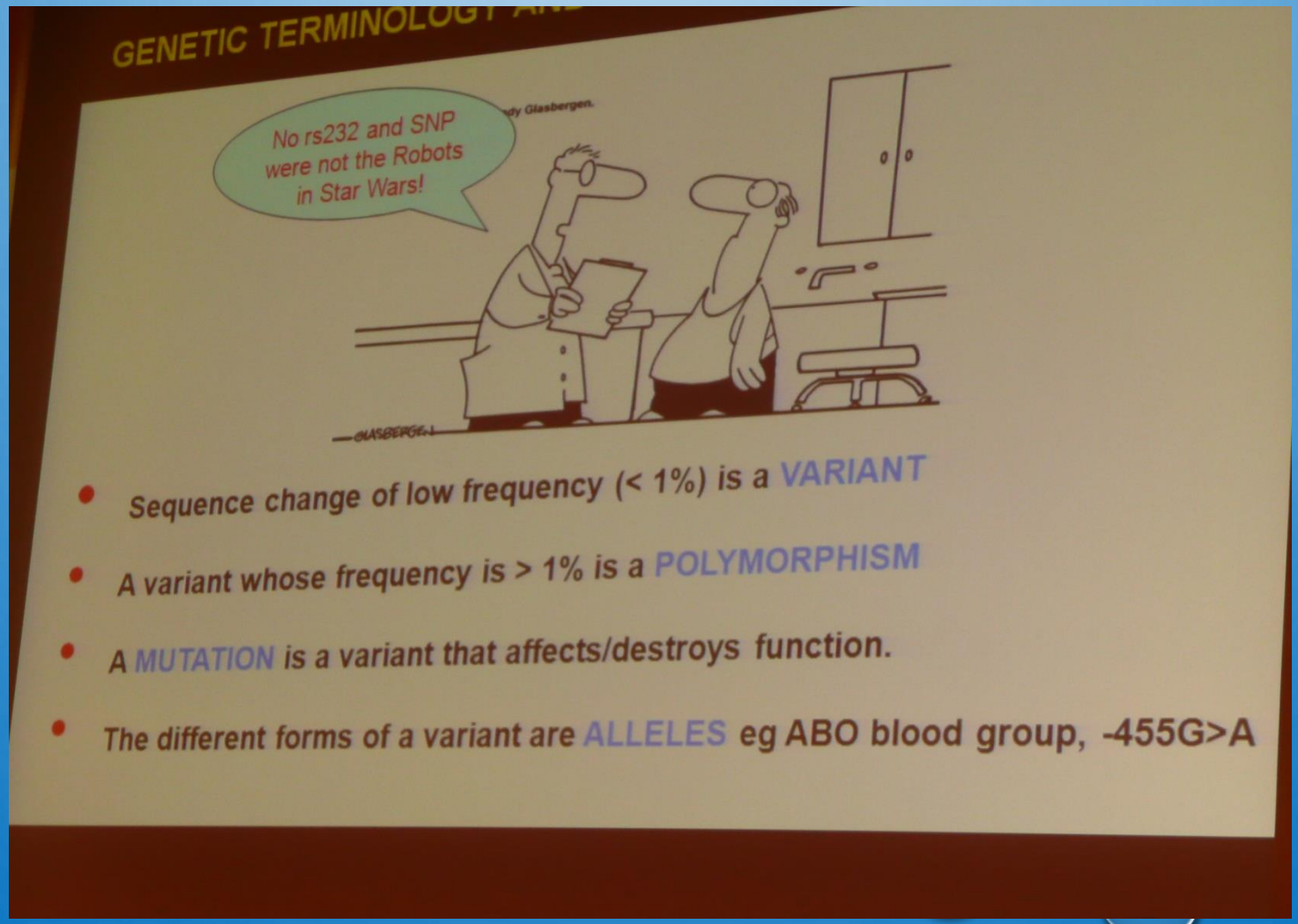
nature genetics

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease

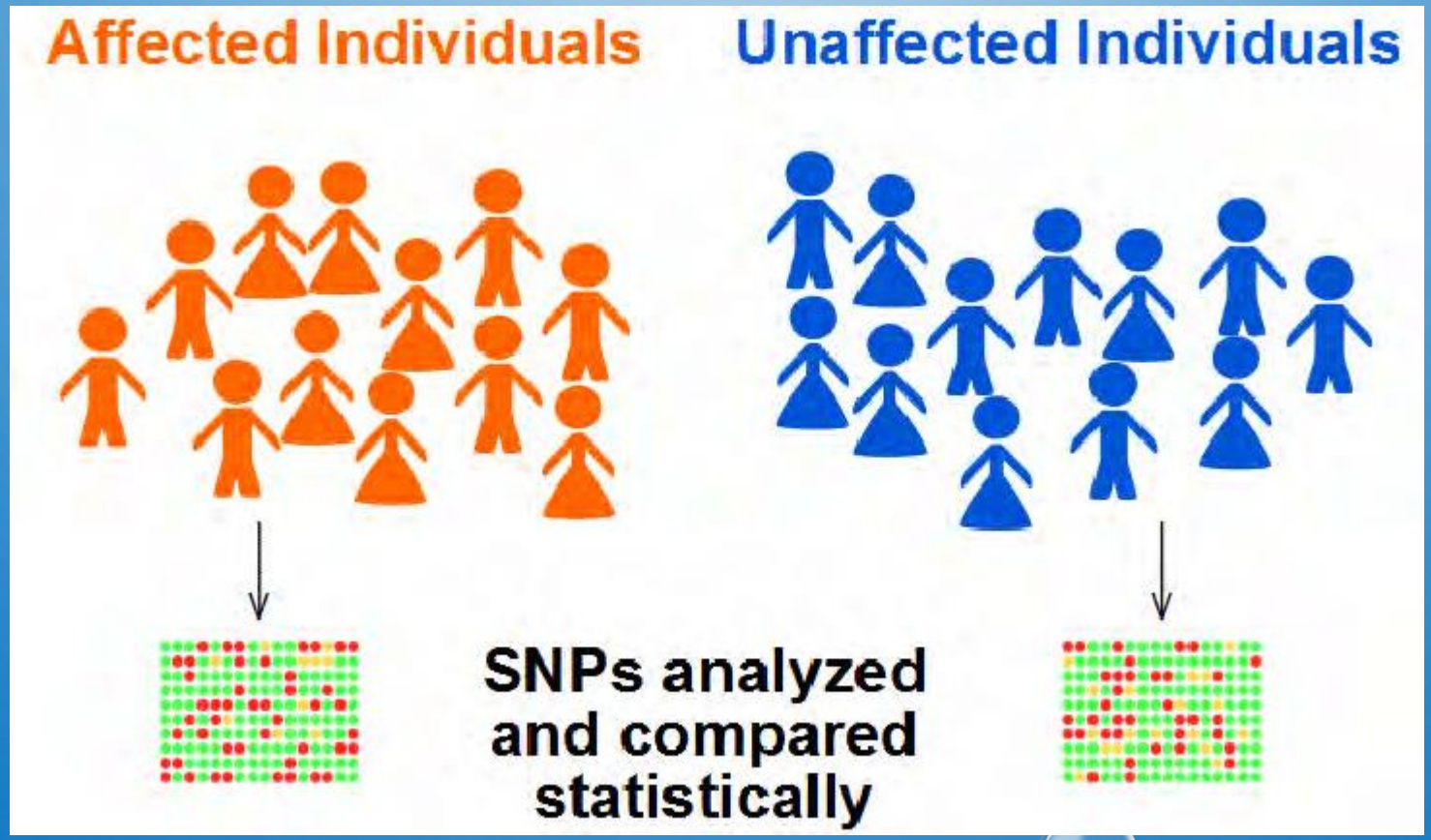
Jeffrey C Barrett[*1], Sarah Hansoul[2], Dan L Nicolae[3], Judy H Cho[4], Richard H Duerr[5,6], John D Rioux[7,8], Steven R Brant[9,10], Mark S Silverberg[11], Kent D Taylor[12], M Michael Barmada[6], Alain Bitton[13], Themistocles Dassopoulos[9], Lisa Wu Datta[9], Todd Green[8], Anne M Griffiths[14], Emily O Kistner[15], Michael T Murtha[4], Miguel D Regueiro[5], Jerome I Rotter[12], L Philip Schumm[15], A Hillary Steinhart[11], Stephan R Targan[12], Ramnik J Xavier[16], the NIDDK IBD Genetics Consortium[33], Cécile Libioulle[2], Cynthia Sandor[2], Mark Lathrop[17], Jacques Belaiche[18], Olivier Dewit[19], Ivo Gut[17], Simon Heath[17], Debby Laukens[20], Myriam Mni[2], Paul Rutgeerts[21], André Van Gossum[22], Diana Zelenika[17], Denis Franchimont[22], Jean-Pierre Hugot[23], Martine de Vos[20], Severine Vermeire[21], Edouard Louis[18], the Belgian-French IBD Consortium[33], the Wellcome Trust Case Control Consortium[33,34], Lon R Cardon[1], Carl A Anderson[1], Hazel Drummond[24], Elaine Nimmo[24], Tariq Ahmad[25], Natalie J Prescott[26], Clive M Onnie[26], Sheila A Fisher[26], Jonathan Marchini[27], Jilur Ghori[28], Suzannah Bumpstead[28], Rhian Gwilliam[28], Mark Tremelling[29], Panos Deloukas[28], John Mansfield[30], Derek Jewell[31], Jack Satsangi[24], Christopher G Mathew[26], Miles Parkes[29], Michel Georges[2] & Mark J Daly[8,32]

Several risk factors for Crohn's disease have been identified in recent genome-wide association studies. To advance gene discovery further, we combined data from three studies on Crohn's disease (a total of 3,230 cases and 4,829 controls) and carried out replication in 3,664 independent cases with a mixture of population-based and family-based controls. The results strongly confirm 11 previously reported loci and provide genome-wide significant evidence for 21 additional loci, including the regions containing *STAT3*, *JAK2*, *ICOSLG*, *CDKAL1* and *ITLN1*. The expanded molecular understanding of the basis of this disease offers promise for informed therapeutic development.

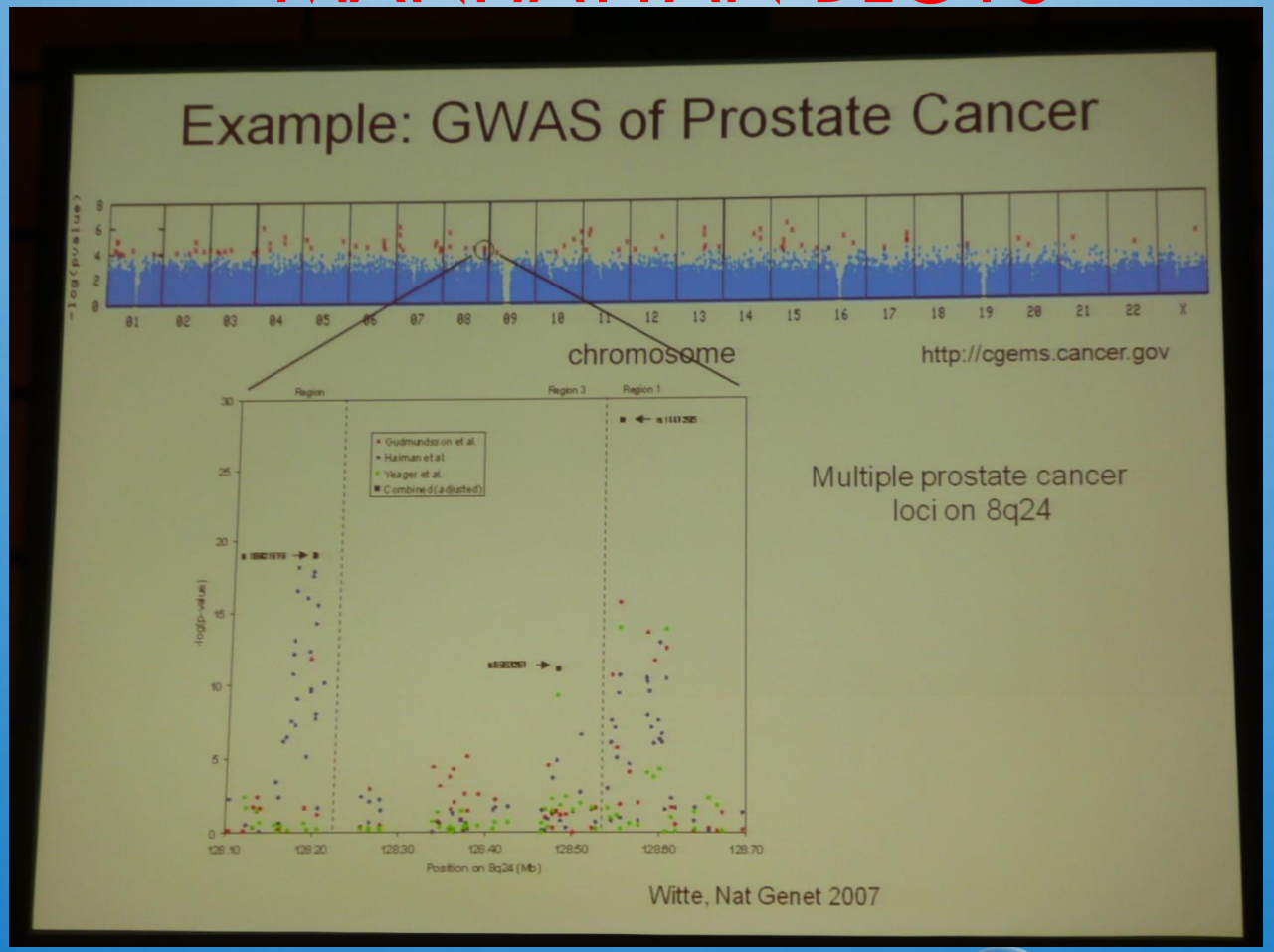
DEFINITIONS

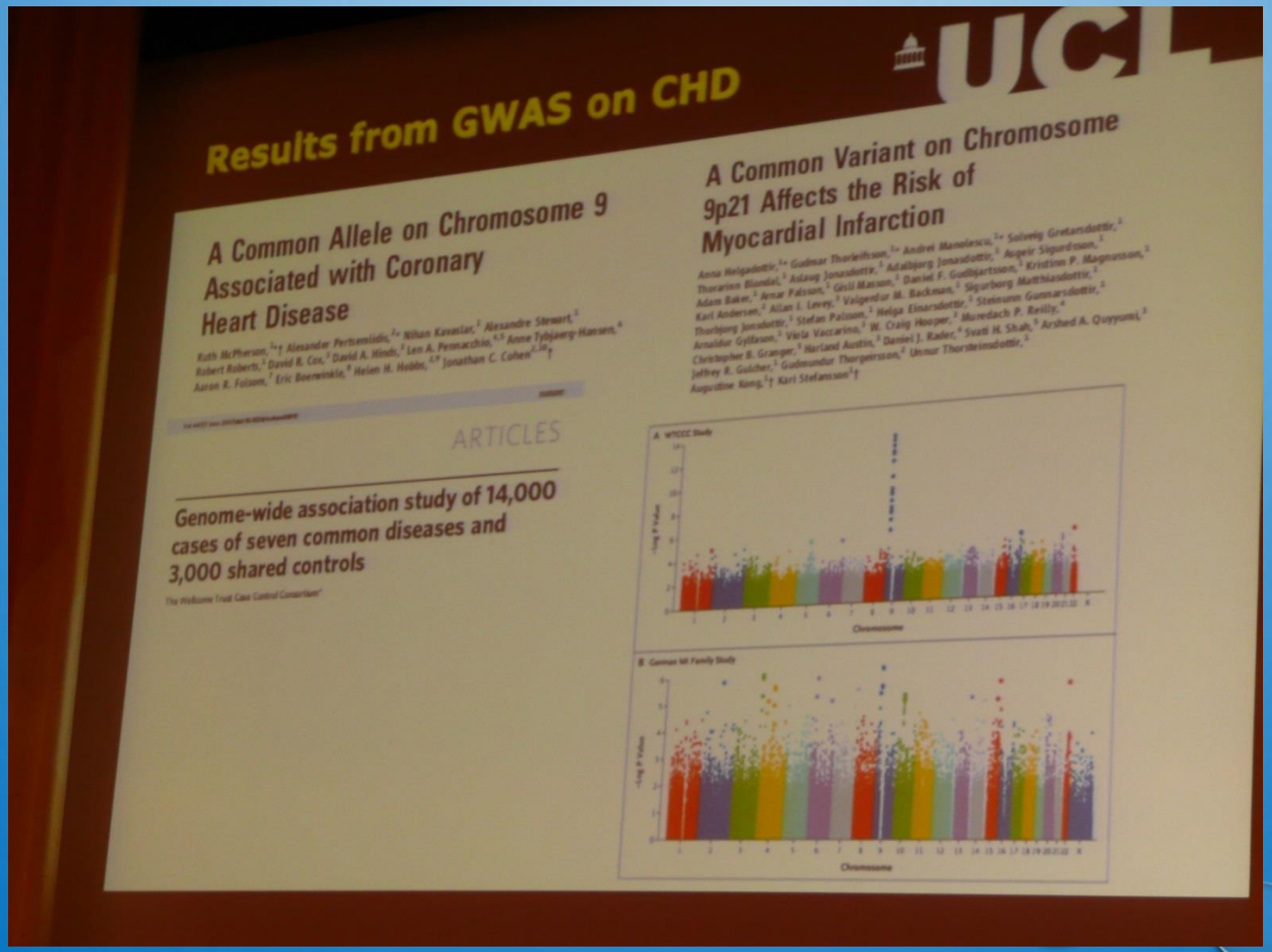


GENOME WIDE ASSOCIATION STUDIES

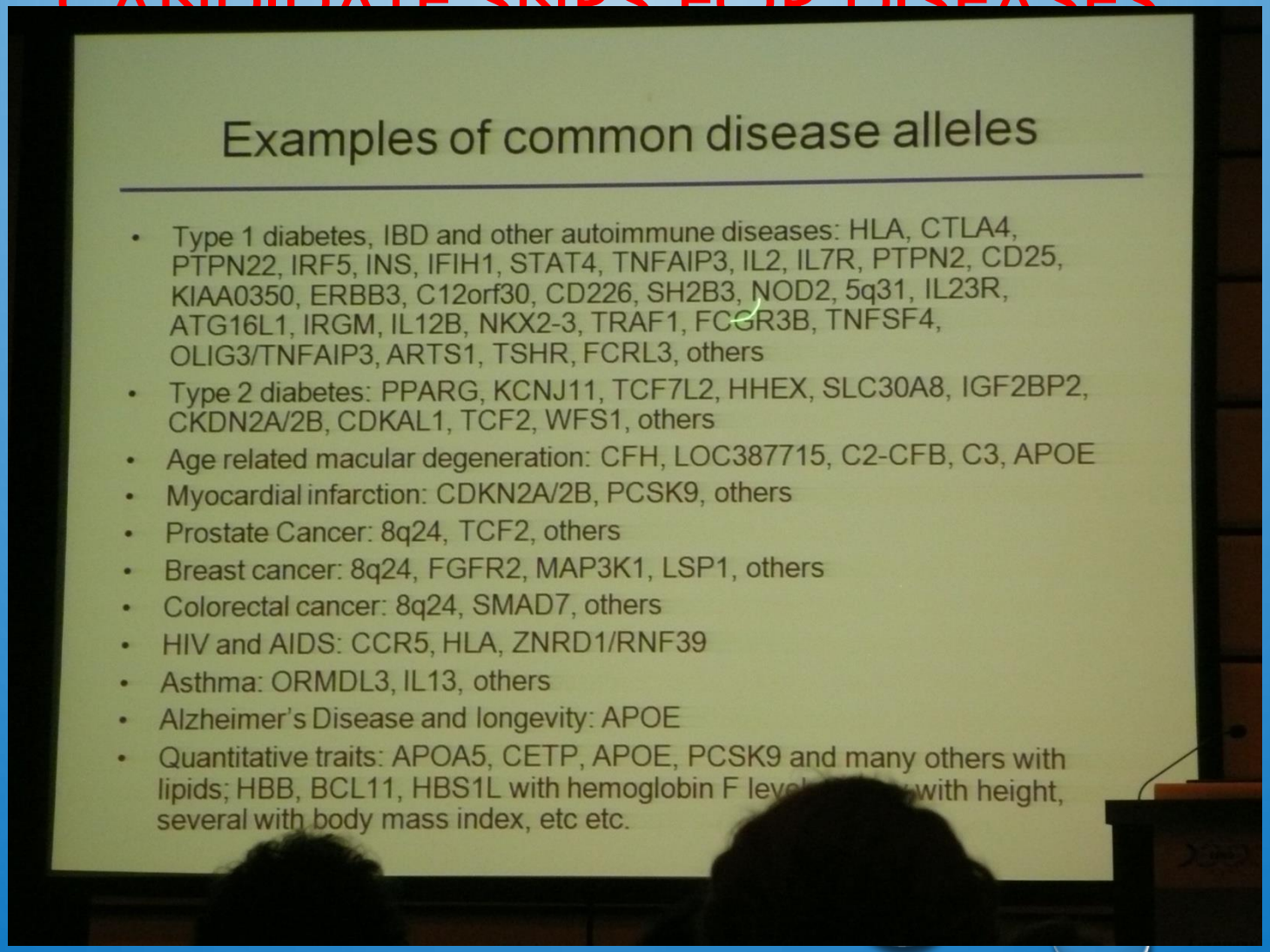


MANHATTAN BLOTS

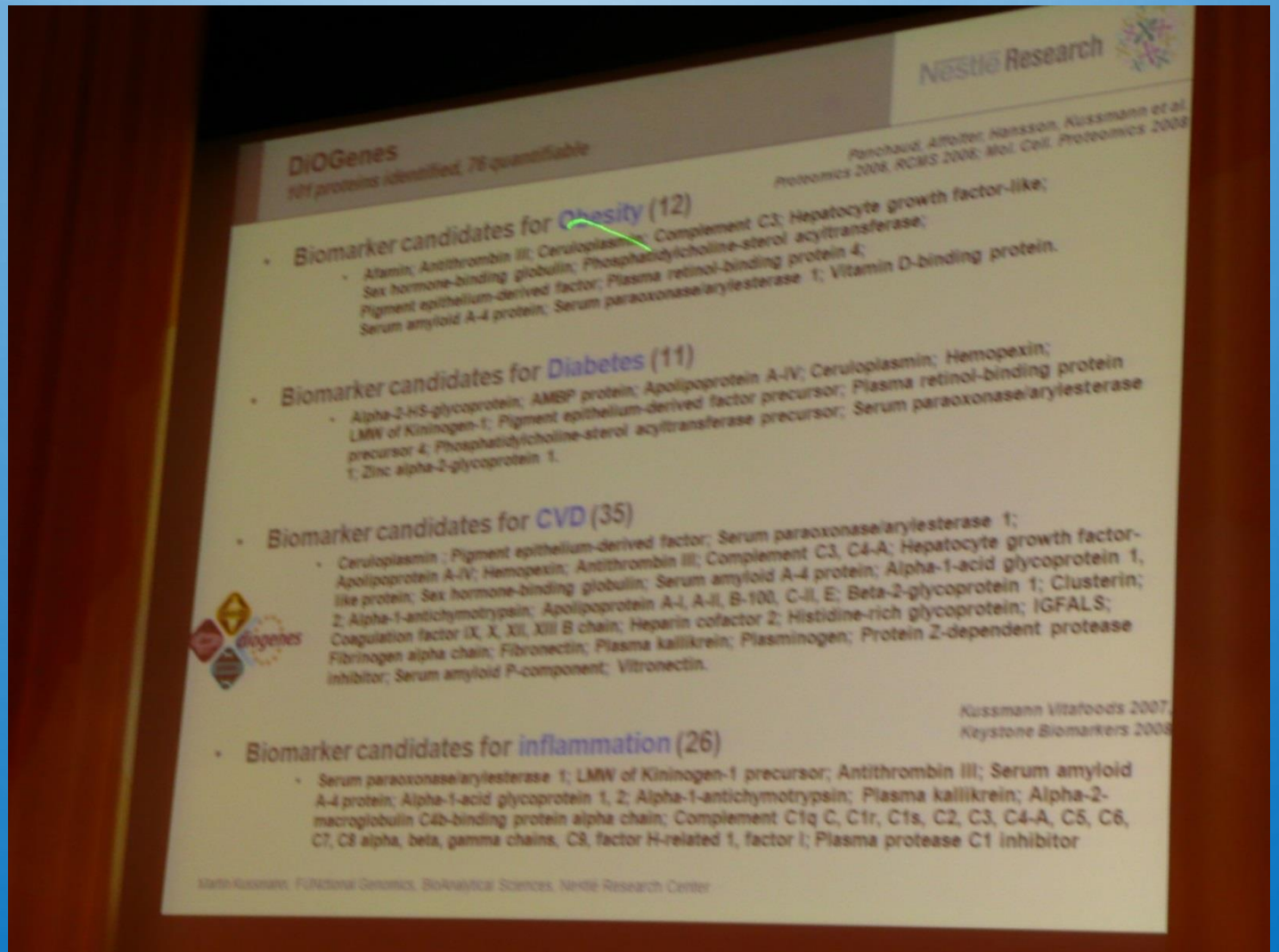



Results from GWAS on CHD
A Common Allele on Chromosome 9 Associated with Coronary Heart Disease
A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction
ARTICLES
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

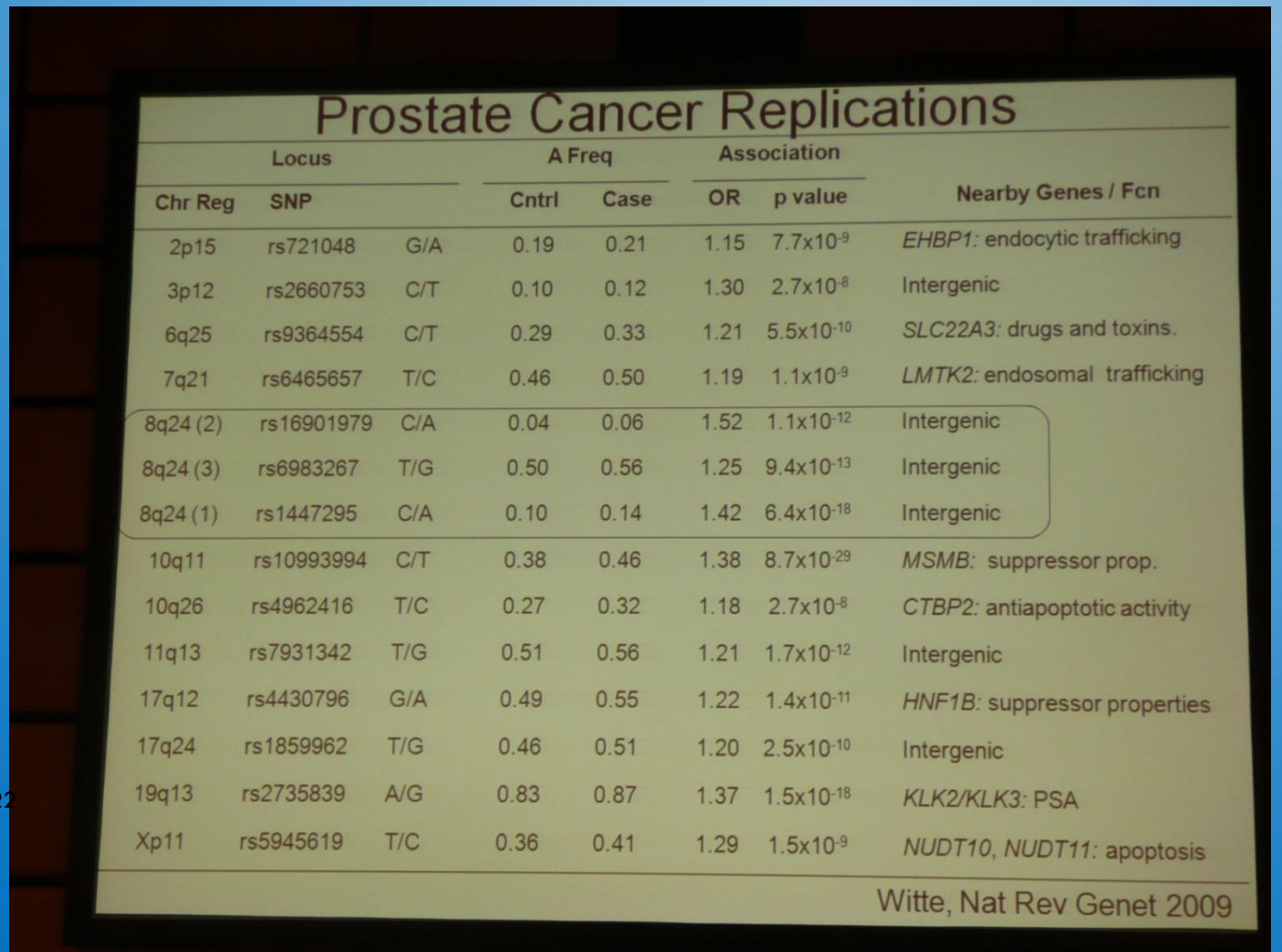
CANDIDATE SNPS FOR DISEASES



TOWARDS SNP MARKERS



ODDS RATIOS, MOSTLY < 1,5

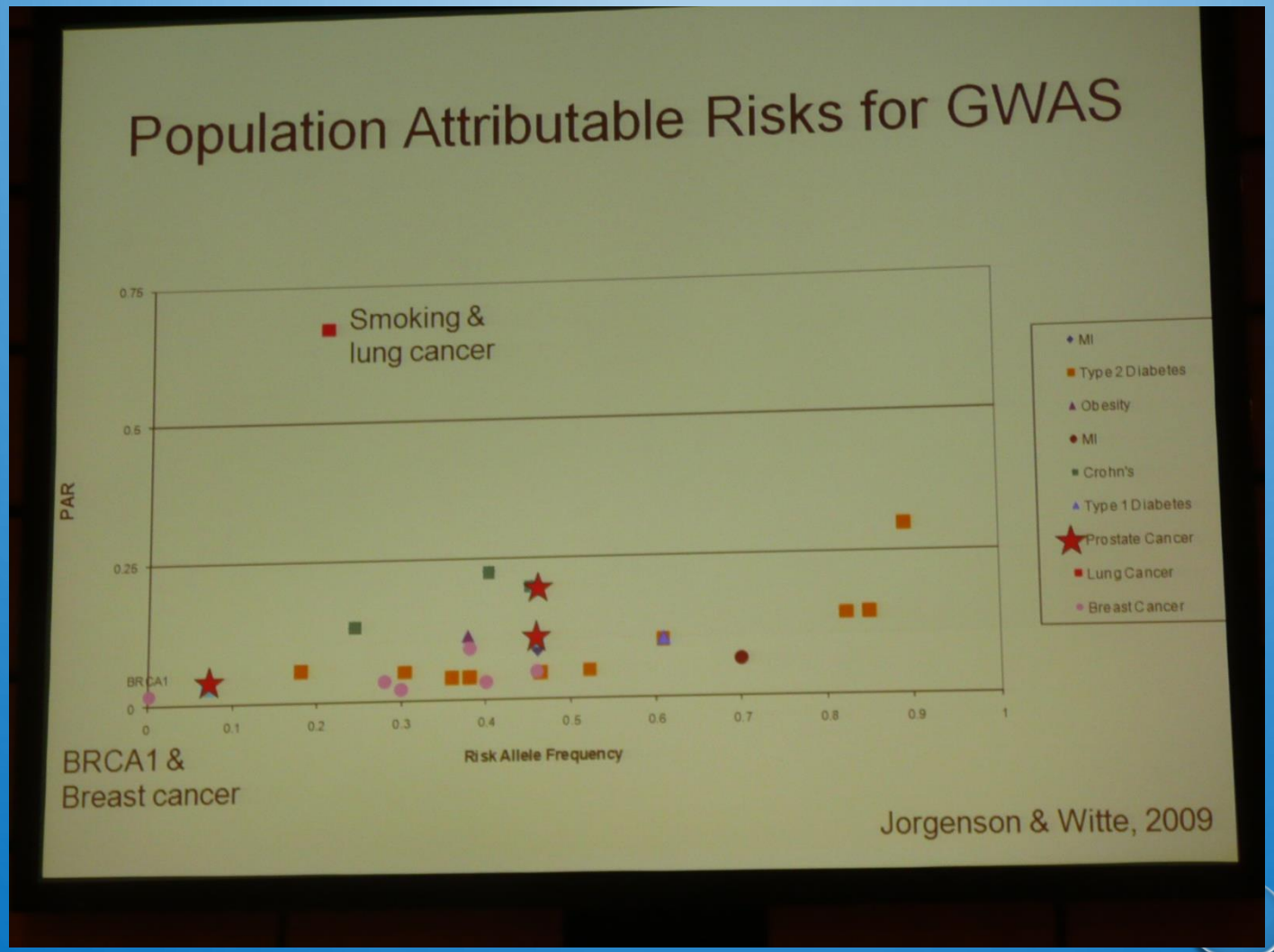


Prostate Cancer Replications

Locus			A Freq		Association		Nearby Genes / Fcn
Chr Reg	SNP		Cntrl	Case	OR	p value	
2p15	rs721048	G/A	0.19	0.21	1.15	7.7×10^{-9}	*EHBP1:* endocytic trafficking
3p12	rs2660753	C/T	0.10	0.12	1.30	2.7×10^{-8}	Intergenic
6q25	rs9364554	C/T	0.29	0.33	1.21	5.5×10^{-10}	*SLC22A3:* drugs and toxins.
7q21	rs6465657	T/C	0.46	0.50	1.19	1.1×10^{-9}	*LMTK2:* endosomal trafficking
8q24 (2)	rs16901979	C/A	0.04	0.06	1.52	1.1×10^{-12}	Intergenic
8q24 (3)	rs6983267	T/G	0.50	0.56	1.25	9.4×10^{-13}	Intergenic
8q24 (1)	rs1447295	C/A	0.10	0.14	1.42	6.4×10^{-18}	Intergenic
10q11	rs10993994	C/T	0.38	0.46	1.38	8.7×10^{-29}	*MSMB:* suppressor prop.
10q26	rs4962416	T/C	0.27	0.32	1.18	2.7×10^{-8}	*CTBP2:* antiapoptotic activity
11q13	rs7931342	T/G	0.51	0.56	1.21	1.7×10^{-12}	Intergenic
17q12	rs4430796	G/A	0.49	0.55	1.22	1.4×10^{-11}	*HNF1B:* suppressor properties
17q24	rs1859962	T/G	0.46	0.51	1.20	2.5×10^{-10}	Intergenic
19q13	rs2735839	A/G	0.83	0.87	1.37	1.5×10^{-18}	*KLK2/KLK3:* PSA
Xp11	rs5945619	T/C	0.36	0.41	1.29	1.5×10^{-9}	*NUDT10, NUDT11:* apoptosis

Witte, Nat Rev Genet 2009

THE RELEVANCE OF SNPS



e.g. Cardivascular: Polymorphisms and pathways

1.α-Adducin
2. ACE
3. ALOX5AP
4. Angiotensin-Rezeptor Typ I
5. Angiotensinogen
6. ApoA1
7. ApoB
8. ApoC-III
9. ApoE
10. ABCA1
11. ANP
12. ANP Clearance Rezeptor
13.β2-adrenergische Rezeptor
14.β3-adrenergische Rezeptor
15.β-Fibrinogen
16. CD14-Rezeptor
17. CC-Chemokine-Rezeptor 2
18. CETP
19. Extrazelluläre Superoxiddismutase (SOD3)
20. FII
21. FV
22. FVII
23. FXII
24. FXIII A-Untereinheit
25. Connexin 37

26. eNOS
27. Endothelin-1
28. E-Selectin
29. FABP2
30. Fractalkin-Rezeptor
31. Glykoprotein Ia
32. Glykoprotein Ibα
33. Glykoprotein IIa
34. Glykoprotein IIIa
35. Glykoprotein PC-1
36. G-Protein β-3 Untereinheit
37. HFE
38. HL
39. IRS1
40. IL1α
41. IL1β
42. IL4
43. IL6
44. IL10
45. Leptin
46. LPL
47. LRP
48. Lp(a)
49. Mangan- Superoxiddismutase

52. MMP12
53. Methioninsynthase
54. MTHFR
55. MCP1
56. P22
57. NPY
58. PON
59. CD31
60. PPARα
61. PPARγ2
62. PAI1
63. PAFAH
64. P-Selectin
65. SRB1
66. Serotonin-Rezeptor 2A
67. Stromelysin 1 (MMP3)
68. Thrombomodulin
69. Thrombopoietin
70. Thrombospondin 1
71. Thrombospondin 4
72. TFPI
73. TGFβ1
74. TNFα

Frequencies, ethnic aspects of typical SNPs

POPULATION FREQUENCY CHART

Gene	Var.	Percentage of Population with Gene Variation						
		Total Frequency*	African American	Asian	Caucasian	Hispanic/Latino	Japanese	Chinese
MTHFR	C677	28.7	10.0	21.1	28.9	47.1	40.3	33.3
MTHFR	A1298C	30.0	25.0	19.2	33.9	17.5	36	14.6
MS_MTRR	A66G	47.3	27.5	28.9	52.5	44.1	31.8	20.5
MTR	A2576G	17.4	32.5	7.9	15.8	14.7	18.5	10.4
CBS	C699T	28.0	20.0	2.6	30.0	32.4	ND	4.3
MnSOD	C-28T	54.2	64.6	<1	53.4	65.2	12	67.7
SOD3	C760G	<3	<3	<3	<3	<3	<3	<3
IL-6	G-174C	36.3	<1	<1	47.5	21.9	<1	<1
IL-6	G-634C	10.3	15.0	63.2	5.6	14.7	22.0	ND
TNF-α	G-308A	16.5	12.5	7.9	15.8	26.5	2	2
APOC3	C3175G	12.6	7.5	31.6	13.2	8.8	32.6	29.8
CETP	G279A	37.0	18.4	36.8	40.0	38.2	40	35.4
LPL	C1595G	9.9	7.5	13.2	7.5	23.2	14	6.5
eNOS	G894T	35.6	22.5	15.8	42.5	17.6	12.5	9
ACE	I/DD	61.0	63.6	77.8	57.9	70.0	62	65
GSTM1	Gene Deletion	69.0	32.0	43.0	50.0	47.0	54.5	50.4
GSTP1	A313G	34.8	52.5	28.9	32.5	32.4	27.5	15.2
GSTP1	C341T	11.5	<1	<1	15.8	2.9	<1	2.0
GSTT1	Gene Deletion	21.9	26.0	80.0	20.0	11.0	48.3	45.4

HYPE IN MEDIA, E.G.DIABETES, REALITY

Variante des KCNJ11-Gens erhöht das Risiko für Alterszucker auch in deutscher Bevölkerung

17.03.08.

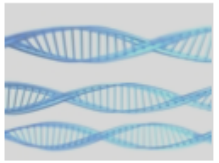
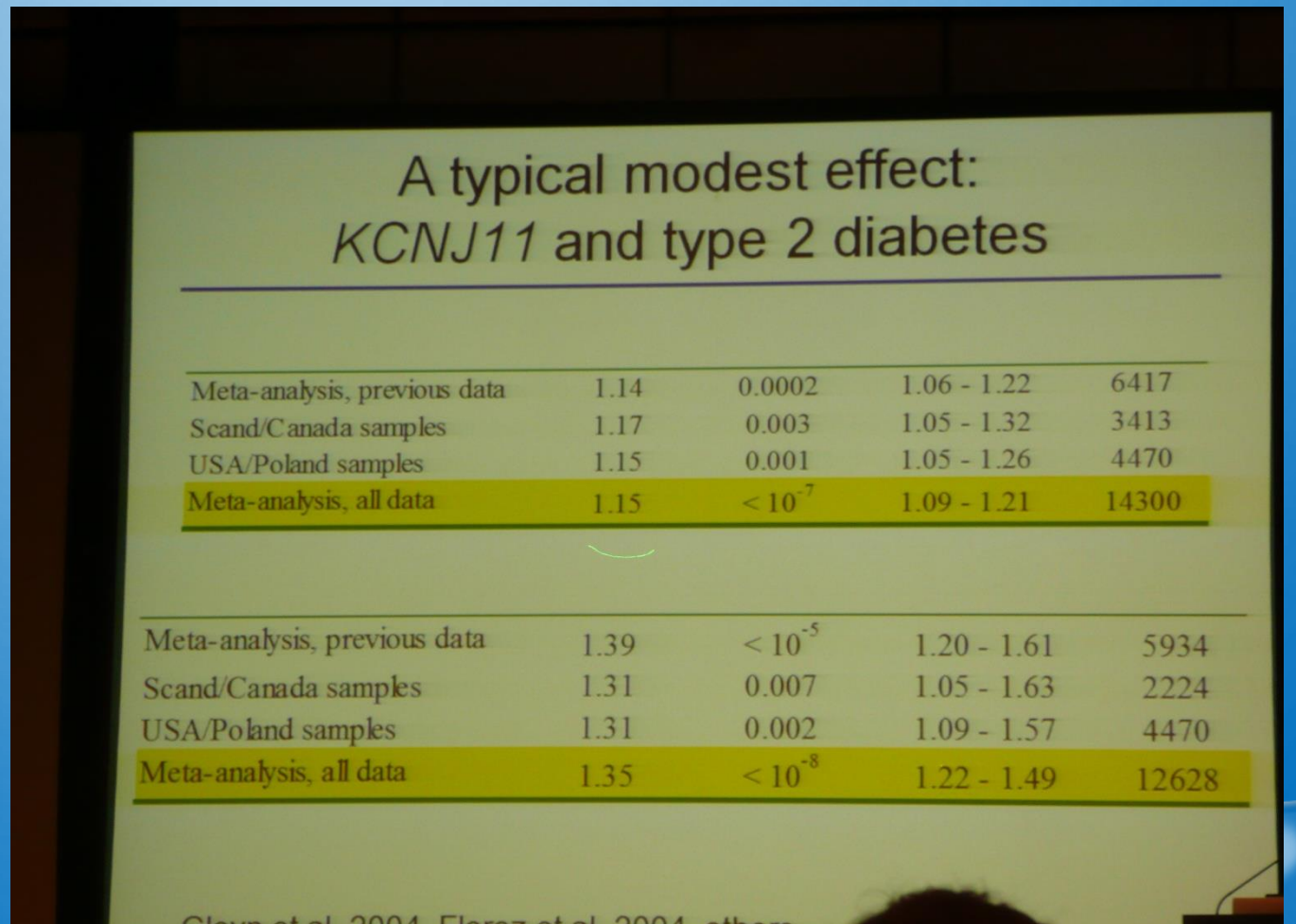


Foto: Shutterstock

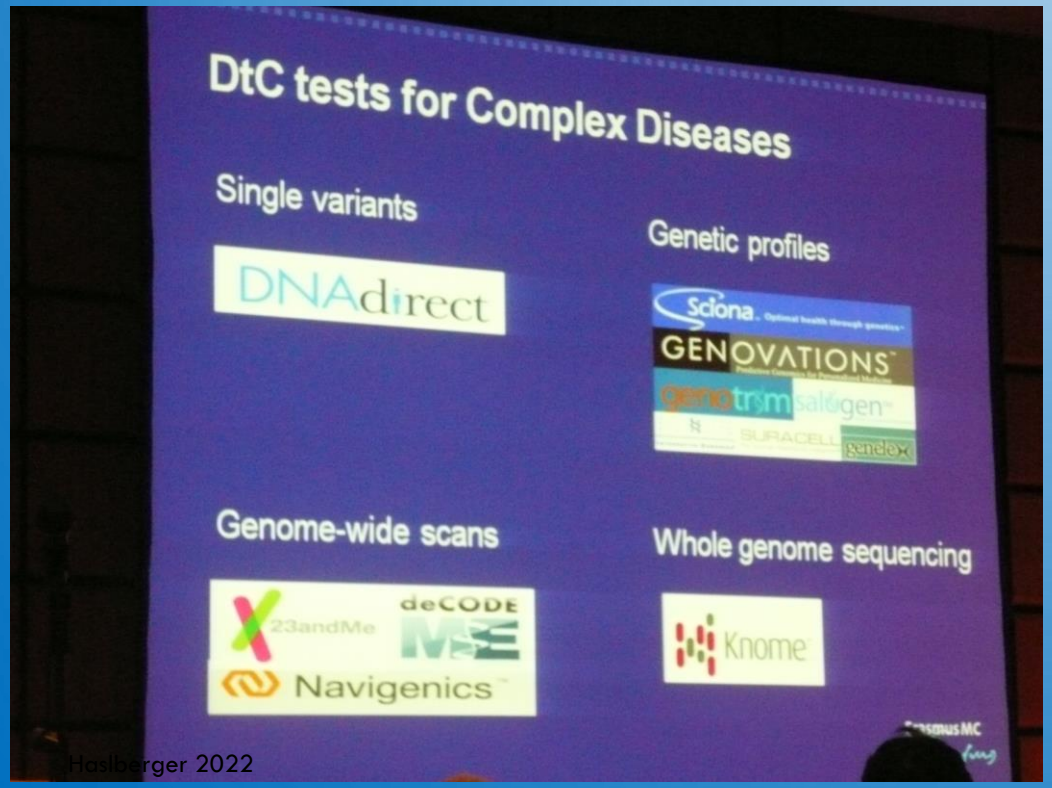
Eine Variante des Gens KCNJ11 erhöht be Menschen der Region Berlin/Brandenburg das Risiko für Alterszucker (Typ-2-Diabetes) um bis zu 25 Prozent. Dies ist ein Ergebnis einer großen Bevölkerungsstudie, die Wissenschaftler des Deutschen Instituts für Ernährungsforschung Potsdam-Rehbrücke (DIfE) durchführten. Ferner wiesen die Forscher nach, dass die mit KCNJ11 23K bezeichnete Genvariante sowohl die Insulinausschüttung als auch die Insulinempfindlichkeit negativ beeinflusst.

„Möglicherweise könnte man unsere Ergebnisse in Zukunft dazu nutzen, die Vorhersagekraft von Diabetes-Risikotests zu erhöhen. Zudem helfen die von uns gefundenen funktionellen Daten, die Mechanismen der Diabetesentstehung aufzuklären", erklärt Joachim Spranger, Leiter der wissenschaftlichen Untersuchung. Die Forscher veröffentlichten ihre Ergebnisse in der Januarausgabe der renommierten Fachzeitschrift Diabetes Care (Fischer et al. 2008; 31:87-92).

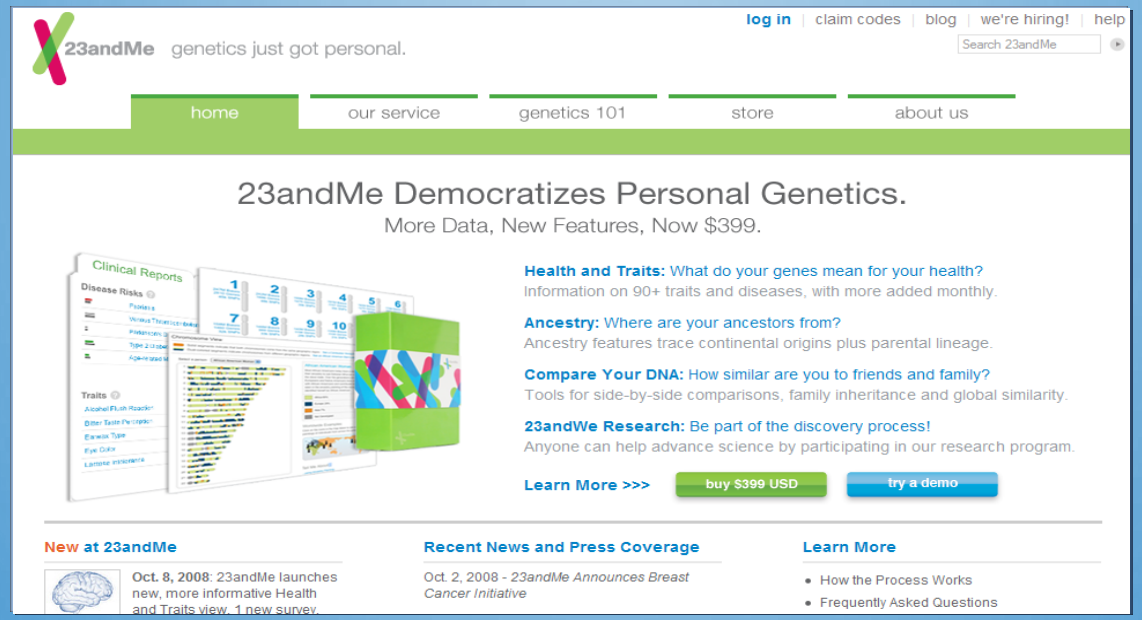
Grundlage der vorliegenden Untersuchung sind die Daten von 2.945 Teilnehmern der Potsdamer EPIC*-Studie sowie von 1.891 Teilnehmern der MeSyBePo**-Studie. Die Teilnehmer beider Studien stammen aus der Region Berlin/Brandenburg.



GENETIC TESTING

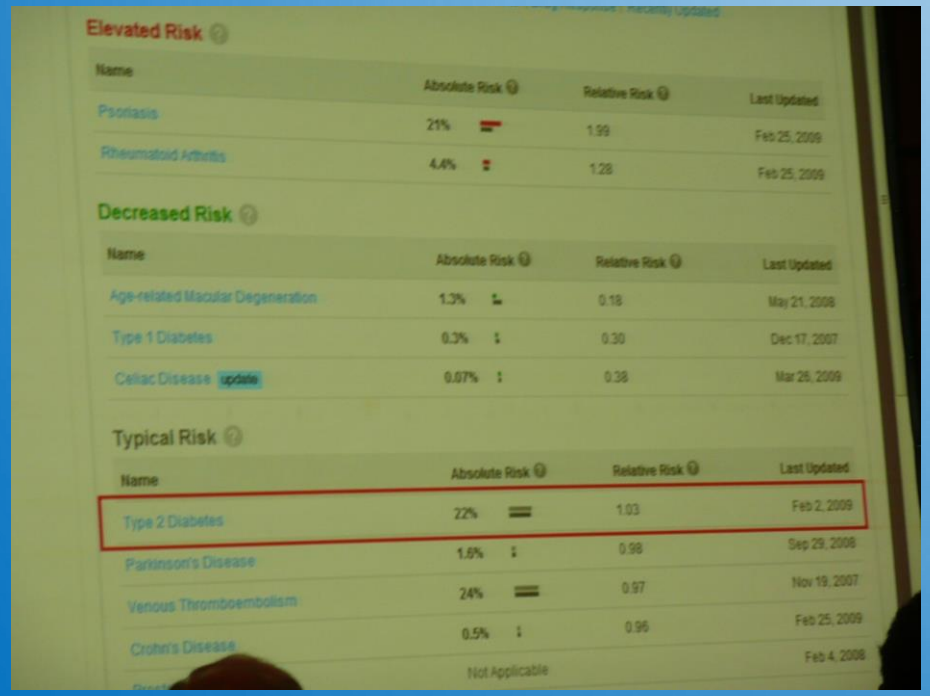


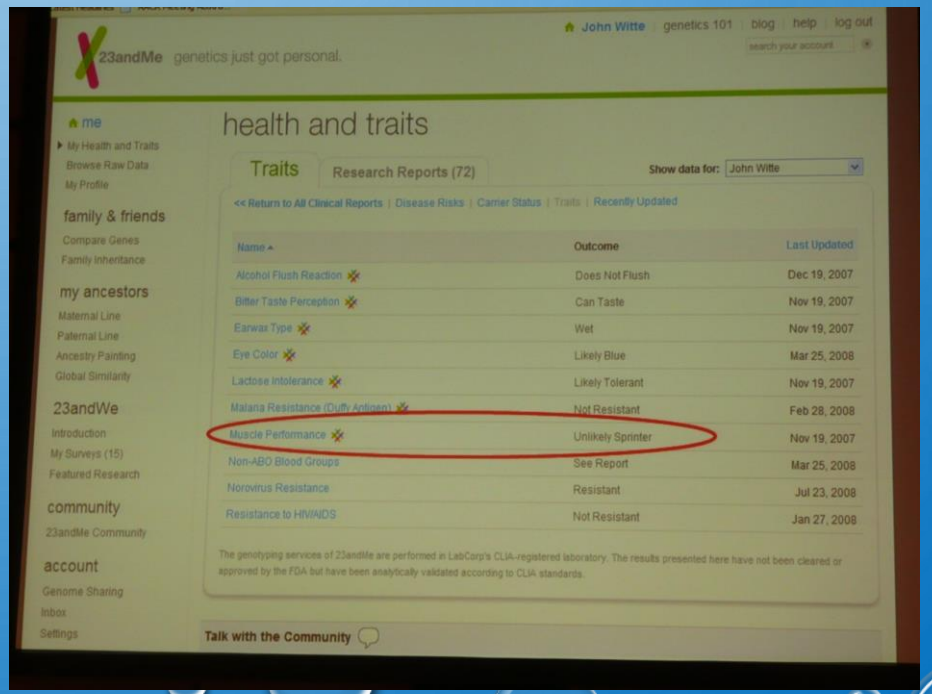
Heart Health			
Gene Analyzed	**Role of the Gene in Heart Health**	**Genetic Variation Screened For Variations Found in Your Gene**	**Percentage of Population with this Gene Variation***
MTHFR	Use of Folic Acid for DNA Synthesis or DNA Repair	C677T A1298C	28.7 30.0
MS_MTRR	Metabolism of Vitamin B12	A66G	47.3
MTR	Removal of Homocysteine	A2756G	17.4
CBS	Metabolism of Vitamin B6 and Removal of Homocysteine	C699T	28.0
MnSOD	Antioxidant Defense	C(-28)T	54.2
		T175C	
SOD3		C760G	
IL-6	Inflammatory Response	G(-174)C	36.3
TNF-α		G(-308)A	16.5
APOC3	Triglyceride Metabolism	C3175G	12.6
CETP	Cholesterol Metabolism	G279A	37.0
LPL		C1595G	9.9
eNOS	Blood Flow	G894T	35.6
ACE		DEL	61.0



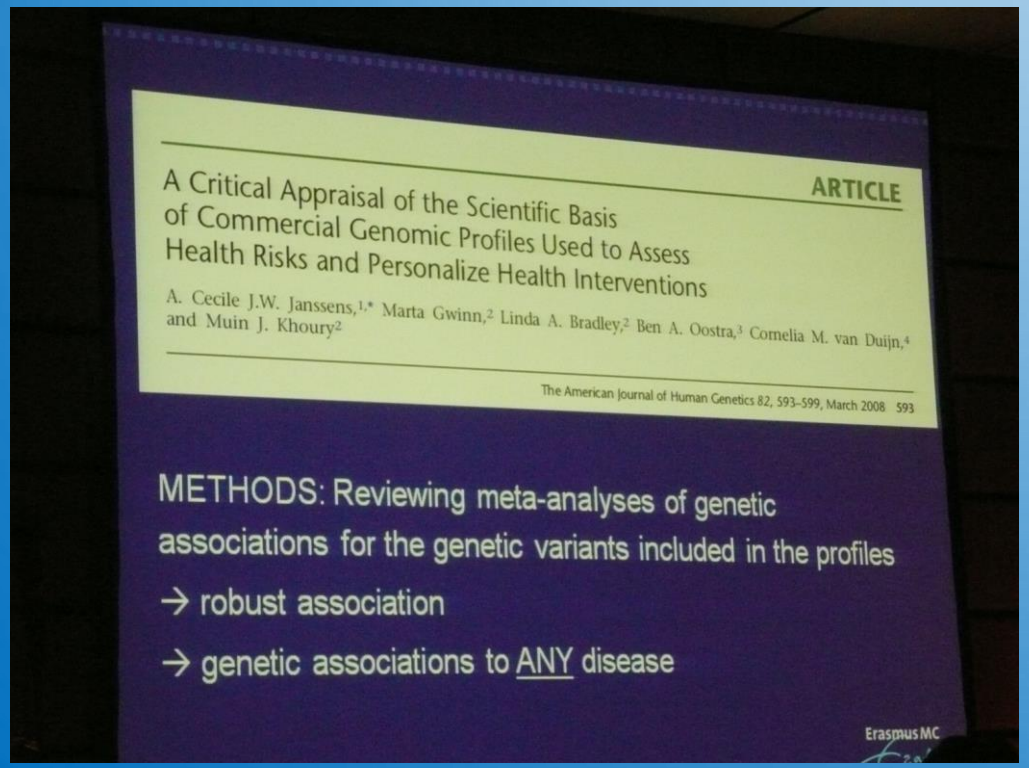
23andme, www.23andme.com
Genelex, www.genelex.com
Genovations, www.genovations.com
Genosolutions, www.genosolutions.com
HuGENet, www.hugenavigator.net
Integrative genomics, www.integrativegenomics.com
Interleukin genetics, www.ilgenetics.com
Navigenics, www.navigenics.com
Nutrilite, www.nutrilite.com
Salugen, www.salugen.com
Sciona, www.sciona.com
Suracell, www.suracell.com

THE OUTCOME 23ANDME





CRITICAL ASPECTS OF GENETIC TESTING FOR CONSUMERS



ARTICLE

A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Health Interventions

A. Cecile J.W. Janssens,[1,*] Marta Gwinn,[2] Linda A. Bradley,[2] Ben A. Oostra,[3] Cornelia M. van Duijn,[4] and Muin J. Khoury[2]

Predictive genomic profiling used to produce personalized nutrition and other lifestyle health recommendations is currently offered directly to consumers. By examining previous meta-analyses and HuGE reviews, we assessed the scientific evidence supporting the purported gene-disease associations for genes included in genomic profiles offered online. We identified seven companies that offer predictive genomic profiling. We searched PubMed for meta-analyses and HuGE reviews of studies of gene-disease associations published from 2000 through June 2007 in which the genotypes of people with a disease were compared with those of a healthy or general-population control group. The seven companies tested at least 69 different polymorphisms in 56 genes. Of the 56 genes tested, 24 (43%) were not reviewed in meta-analyses. For the remaining 32 genes, we found 260 meta-analyses that examined 160 unique polymorphism-disease associations, of which only 60 (38%) were found to be statistically significant. Even the 60 significant associations, which involved 29 different polymorphisms and 28 different diseases, were generally modest, with synthetic odds ratios ranging from 0.54 to 0.88 for protective variants and from 1.04 to 3.2 for risk variants. Furthermore, genes in cardiogenomic profiles were more frequently associated with noncardiovascular diseases than with cardiovascular diseases, and though two of the five genes of the osteogenomic profiles did show significant associations with disease, the associations were not with bone diseases. There is insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention.

COMPLEX DISEASES: THE NEED TO UNDERSTAND GENE- ENVIRONMENT INTERACTIONS

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Science 1 June 2007:
Vol. 316. no. 5829, pp. 1341 - 1345
DOI: 10. ence.1142382

< Prev | Table of Contents | Next >

REPOR

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen
Michael R. Erdos,[3] Hea
Ludmila Prokunina-Ol
Rui Xiao,[1] Xiao-Yi Li,[1]
Peggy P. White,[1] Kurt

OPEN ACCESS Freely line

PLoS one

An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus

Chirag J. Patel[1,2,3], Jayanta Bhattacharya[4], Atul J. Butte[1,2,3]*

1 Department of Pediatrics and Medicine, Stanford University School of Medicine, Stanford, California, United States of America, **2** Stanford Center for Biomedical Informatics Research, Stanford University School of Medicine, Stanford, California, United States of America, **3** Lucile Packard Children's Hospital, Palo Alto, California, United States of America, **4** Center For Primary Care and Outcomes Research, Stanford University School of Medicine, Stanford, California, United States of America

significant findings were validated with other cohorts. We discovered significant associations for the pesticide-derivative heptachlor epoxide (adjusted OR in three combined cohorts of 1.7 for a 1 SD change in exposure amount; $p<0.001$), and the vitamin γ-tocopherol (adjusted OR 1.5; $p<0.001$). Higher concentrations of polychlorinated biphenyls (PCBs) such as PCB170 (adjusted OR 2.2; $p<0.001$) were also found. Protective factors associated with T2D included β-carotenes (adjusted

THE PHGEN EU NETWORK

public health genomics
European Network

Public Health Genomics

Modern research in genetics and molecular biology offers new opportunities for the promotion of population health. **Public Health Genomics** (PHG) is the responsible and effective integration of genome-based knowledge and technologies into public policy and into health services for the benefit of population health.

Aims of PHGEN

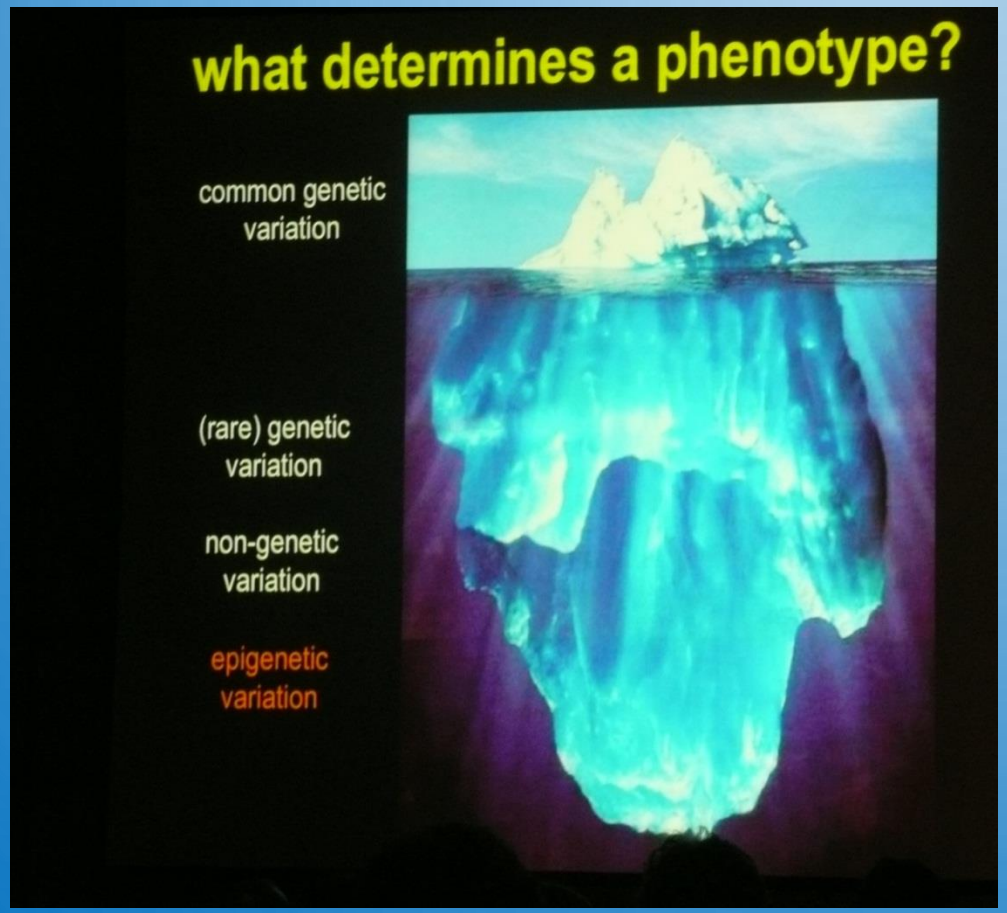
To conduct a networking exercise on Public Health Genomics (PHG) covering all EU Member States

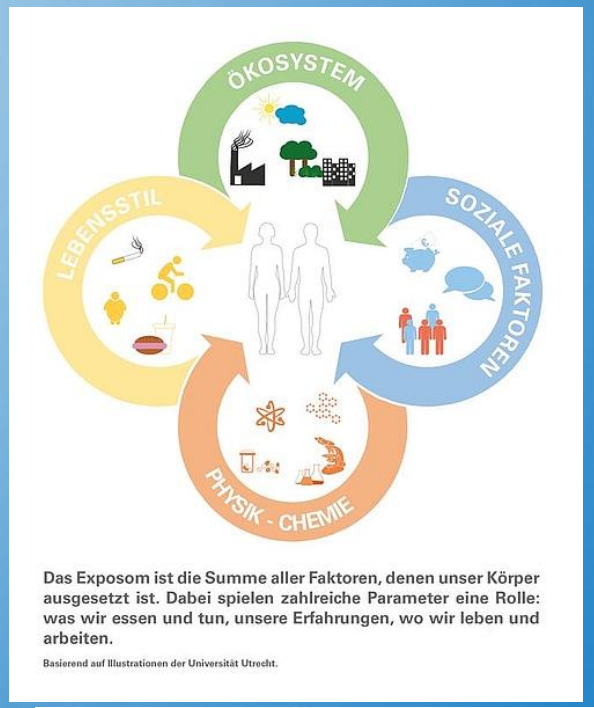
To provide an inventory of PHG-issues and priorities in Europe.

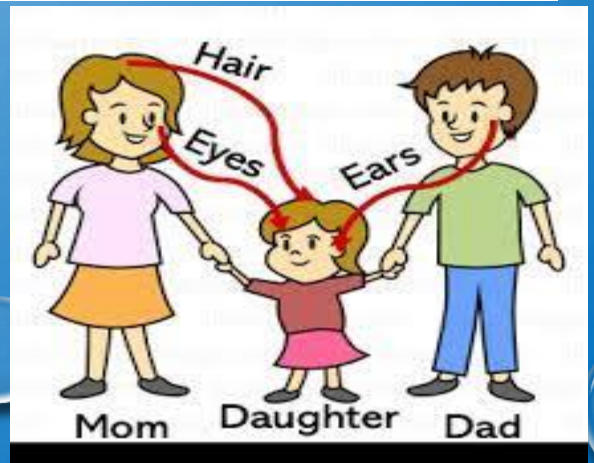
To contribute to the co-operation and exchange of information in order to enhance coherence and disseminate best practice.

To identify legal diversities and barriers in a cross-border market.

GENETIC – ENVIRONMENT, MISSING HERITABILITY







EPIGENETIC, FIRST EVIDENCES

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

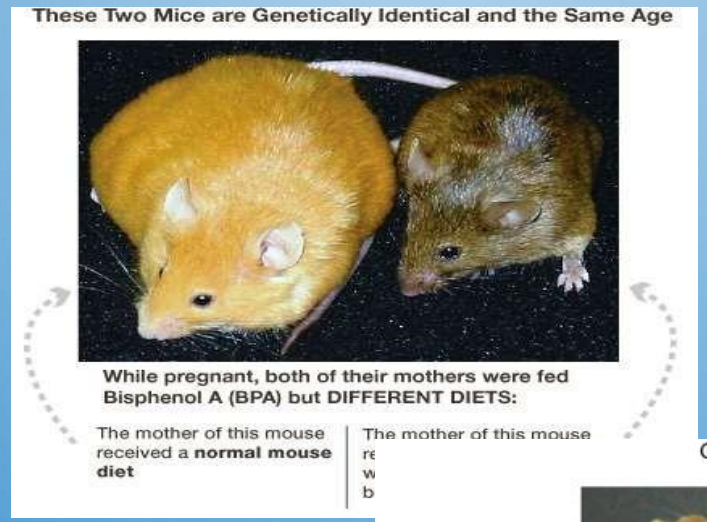
Matthew D. Anway, Andrea S. Cupp,* Mehmet Uzumcu,† Michael K. Skinner‡

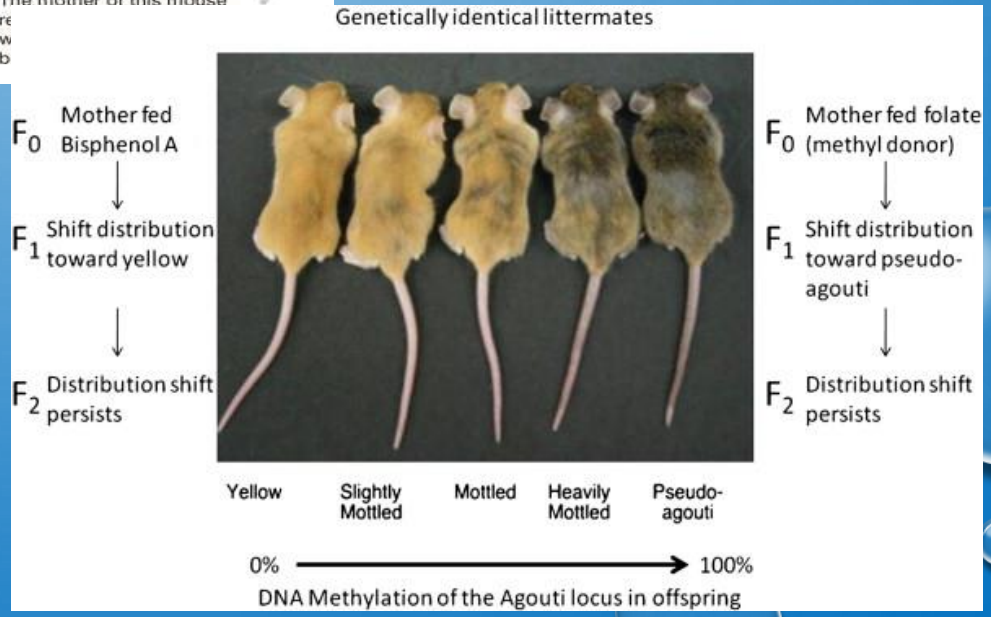
Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F_1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F_1 to F_4). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

3 JUNE 2005 VOL 308 SCIENCE www.sciencemag.org

ENDOGENE DIRUPTORS
The fungicide vinclozolin, which is sprayed on vineyards can cause fertility problems in male offspring of exposed rats.

EPIGENETIC PROOF AGOUTI MOUSE,





EFFECTS FROM THE ENVIRONMENT: PRENATAL NUTRITION. THE DUTCH FAMINE STUDY

PNAS

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline Slagboom[a], and L. H. Lumey[e,1]

Departments of [a]Molecular Epidemiology, [c]Medical Statistics, and [d]Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands; [b]Hubert Department of Global Health, Rollins School of Public Health, Emory University Atlanta, GA 30322; [e]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032; and [f]New York State Psychiatric Institute, New York, NY 10032

Edited by Charles R. Cantor, Sequenom Inc., San Diego, CA, and approved September 17, 2008 (received for review July 7, 2008)

Table 2. *IGF2* DMR methylation among individuals exposed to famine late in gestation and their unexposed, same-sex siblings

IGF2 DMR methylation	Mean methylation fraction (SD)				Relative change exposed	Difference in SDs	*P*
	Exposed (n = 62)		Controls (n = 62)				
Average	0.514	0.045	0.519	0.036	−0.9%	−0.12	.64
CpG 1	0.460	0.044	0.464	0.048	−0.9%	−0.09	.68
CpG 2 and 3	0.462	0.039	0.471	0.039	−1.7%	−0.21	.46
CpG 4	0.602	0.085	0.612	0.073	−1.5%	−0.12	.30
CpG 5	0.529	0.060	0.531	0.060	−0.3%	−0.02	.77

P values were obtained using a linear mixed model and adjusted for age.

LIVE TIME: EPIGENETIC DIVERSITY: TWIN STUDIES

NAS

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, María F. Paz*, Santiago Ropero*, Fernando Setien*, María L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

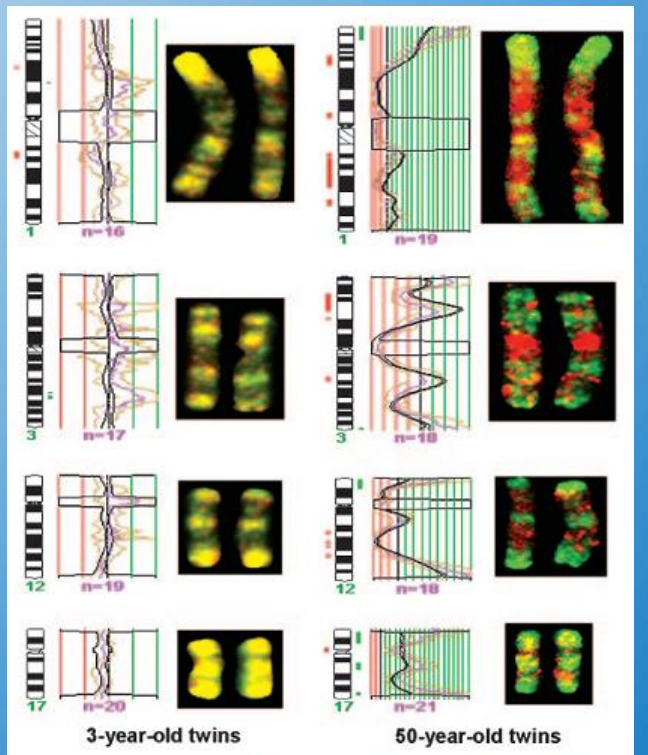
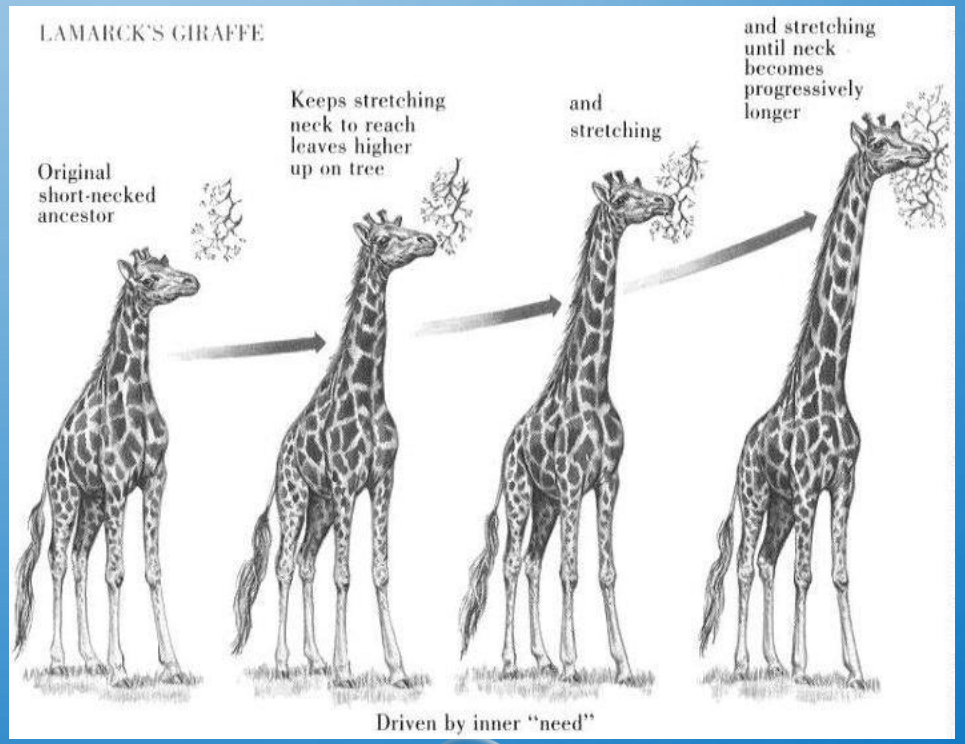
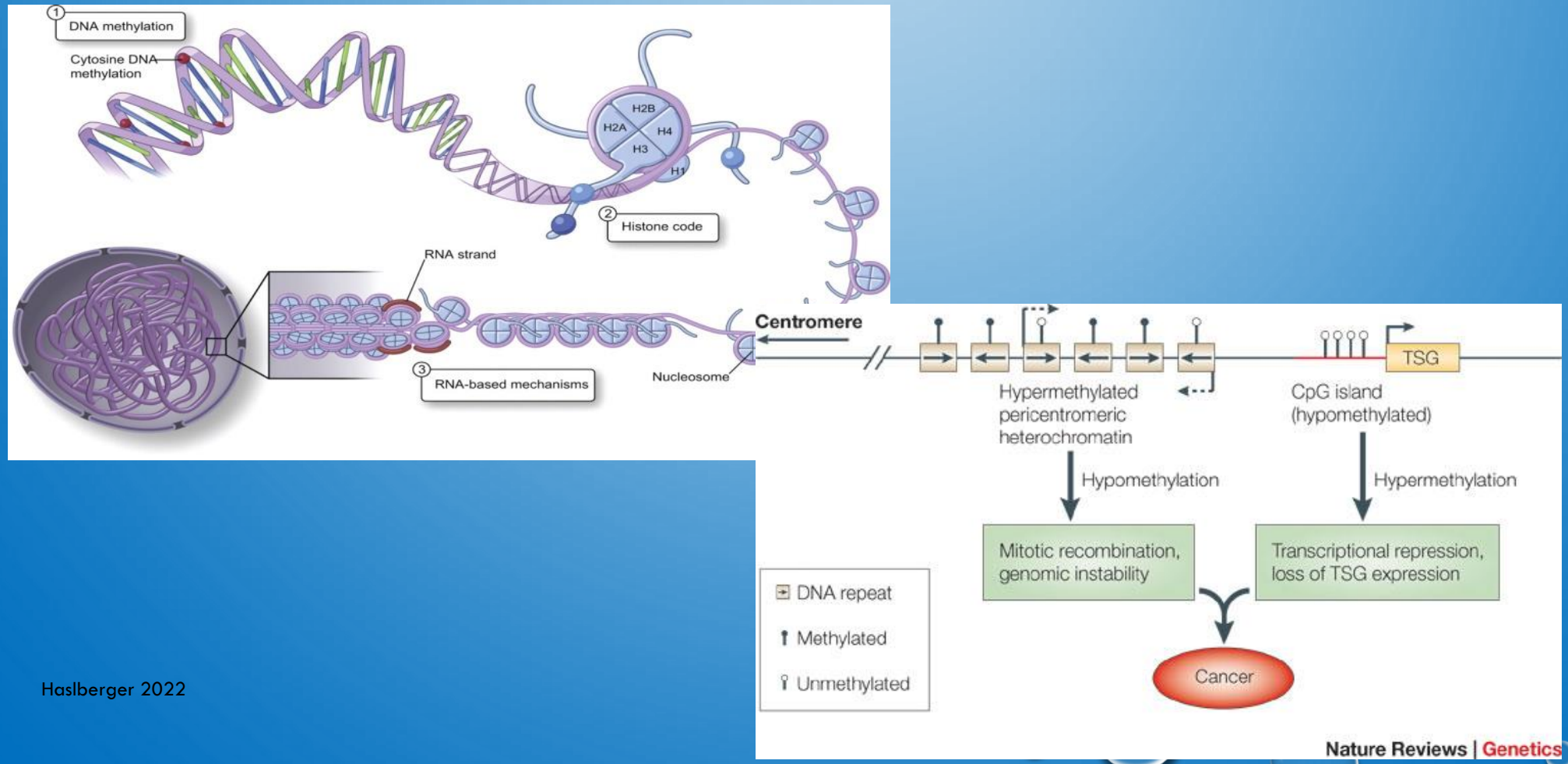


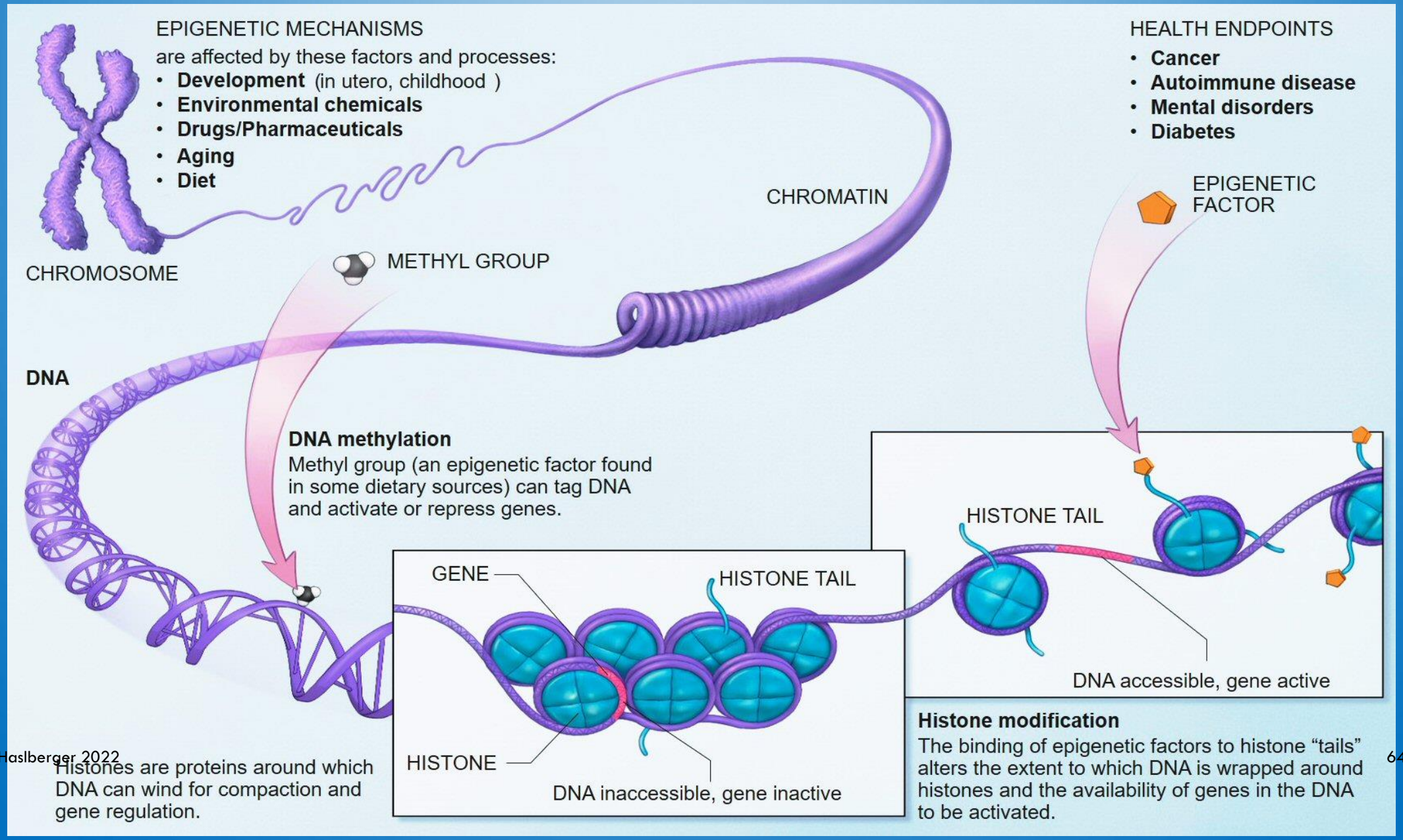
Fig. 3. Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA. Competitive hybridization onto normal metaphase chromosomes of the AIMS products generated from 3- and 50-year-old twin pairs. Examples of the hybridization of chromosomes 1, 3, 12, and 17 are displayed. The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation observed by the presence of green and red signals that indicate hypermethylation and hypomethylation events, whereas the 3-year-old twins have a very similar distribution of DNA methylation indicated by the presence of the yellow color obtained by equal amounts of the green and red dyes. Significant DNA methylation changes are indicated as thick red and green blocks in the ideograms.

DARWIN, LAMARCK AND EPIGENETICS ?



EPIGENETICS: SEQUENCE INDEPENDENT REGULATION OF GENE EXPRESSION AND DNA STABILITY




EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Histones are proteins around which DNA can wind for compaction and gene regulation.

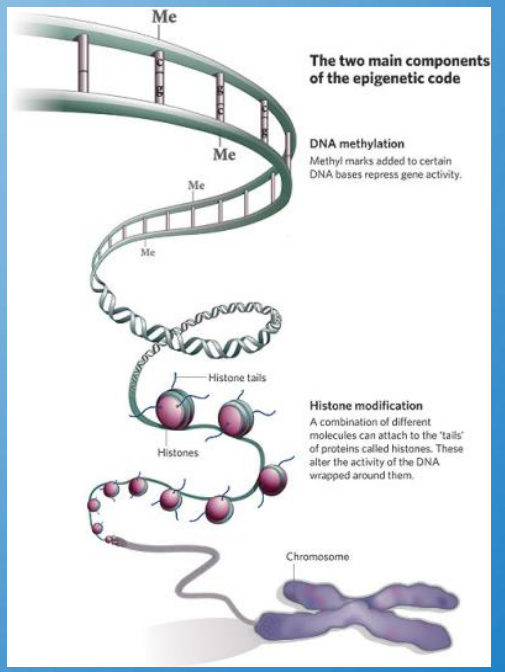
THREE MAIN TYPES OF EPIGENETIC INFORMATION

The three main types of epigenetic information

Cytosine DNA methylation is a covalent modification of DNA, in which a methyl group is transferred from *S-adenosylmethionine to the C-5 position of cytosine by a family of cytosine* (DNA-5)-methyltransferases. DNA methylation occurs almost exclusively at CpG nucleotides and has an important contributing role in the regulation of gene expression and the silencing of repeat elements in the genome.

Genomic imprinting is parent-of-origin-specific allele silencing, or relative silencing of one parental allele compared with the other parental allele. It is maintained, in part, by differentially methylated regions within or near imprinted genes, and it is normally reprogrammed in the germline.

Histone modifications — including acetylation, methylation and phosphorylation — are important in transcriptional regulation and many are stably maintained during cell division, although the mechanism for this epigenetic Inheritance is not yet well understood. Proteins that mediate these modifications are often associated within the same complexes as those that regulate DNA methylation.



RNA (interference)

2004

Andrew P. Feinberg and Benjamin Tycko,

EPIGENETICS

Epigenetics : C. H. Waddington in 1942 conceptual model of how genes might interact with their surroundings to produce a phenotype.

E*pigenetic*: heritable traits (over rounds of cell division and sometimes transgenerationally) that do not involve changes to the underlying DNA sequence

EPIGENETIC EFFECTS: TRANSGENERATIONAL

VOLUME 84, NO. 2 *THE QUARTERLY REVIEW OF BIOLOGY* JUNE 2009

TRANSGENERATIONAL EPIGENETIC INHERITANCE: PREVALENCE, MECHANISMS, AND IMPLICATIONS FOR THE STUDY OF HEREDITY AND EVOLUTION

EVA JABLONKA

The Cohn Institute for the History and Philosophy of Science and Ideas, Tel-Aviv University, Tel-Aviv 69978, Israel

E-MAIL: JABLONKA@POST.TAU.AC.IL

GAL RAZ

The Graduate School of Medicine, Tel-Aviv University, Tel-Aviv 69978, Israel

E-MAIL: GALRAZ@POST.TAU.AC.IL

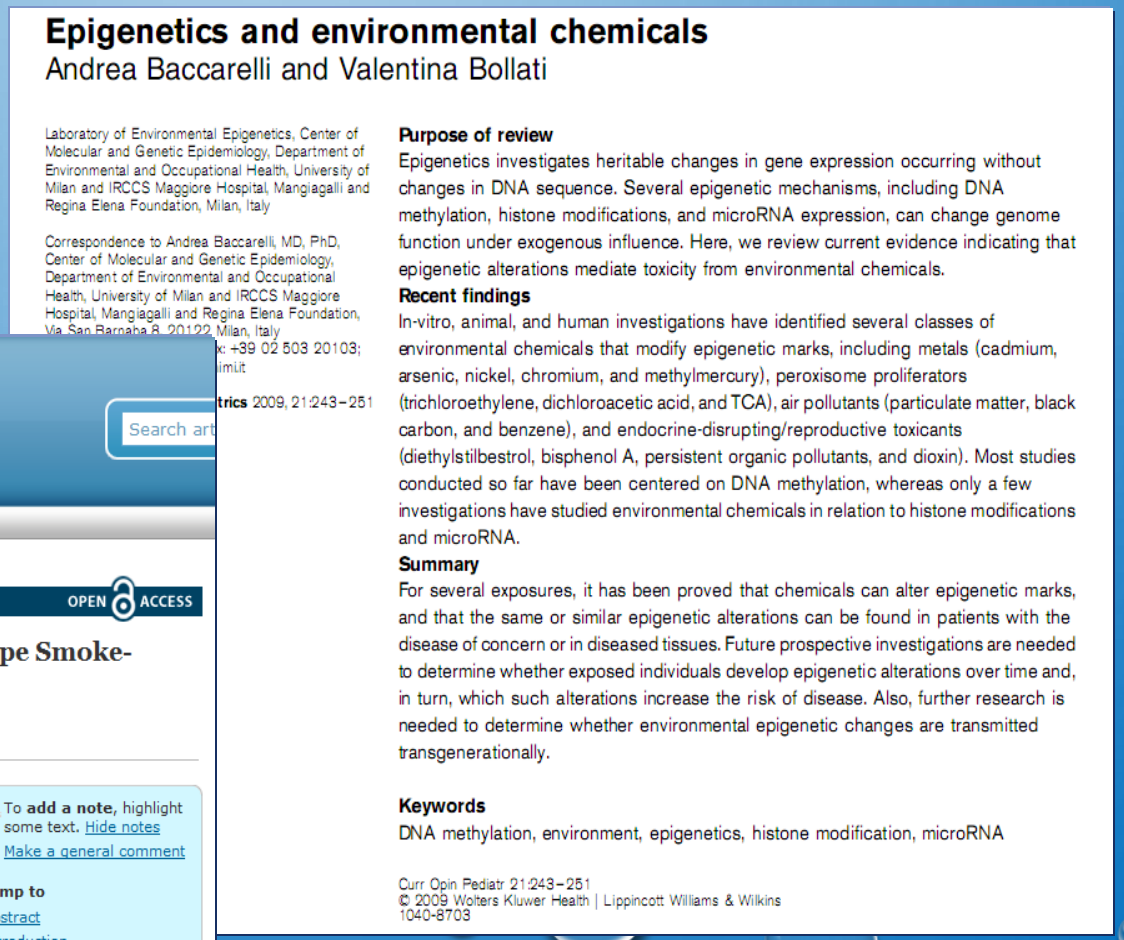
KEYWORDS

cell memory, epigenetics, induced heritable variations, Lamarckism, microevolution, macroevolution

ABSTRACT

This review describes new developments in the study of transgenerational epigenetic inheritance, a component of epigenetics. We start by examining the basic concepts of the field and the mechanisms that underlie epigenetic inheritance. We present a comprehensive review of transgenerational cellular epigenetic inheritance among different taxa in the form of a table, and discuss the data contained therein. The analysis of these data shows that epigenetic inheritance is ubiquitous and suggests lines of research that go beyond present approaches to the subject. We conclude by exploring some of the consequences of epigenetic inheritance for the study of evolution, while also pointing to the importance of recognizing and understanding epigenetic inheritance for practical and theoretical issues in biology.

EFFECTS FROM ENVIRONMENT, TOXINS: EPITOXICOLOGY, BISPHENOLS?



Epigenetics and environmental chemicals

Andrea Baccarelli and Valentina Bollati

Laboratory of Environmental Epigenetics, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, University of Milan and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy

Correspondence to Andrea Baccarelli, MD, PhD, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, University of Milan and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Via San Barnaba 8, 20122 Milan, Italy

trics 2009, 21:243–251

Purpose of review

Epigenetics investigates heritable changes in gene expression occurring without changes in DNA sequence. Several epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA expression, can change genome function under exogenous influence. Here, we review current evidence indicating that epigenetic alterations mediate toxicity from environmental chemicals.

Recent findings

In-vitro, animal, and human investigations have identified several classes of environmental chemicals that modify epigenetic marks, including metals (cadmium, arsenic, nickel, chromium, and methylmercury), peroxisome proliferators (trichloroethylene, dichloroacetic acid, and TCA), air pollutants (particulate matter, black carbon, and benzene), and endocrine-disrupting/reproductive toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants, and dioxin). Most studies conducted so far have been centered on DNA methylation, whereas only a few investigations have studied environmental chemicals in relation to histone modifications and microRNA.

Summary

For several exposures, it has been proved that chemicals can alter epigenetic marks, and that the same or similar epigenetic alterations can be found in patients with the disease of concern or in diseased tissues. Future prospective investigations are needed to determine whether exposed individuals develop epigenetic alterations over time and, in turn, which such alterations increase the risk of disease. Also, further research is needed to determine whether environmental epigenetic changes are transmitted transgenerationally.

Keywords

DNA methylation, environment, epigenetics, histone modification, microRNA

Curr Opin Pediatr 21:243–251

1040-8703

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RESEARCH ARTICLE OPEN ACCESS

Investigating the Epigenetic Effects of a Prototype Smoke-Derived Carcinogen in Human Cells

Article Metrics Related Content Comments: 0

Stella Tommasi[1], Sang-in Kim[1], Xueyan Zhong[1], Xiwei Wu[2], Gerd P. Pfeifer[1], Ahmad Besaratinia[1*]

1 Department of Cancer Biology, Beckman Research Institute of the City of Hope National Medical Center, Duarte, California, United States of America, 2 Division of Information Sciences, Beckman Research Institute of the City of Hope National Medical Center, Duarte, California, United States of America

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Make a general comment

Jump to

Abstract

Introduction

EFFECTS FROM THE SOCIAL ENVIRONMENT, STRESS

Review

Epigenetic programming of the stress response in male and female rats by prenatal restraint stress

Muriel Darnaudéry[a], *Stefania Maccari*[a,b,*,1]

[a]*Perinatal Stress Team, University of Lille 1, 59655 Villeneuve d'Ascq Cedex, France*
[b]*Department Human Physiology and Pharmacology, Sapienza University of Rome, Italy*

ARTICLE INFO

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Maternal behavior
Circadian rhythm
Depression
Anxiety
Animal model
Epigenetic
Alcohol

ABSTRACT

Exposure to hostile conditions results in a series of coordinated responses aimed at enhancing the probability of survival. The activation of the hypothalamo-pituitary-adrenocortical (HPA) axis plays a pivotal role in the stress response. While the short-term activation of the HPA axis allows adaptive responses to the challenge, in the long run this can be devastating for the organism. In particular, life events occurring during the perinatal period have strong long-term effects on the behavioral and neuroendocrine response to stressors. In male and female rats exposed to prenatal restraint stress (PRS), these effects include a long-lasting hyperactivation of the HPA response associated with an altered circadian rhythm of corticosterone secretion. Furthermore, male animals exhibit sleep disturbances. In males, these HPA dysfunctions have been reported in infant, young, adult and aged animals, thus suggesting a permanent effect of early stress. Interestingly, after exposure to an intense inescapable footshock, female PRS rats durably exhibit a blunted corticosterone secretion response to stress. In male PRS rats exposed to an alcohol challenge, the HPA axis is similarly hyporesponsive. Rats exposed to PRS also show behavioral disturbances. Both male and female PRS rats show high anxiety levels and depression-like behavior during adulthood, although some studies suggest that female PRS rats present low anxiety levels. With ageing, male and female PRS rats exhibit memory impairments in hippocampus-dependent tasks, while female PRS rats improve their memory performance during adulthood. The gender effect on behavior seems to be related to a reduction in hippocampal plasticity in male PRS rats, and an increase in female PRS rats. Despite the permanent imprinting induced by early stress, the dysfunctions observed after PRS can be reversed by environmental or pharmacological strategies such as environmental enrichment or antidepressive and neurotrophic treatments. Mechanisms underlying the effects of PRS on the offspring remain largely unknown. However, previous studies have demonstrated that maternal glucocorticoids during pregnancy play an important role in the HPA disturbances reported

EPIGENETIC EFFECTS FROM SOCIAL ENVIRONMENT: CARE, STRESS

Available online at www.sciencedirect.com
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Frontiers in Neuroendocrinology
Frontiers in Neuroendocrinology 29 (2008) 386–397
www.elsevier.com/locate/yfrne

Review

Epigenetic mechanisms and the transgenerational effects of maternal care

Frances A. Champagne *

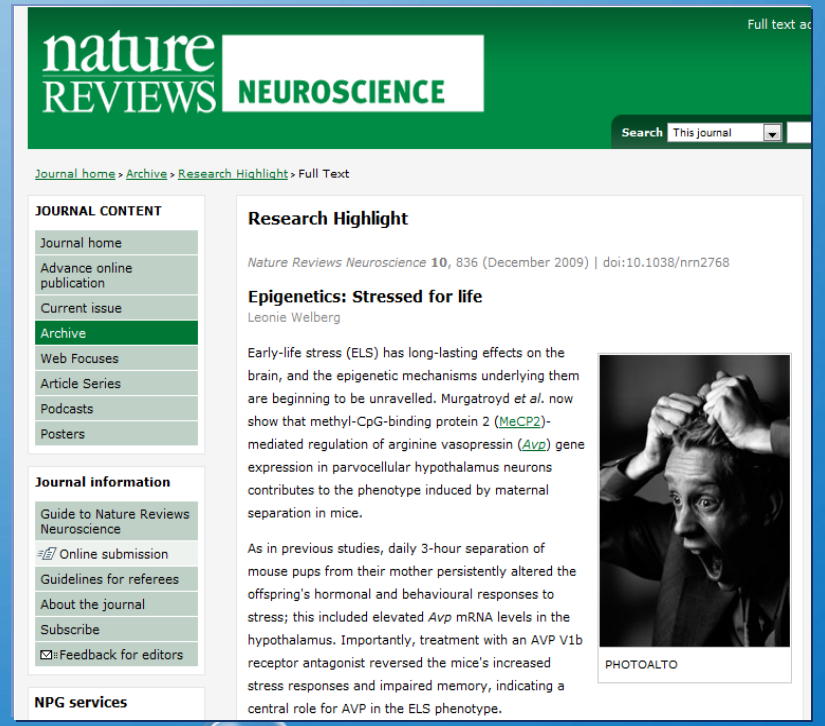
Department of Psychology, Columbia University, Room 406, Schermerhorn Hall, 1190 Amsterdam Avenue, New York, NY 10017, USA

Available online 28 March 2008

Abstract

The transmission of traits across generations has typically been attributed to the inheritance by offspring of genomic information from parental generations. However, recent evidence suggests that epigenetic mechanisms are capable of mediating this type of transmission. In the case of maternal care, there is evidence for the behavioral transmission of postpartum behavior from mothers to female offspring. The neuroendocrine and molecular mediators of this transmission have been explored in rats and implicate estrogen–oxytocin interactions and the differential methylation of hypothalamic estrogen receptors. These maternal effects can influence multiple aspects of neurobiology and behavior of offspring and this particular mode of inheritance is dynamic in response to environmental variation. In this review, evidence for the generational transmission of maternal care and the mechanisms underlying this transmission will be discussed as will the implications of this inheritance system for offspring development and for the transmission of environmental information from parents to offspring.

Keywords: Maternal; Epigenetic; DNA methylation; Estrogen receptor α; Oxytocin; Environment; Cross-fostering



EPIGENETIC EFFECTS FROM THE SOCIAL ENVIRONMENT

Frances A. Champagne
Department of Psychology
Columbia University
Room 406 Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027
E-mail: fac2105@columbia.edu

Epigenetic Influence of Social Experiences Across the Lifespan

ABSTRACT: *The critical role of social interactions in driving phenotypic variation has long been inferred from the association between early social deprivation and adverse neurodevelopmental outcomes. Recent evidence has implicated molecular pathways involved in the regulation of gene expression as one possible route through which these long-term outcomes are achieved. These epigenetic effects, though not exclusive to social experiences, may be a mechanism through which the quality of the social environment becomes embedded at a biological level. Moreover, there is increasing evidence for the transgenerational impact of these early experiences mediated through changes in social and reproductive behavior exhibited in adulthood. In this review, recent studies which highlight the epigenetic effects of parent–offspring, peer and adult social interactions both with and across generations will be discussed and the implications of this research for understanding the developmental origins of individual differences in brain and behavior will be explored.* © *2010 Wiley Periodicals, Inc.* Dev Psychobiol

Keywords: *epigenetic; maternal; social; transgenerational; development*

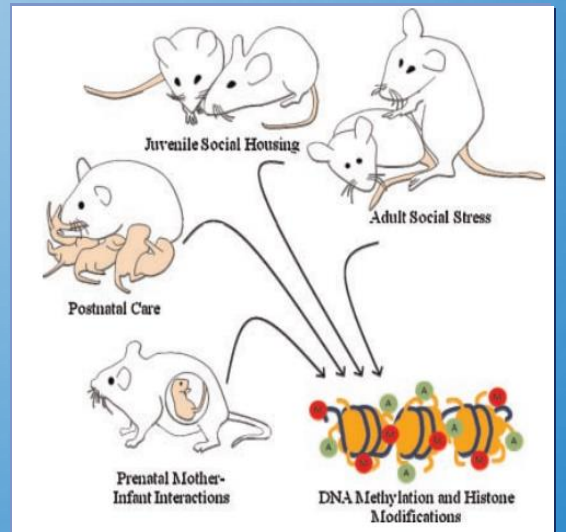
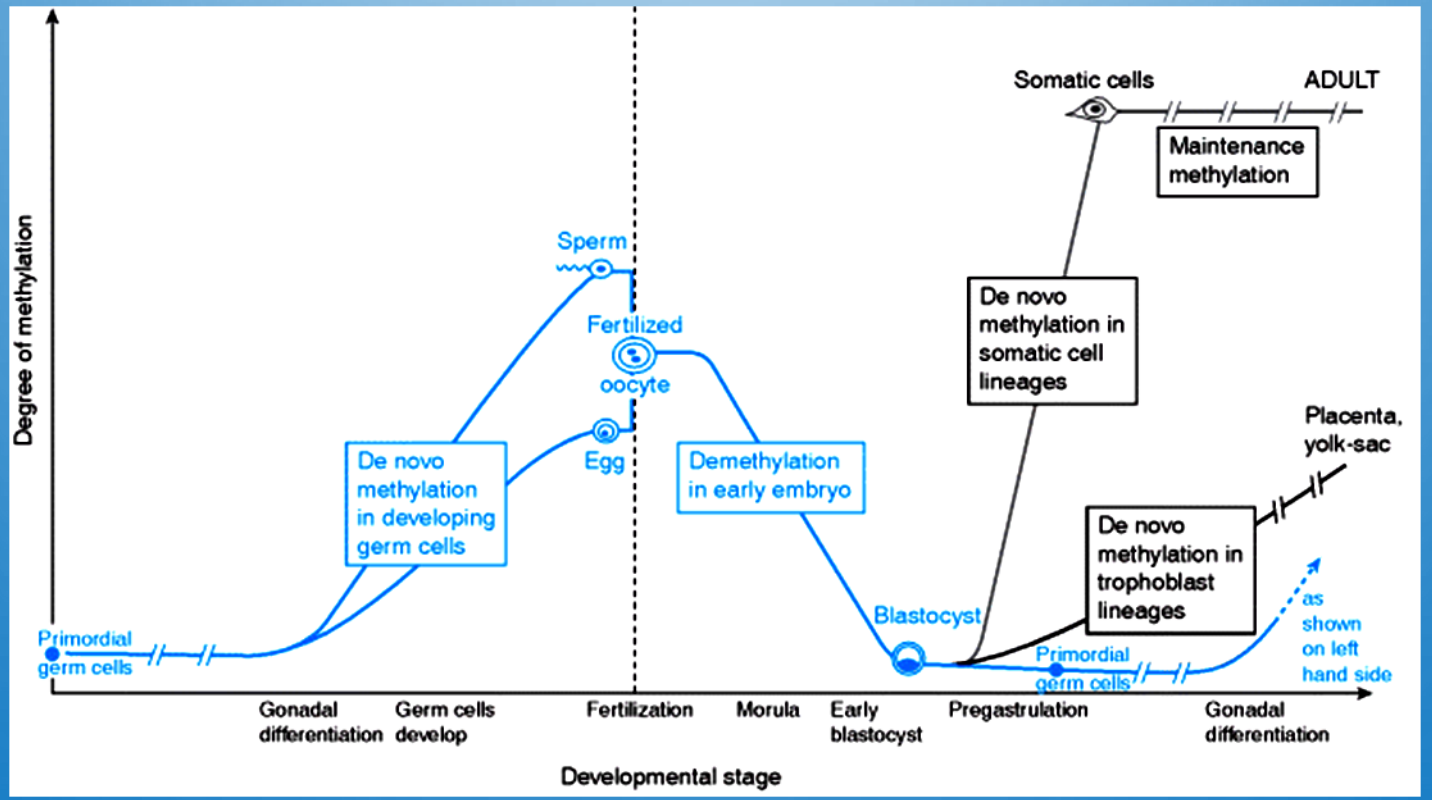
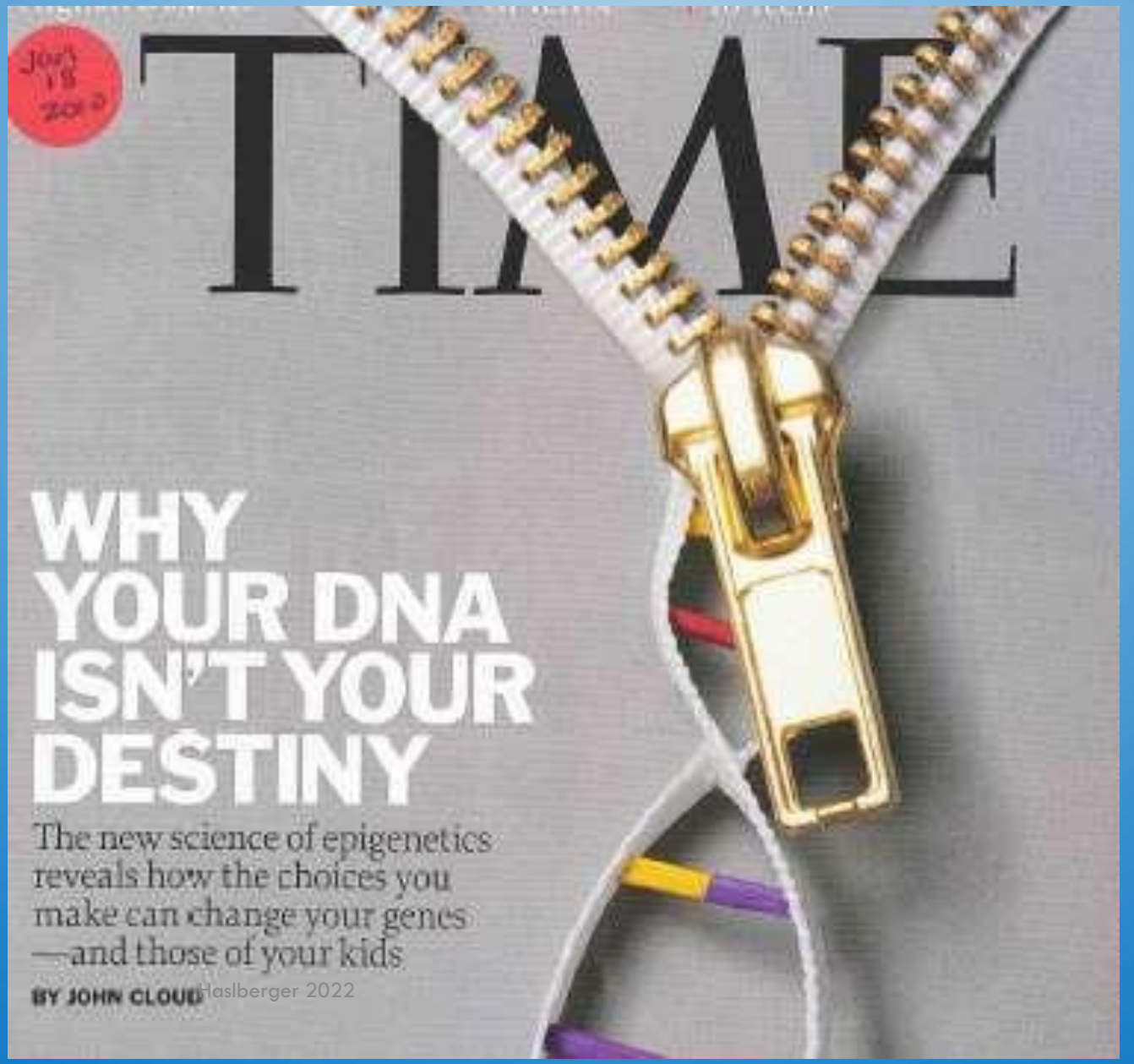


FIGURE 1 Epigenetic consequences of social experiences across the lifespan. Emerging evidence suggests that prenatal environmental exposures, postnatal mother–infant interactions, juvenile social rearing, and adult social stress can alter epigenetic processes such as DNA methylation (red circles) and histone acetylation (green circles)/methylation with long-term consequences for gene expression, physiology, and behavior.

Rev., Dev. Psychobiol. 2010

LIFE TIME CHANGES IN DNA METHYLATION EPIGENETIC TISSUE SPECIFIC, TRANSGENERATIONAL BUT HOW ?

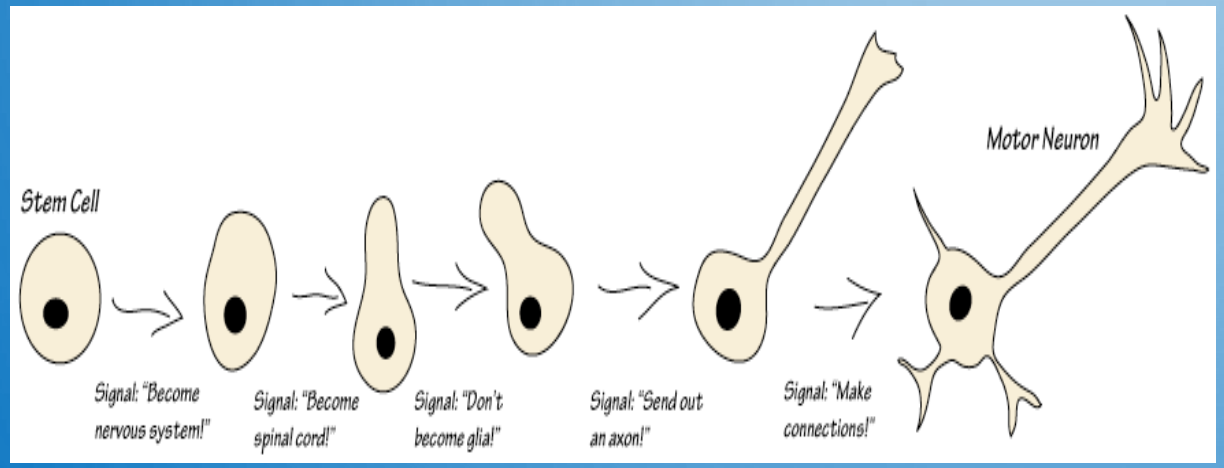


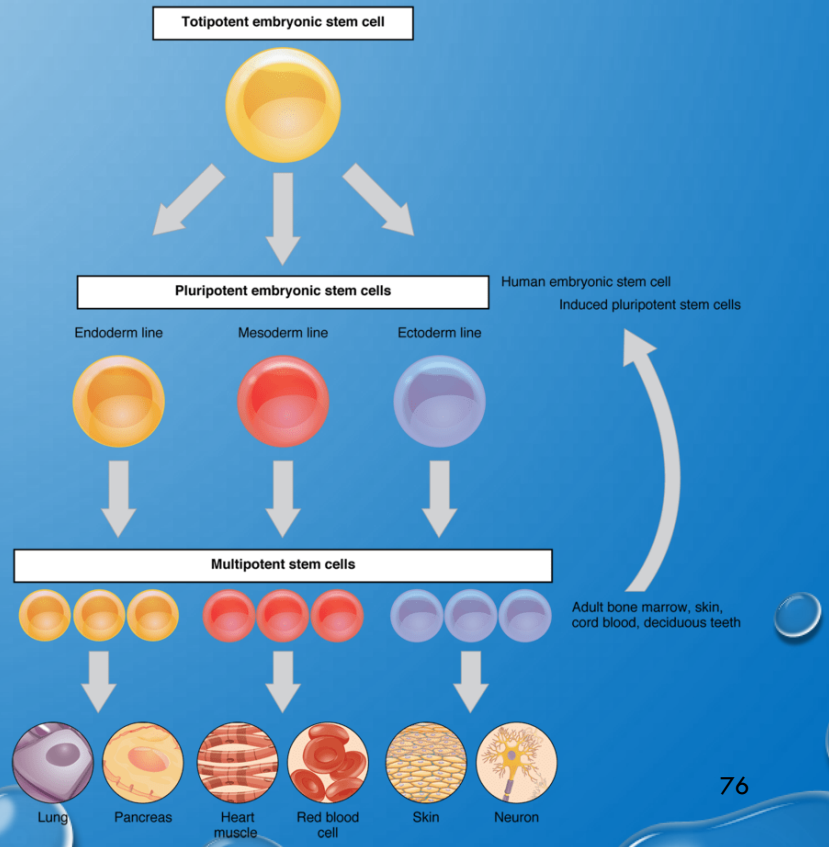

TIME
WHY YOUR DNA ISN'T YOUR DESTINY
The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids
BY JOHN CLOUD

The term epigenetics refers to heritable changes in gene expression (active versus inactive genes) that does not involve changes to the underlying DNA sequence; a change in phenotype without a change in genotype.

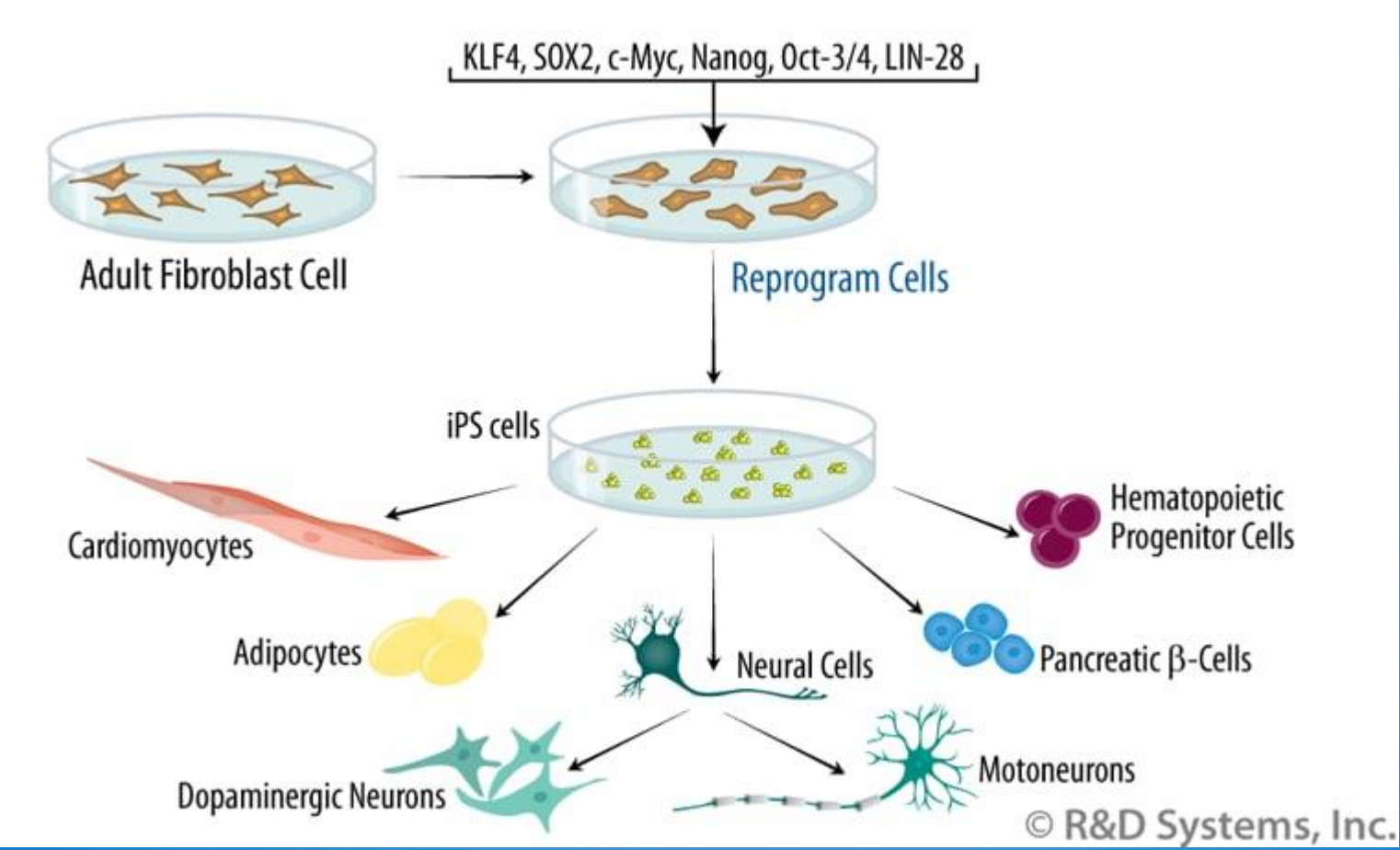
- The term epigenetics, which was coined by Conrad H. Waddington in 1942, was derived from the Greek word “epigenesis” which originally described the influence of genetic processes on development. Conrad H. Waddington and Ernst Hadorn, started the study of epigenetics.

EPIGENETICS IN DIFFERENTIATION



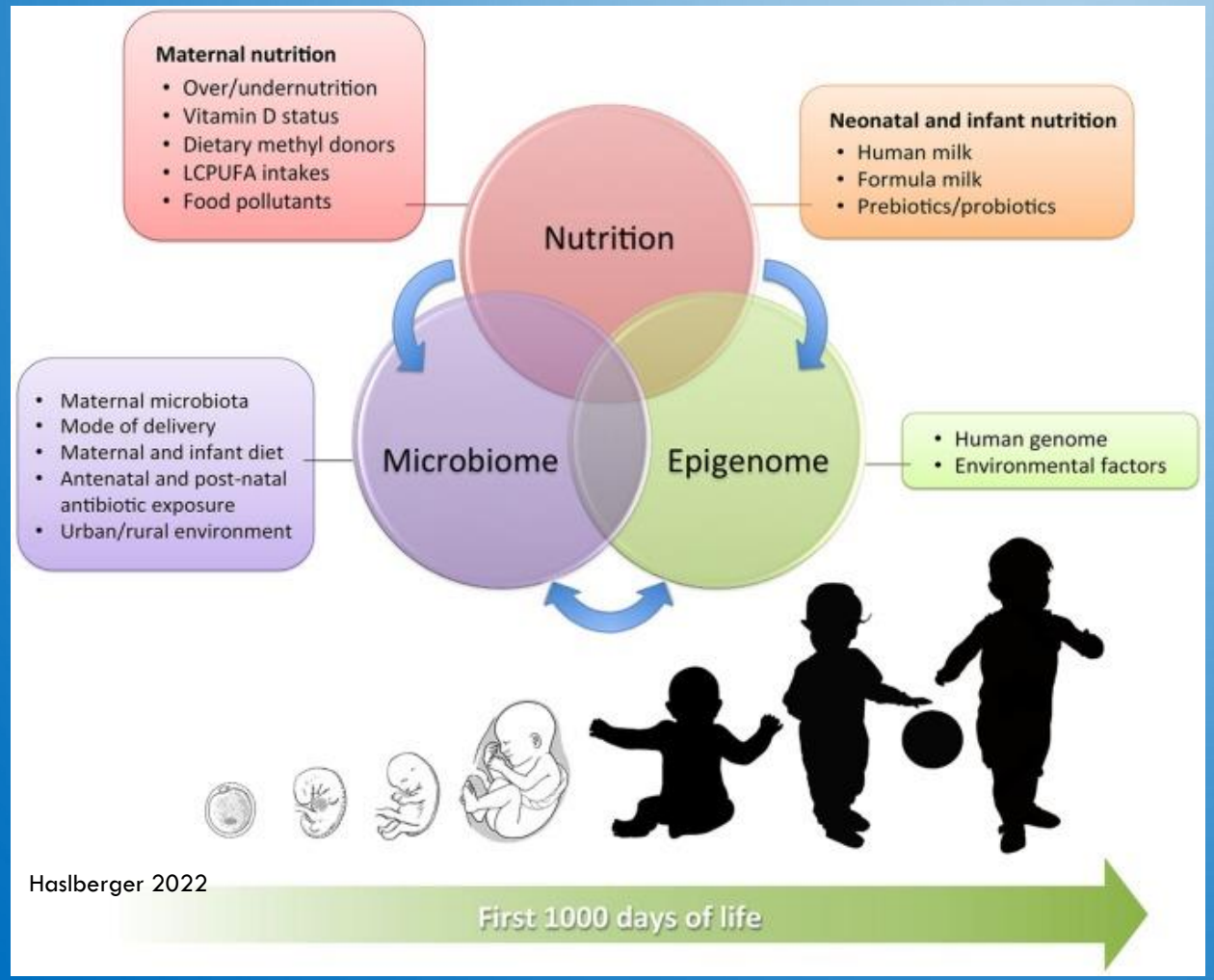


EPIGENETICS IN RE-DIFFERENTIATION



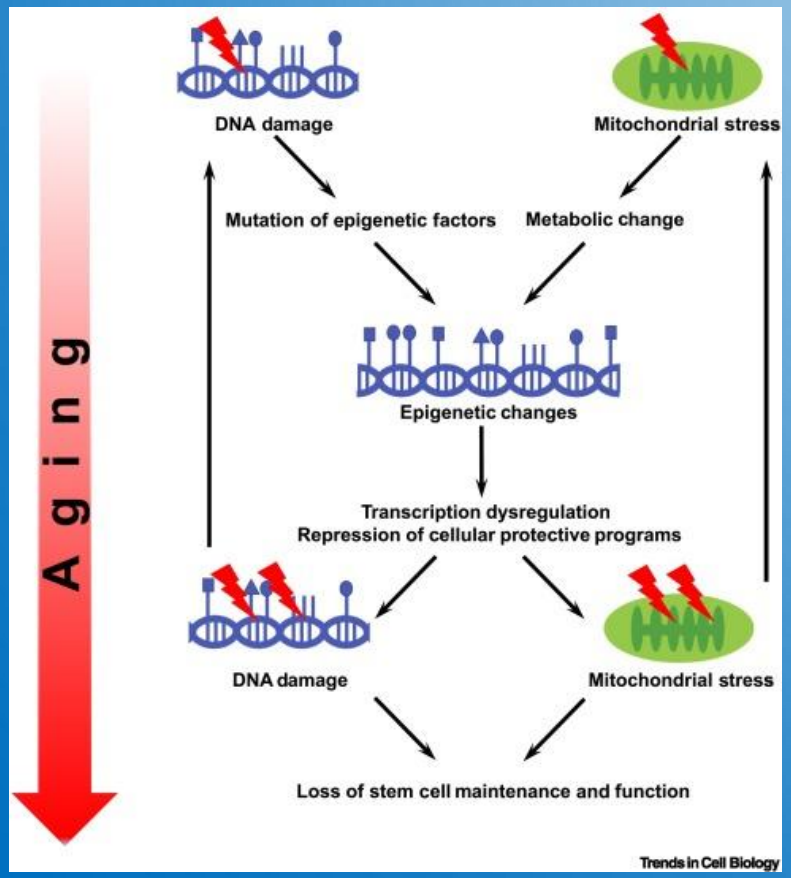
. For most cell types, four factors (c-Myc, Oct-3/4, SOX2, and KLF4) are used

THE FIRST 1000 DAYS OF LIFE



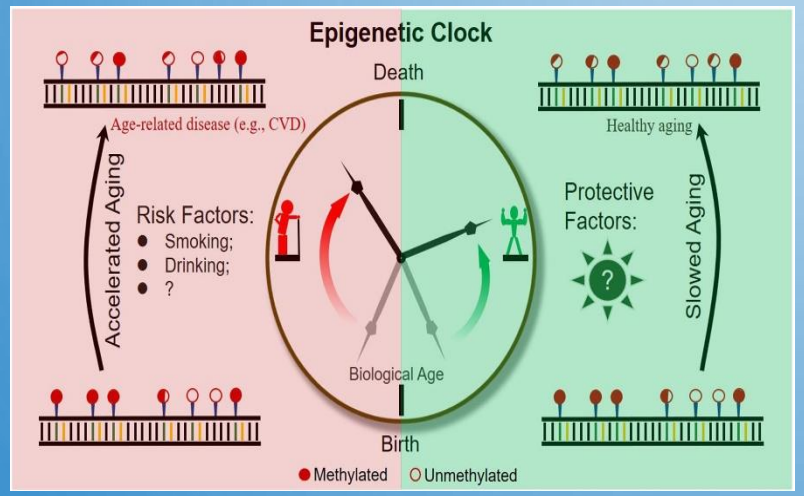
- Epigenetic tags act as a kind of **cellular memory**. A cell's epigenetic profile -- a collection of tags that tell genes whether to be on or off -- is the sum of the signals it has received during its lifetime.
- First 100 days of life imprinting

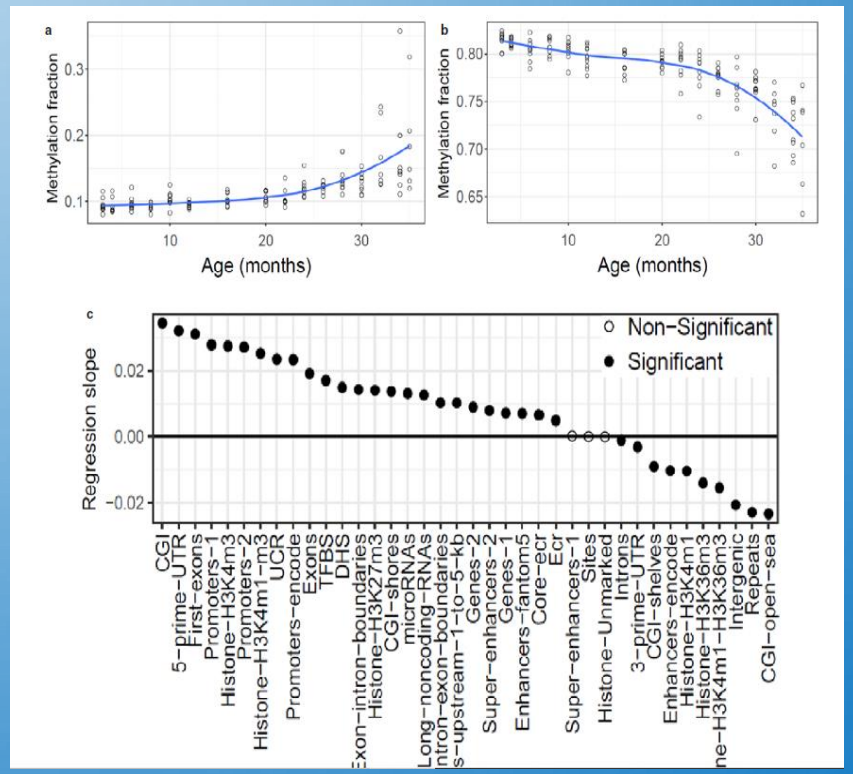
EVEN INTO OLD AGE, EPIGENETICS AND STEM CELLS



DURING THESE PROCESSES, JUST LIKE DURING EMBRYONIC DEVELOPMENT, THE CELL'S EXPERIENCES ARETRANSFERRED TO THE EPIGENOME, WHERE THEY SHUT DOWN AND ACTIVATE SPECIFIC SETS OF GENES.

Epigenetic clock





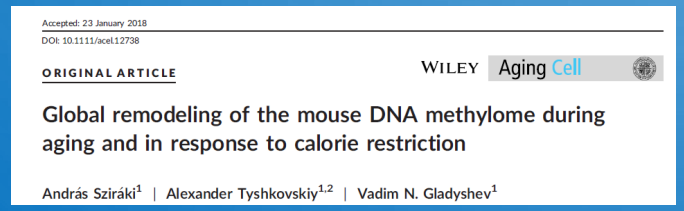

International Journal of *Molecular Sciences*

MDPI

Review

The Impact of Caloric Restriction on the Epigenetic Signatures of Aging

Noémie Gensous [1], Claudio Franceschi [2,3], Aurelia Santoro [1], Maddalena Milazzo [1], Paolo Garagnani [1,4,5,6,7,*] and Maria Giulia Bacalini [2]


Accepted: 23 January 2018

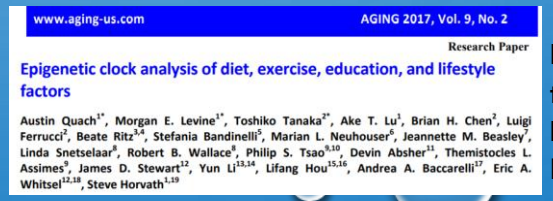
DOI: 10.1111/acel.12738

ORIGINAL ARTICLE

WILEY Aging Cell

Global remodeling of the mouse DNA methylome during aging and in response to calorie restriction

András Sziráki[1] | Alexander Tyshkovskiy[1,2] | Vadim N. Gladyshev[1]


www.aging-us.com AGING 2017, Vol. 9, No. 2

Research Paper

Epigenetic clock analysis of diet, exercise, education, and lifestyle factors

Austin Quach[1*], Morgan E. Levine[1*], Toshiko Tanaka[2*], Ake T. Lu[1], Brian H. Chen[2], Luigi Ferrucci[2], Beate Ritz[3,4], Stefania Bandinelli[5], Marian L. Neuhouser[6], Jeannette M. Beasley[7], Linda Snetselaar[8], Robert B. Wallace[8], Philip S. Tsao[9,10], Devin Absher[11], Themistocles L. Assimes[9], James D. Stewart[12], Yun Li[13,14], Lifang Hou[15,16], Andrea A. Baccarelli[17], Eric A. Whitsel[12,18], Steve Horvath[1,19]

Intrinsic age: horvath multiple tissues.
Extrinsic Hannum, blood cell

EPIGENETIC DIEASES MENTAL RETARDATION DISORDERS

- Epigenetic changes are also linked to several disorders that result in intellectual disabilities such as ATR-X, Fragile X, Rett, Beckwith-Weidman (BWS), Prader-Willi and Angelman syndromes. For example, the imprint disorders Prader-Willi syndrome and Angelman syndrome, display an abnormal phenotype as a result of the absence of the paternal or maternal copy of a gene, respectively.

NEUROPSYCHIATRIC DISORDERS

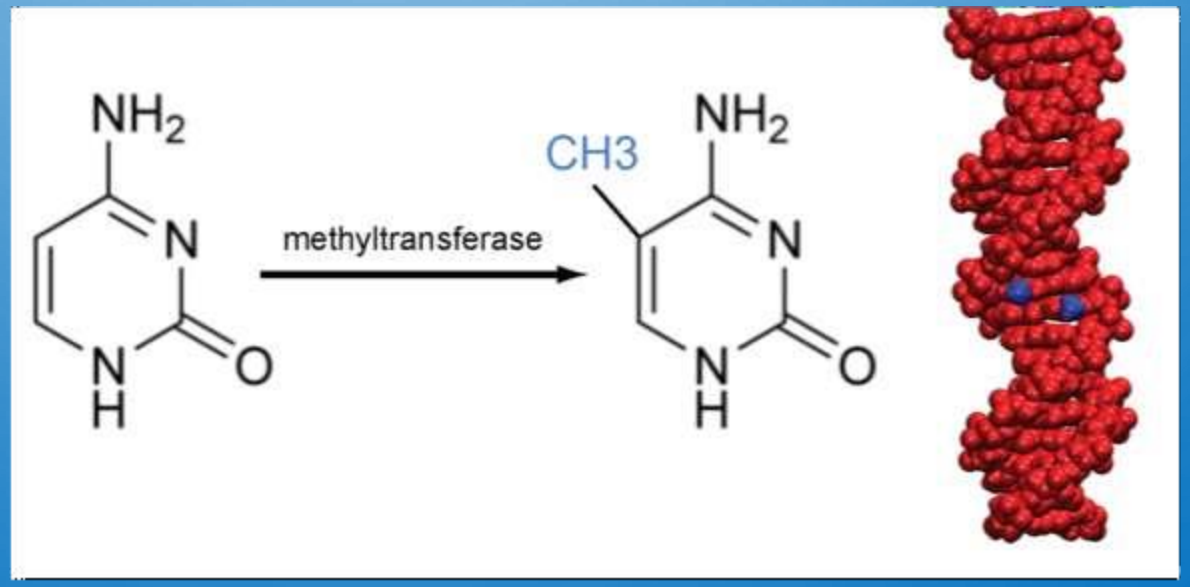
- Epigenetic errors also play a role in the causation of complex adult psychiatric, autistic, and neurodegenerative disorders. Several reports have associated schizophrenia and mood disorders with DNA rearrangements that include the DNMT genes.

NEUROPSYCHIATRIC DISORDERS

- DNMT1 is selectively overexpressed in gamma-aminobutyric acid (GABA)-ergic interneurons of schizophrenic brains,
  whereas hypermethylation has been shown to repress expression of Reelin (a protein required for normal neurotransmission, memory formation and synaptic plasticity) in brain tissue from patients with schizophrenia and patients with bipolar illness and psychosis.

DNA METHYLATION

- DNA methylation is an epigenetic mechanism used by cells to control gene expression. A number of mechanisms exist to control gene expression in eukaryotes, but DNA methylation is a commonly used epigenetic signaling tool that can fix genes in the “off” position.



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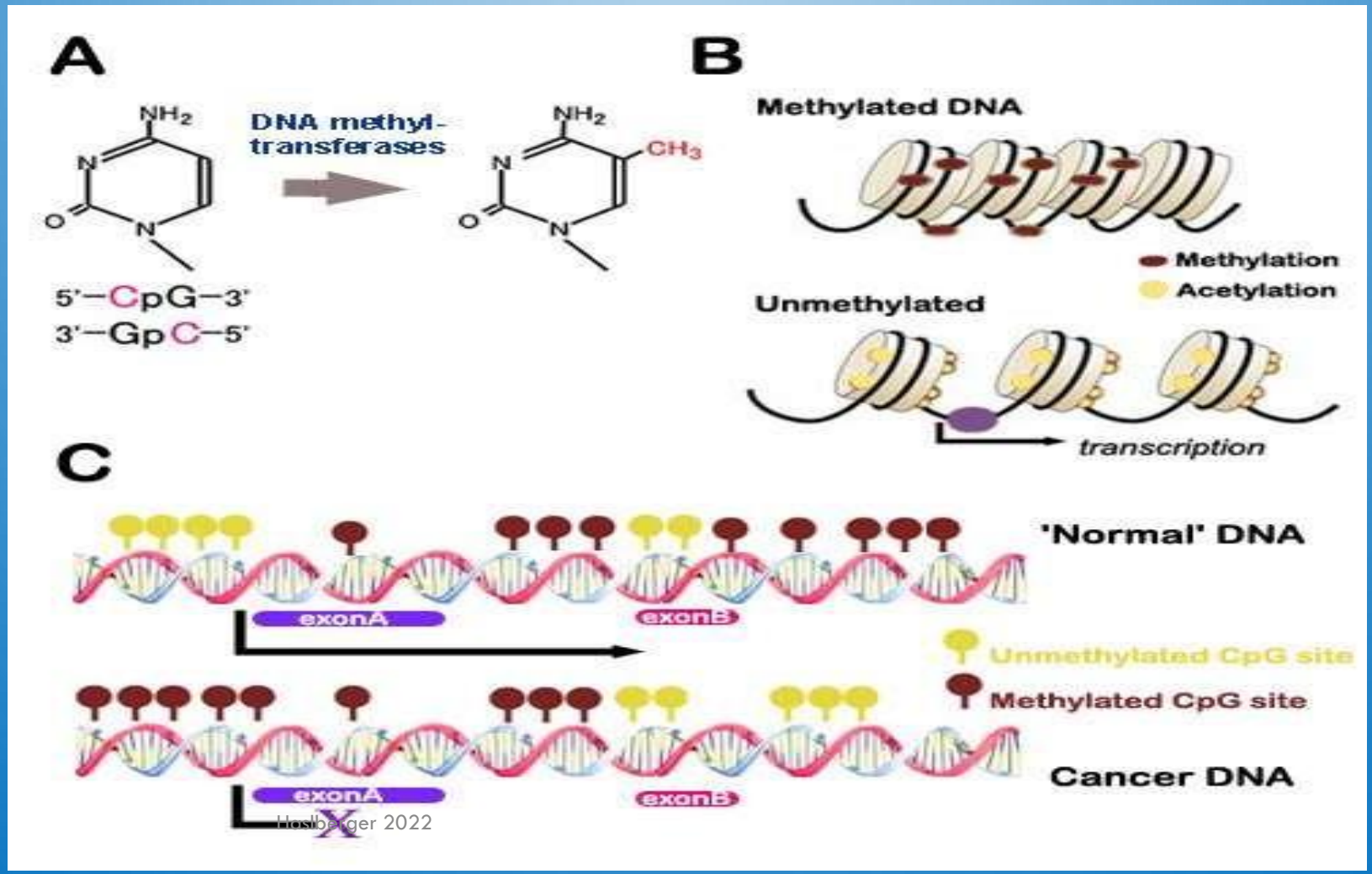
DNA METHYLATION



NATURAL ROLES OF DNA METHYLATION IN MAMMALIAN SYSTEM

- Imprinting
- X chromosome inactivation
- Heterochromatin maintenance
- Developmental controls
- Tissue specific expression controls

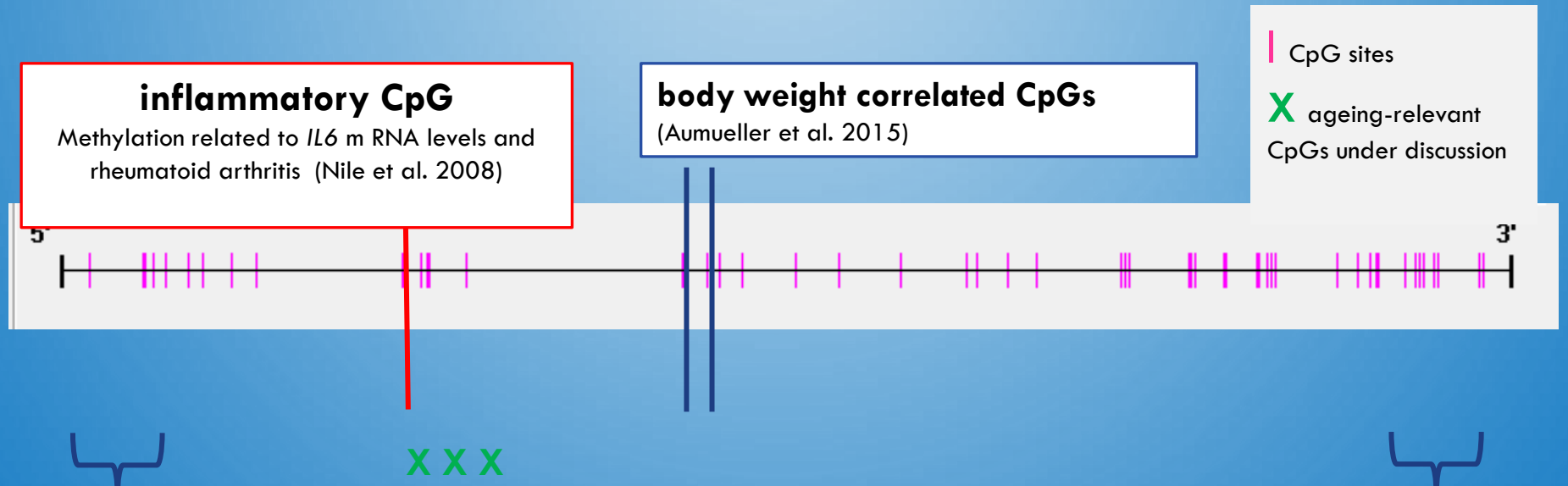
DNA METHYLATION AND OTHER HUMAN DISEASES

- **-- Imprinting Disorder:**
  - Beckwith-Wiedemann syndrom (BWS)
  - Prader-Willi syndrome (PWS)
  - Transient neonatal diabetes mellitus (TNDM)

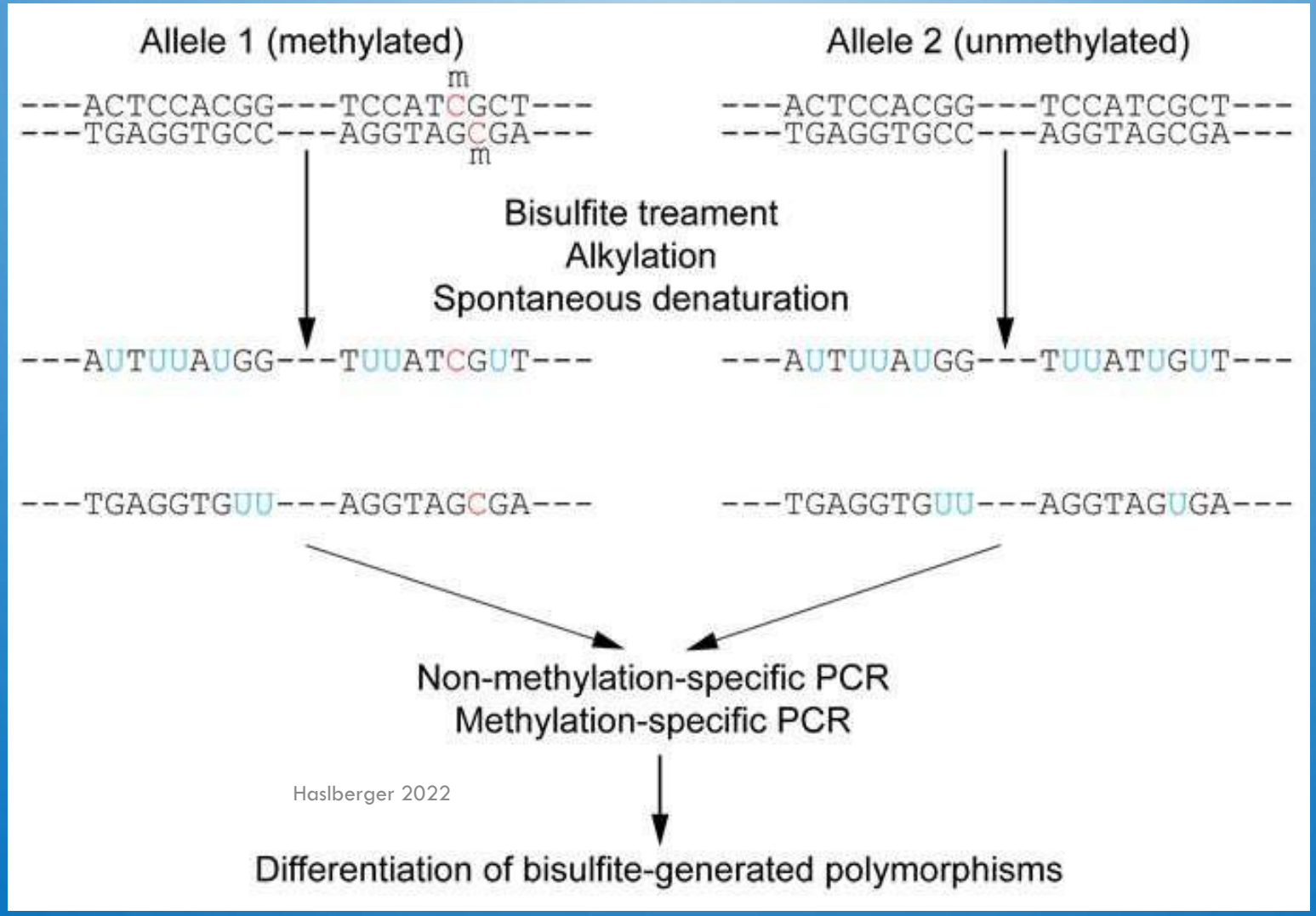
- **-- Repeat-instability diseases**
  - Fragile X syndrome (FRAXA)
  - Facioscapulohumeral muscular dystroph

- **-- Defects of the methylation machinery**
  - Systemic lupus erythemtosus (SLE)
  - Immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome

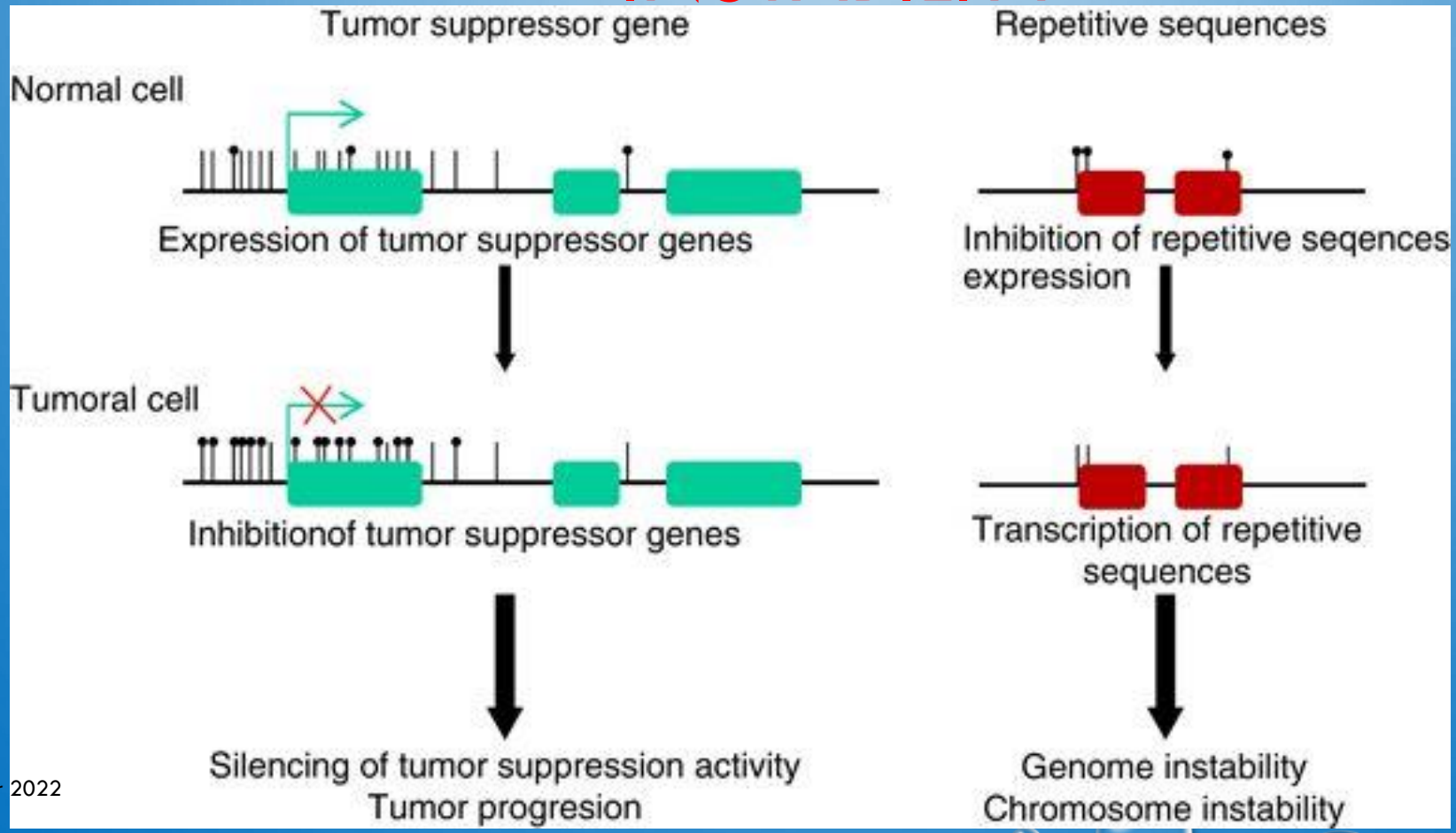
DIFFERENT EPIGENETIC CPG SITES IN GENES, E.G. IN IL-6 PROMOTOR



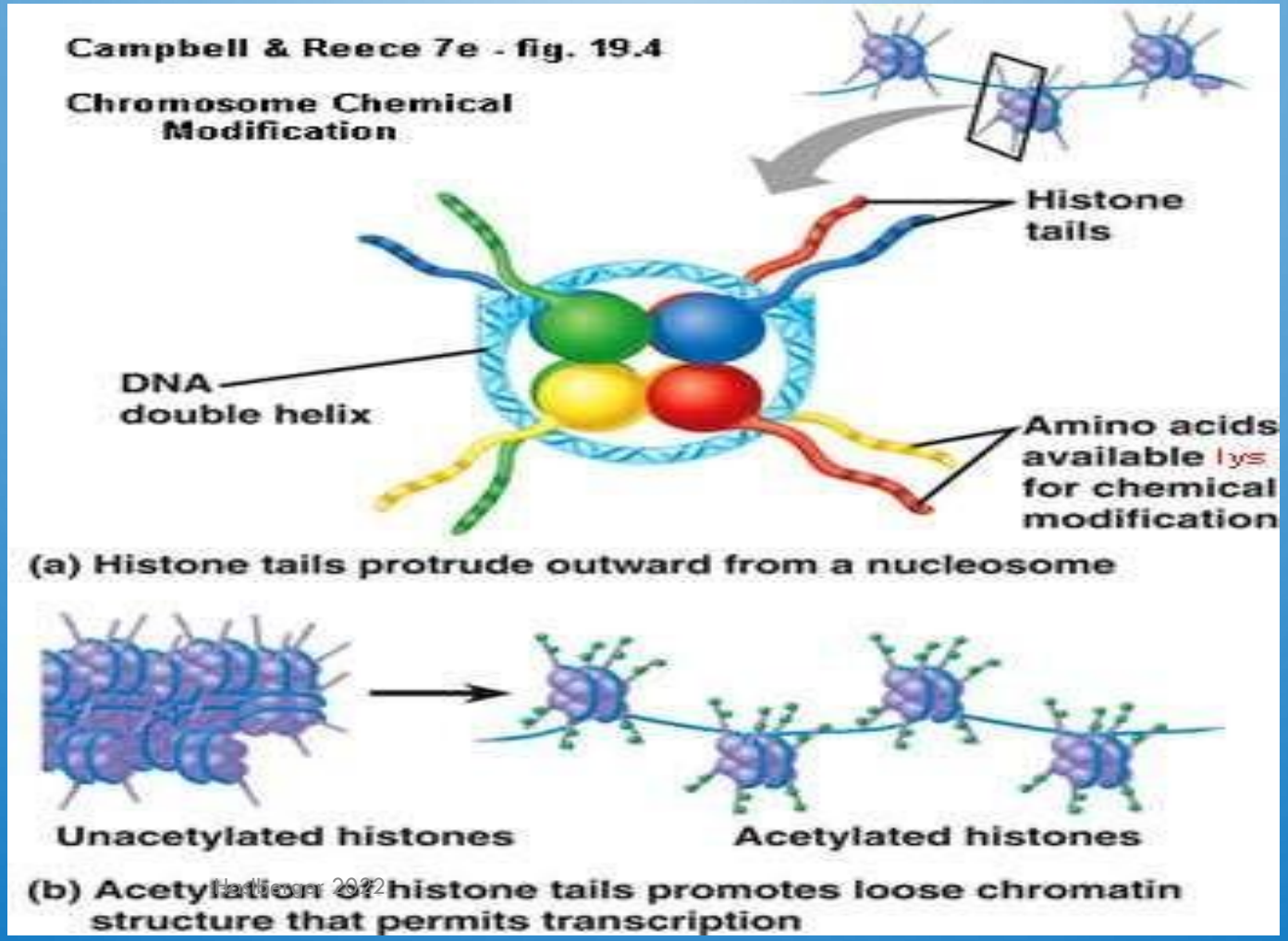
CPG METHYLATION: METHOD BISULFITE SEQUENCING



METHYLATION, TUMOR SUPPRESSOR, DNA INSTABILITY



HISTONE MODIFICATIONS



HISTONE MODIFICATION THE HISTONE CODE

- Acetylation
- Methylation
- Phosphorylation
- Ubiquitylation
- sumoylation

- Enzymes catalyzing
  - Histone acetyltransferase
  - Histone deacetylase
  - Histone methyltransferase
  - Histone kinase

Table 1 | Chromatin modifications

Mark*	Transcriptionally relevant sites†	Transcriptional role‡
DNA methylation		
Methylated cytosine (meC)	CpG islands	Repression
Histone PTMs		
Acetylated lysine (Kac)	H3 (9, 14, 18, 56), H4 (5, 8, 13, 16), H2A, H2B	Activation
Phosphorylated serine/threonine (S/Tph)	H3 (3, 10, 28), H2A, H2B	Activation
Methylated arginine (Rme)	H3 (17, 23), H4 (3)	Activation
Methylated lysine (Kme)	H3 (4, 36, 79) H3 (9, 27), H4 (20)	Activation Repression
Ubiquitylated lysine (Kub)	H2B (123§/120¶) H2A (119¶)	Activation Repression
Sumoylated lysine (Ksu)	H2B (6/7), H2A (126)	Repression
Isomerized proline (Pisom)	H3 (30–38)	Activation/repression

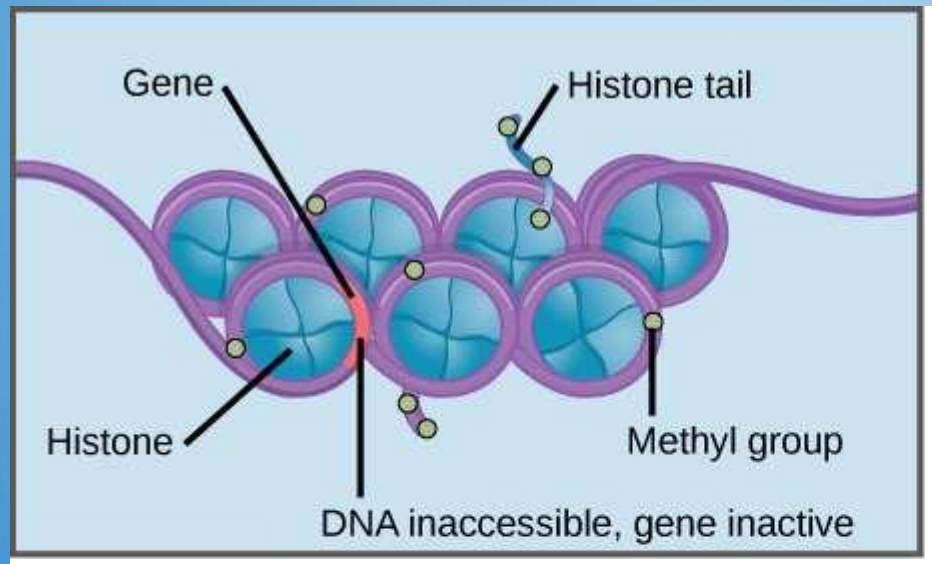
HISTONE MODIFICATION

- Histones are subject to a wide variety of posttranslational modifications including but not limited to, lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation (Vasquero 2003). These modifications occur primarily within the histone amino-terminal tails protruding from the surface of the nucleosome as well as on the globular core region (Cosgrove 2004).

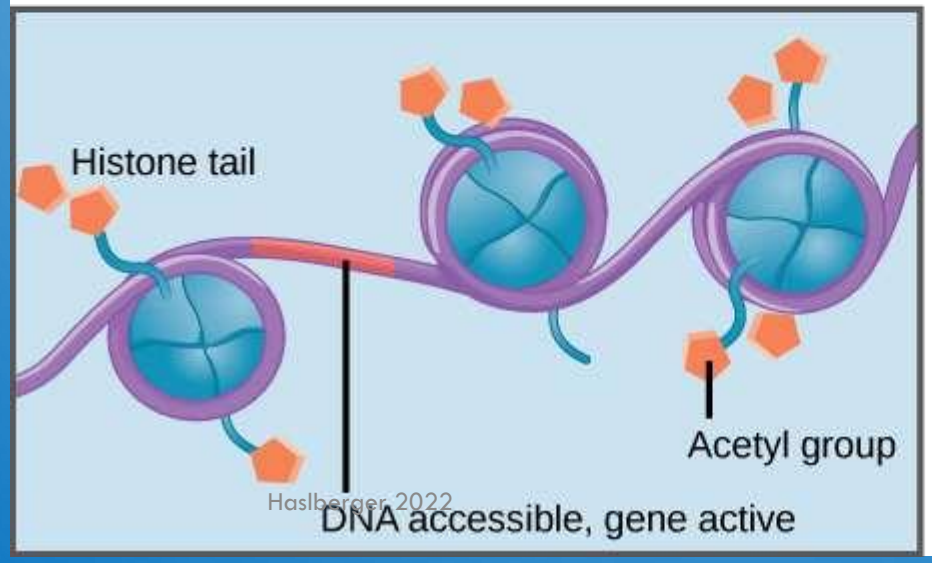
HISTONE MODIFICATION

- Histone modifications are proposed to affect chromosome function through at least two distinct mechanisms. The first mechanism suggests modifications may alter the electrostatic charge of the histone resulting in a structural change in histones or their binding to DNA.

- The second mechanism proposes that these modifications are binding sites for protein recognition modules, such as the bromodomains or chromodomains, that recognize acetylated lysines or methylated lysine, respectively.

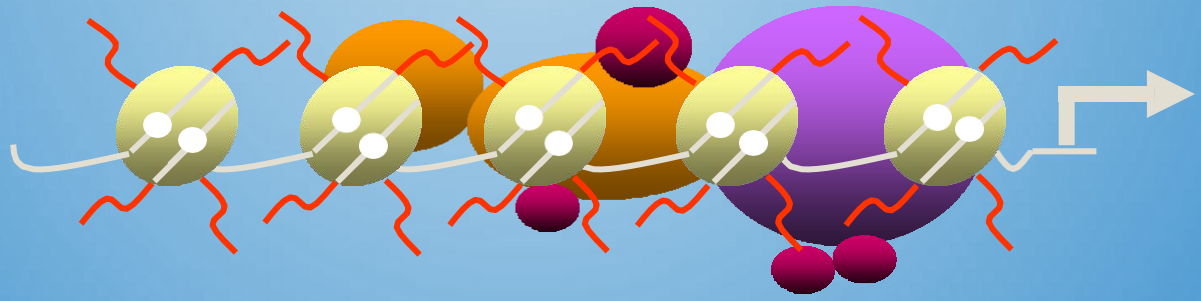


Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

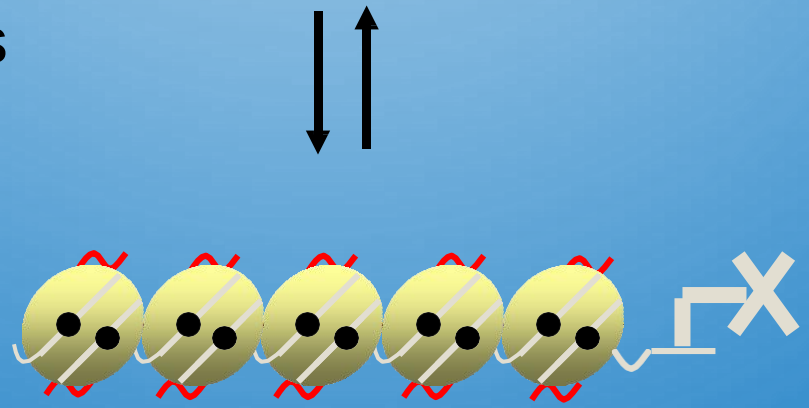


Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

EFFECT OF HISTONE MODIFICATION



Methylation turns off genes. Acetylation turn genes on.



Methylated DNA

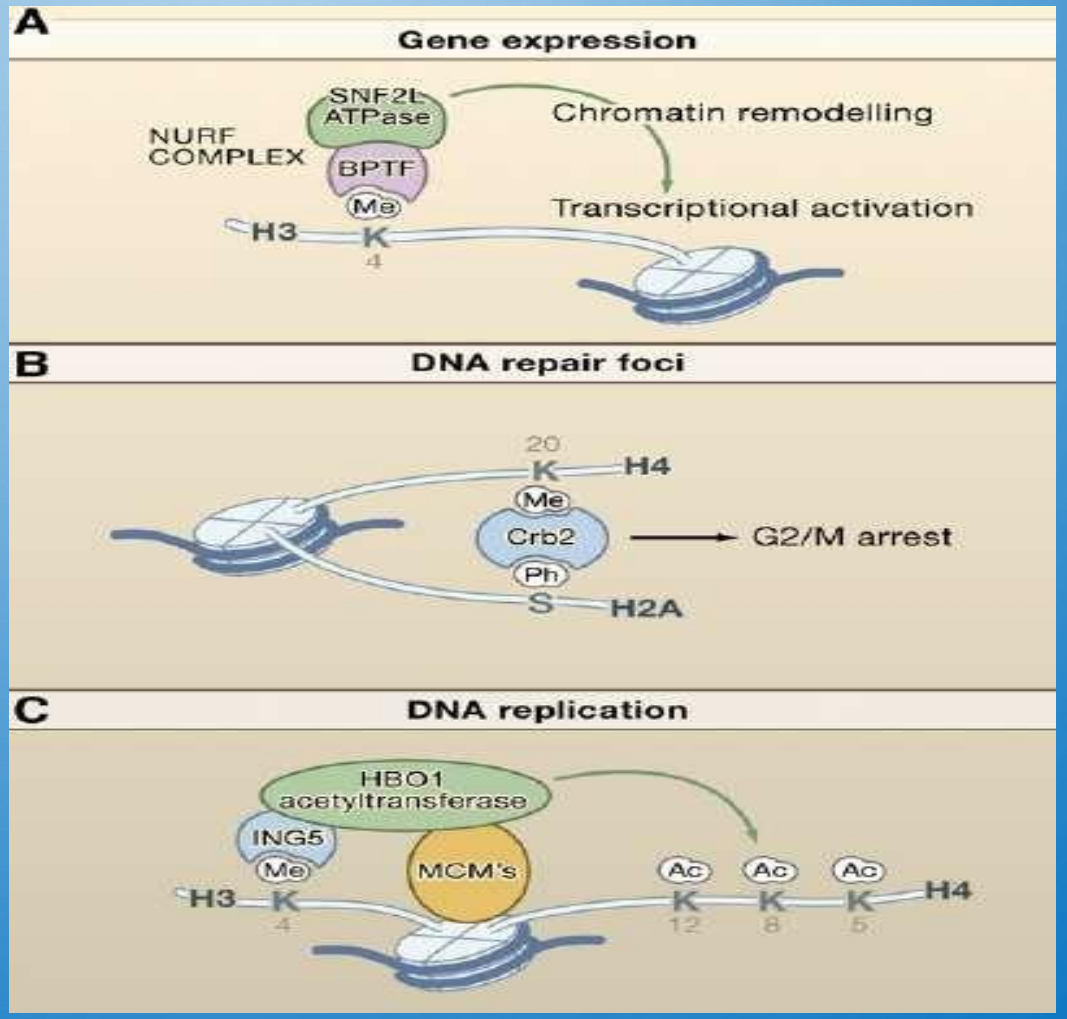
Histone

HISTONE MODIFICATION STATUS CORRELATES WITH TRANSCRIPTIONAL ACTIVITY

- Gene activation correlated with **H3-K9 acetylation**
- Gene silencing associated with **H3-K9 methylation**

ROLE OF HISTONE MODIFICATION

- DNA transcription
- DNA repair
- DNA replication

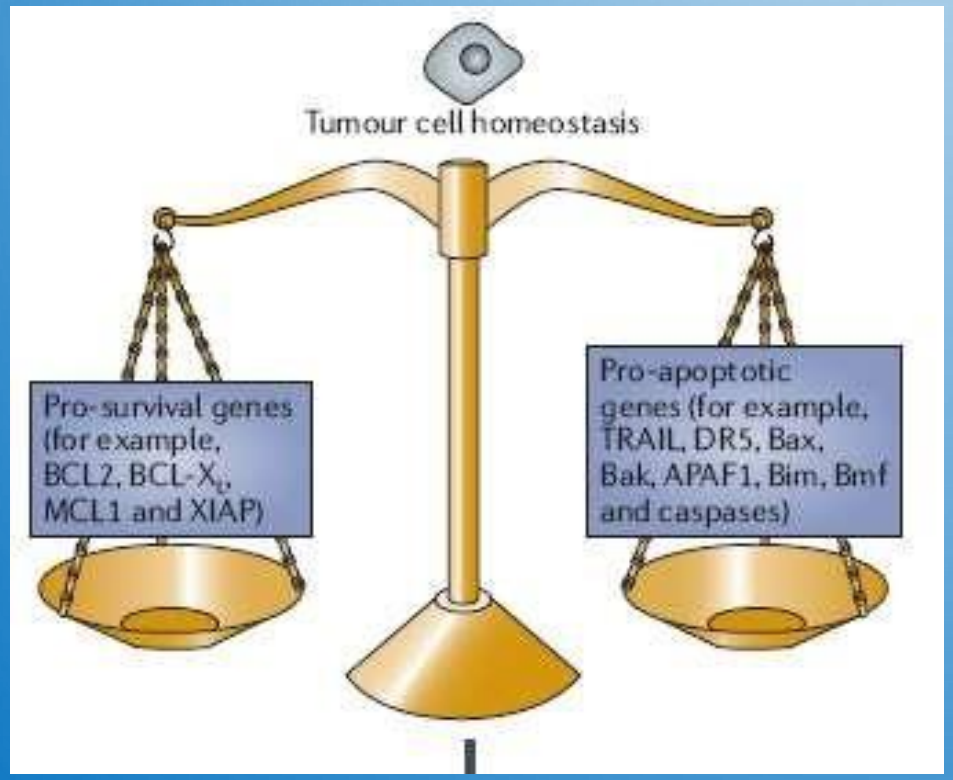


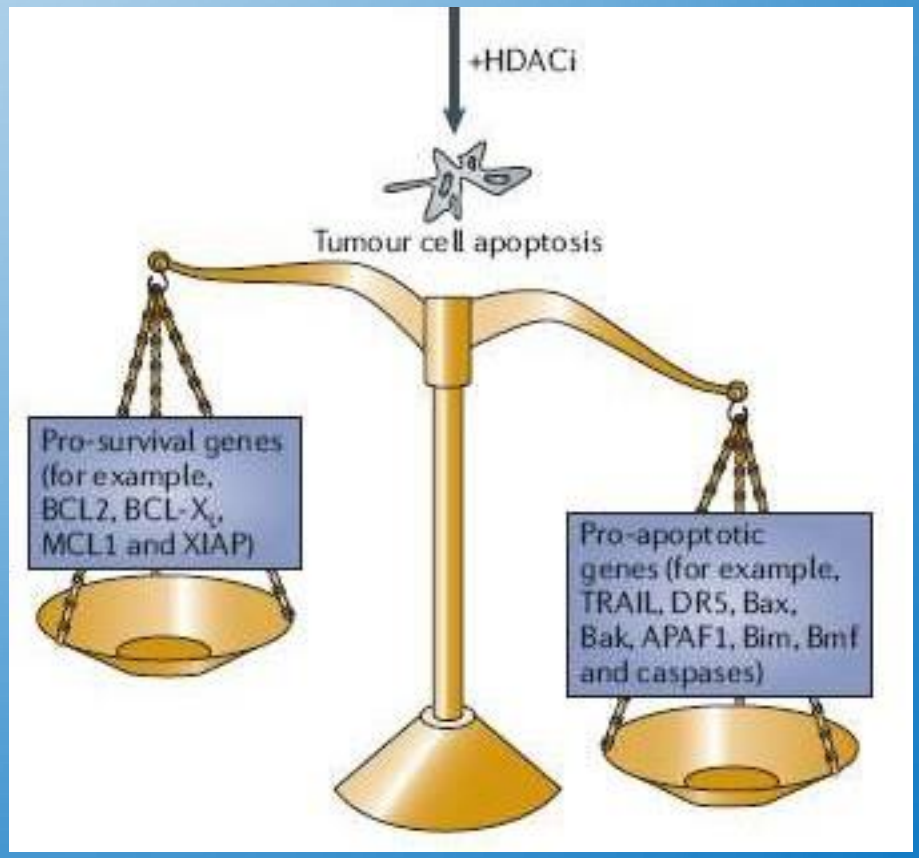
HISTONE MODIFICATIONS AND HUMAN DISEASES

Coffin-Lowry syndrome is a rare genetic disorder characterized by mental retardation and abnormalities of the head and facial and other areas. It is caused by mutations in the RSK2 gene (histone phosphorylation) and is inherited as an X-linked dominant genetic trait. Males are usually more severely affected than females.

Rubinstein-Taybi syndrome is characterized by short stature, moderate to severe intellectual disability, distinctive facial features, and broad thumbs and first toes. It is caused by mutations in CREB-binding protein (histone acetylation)

HISTONE MODIFICATION INTERFERS WITH APOPTOSIS

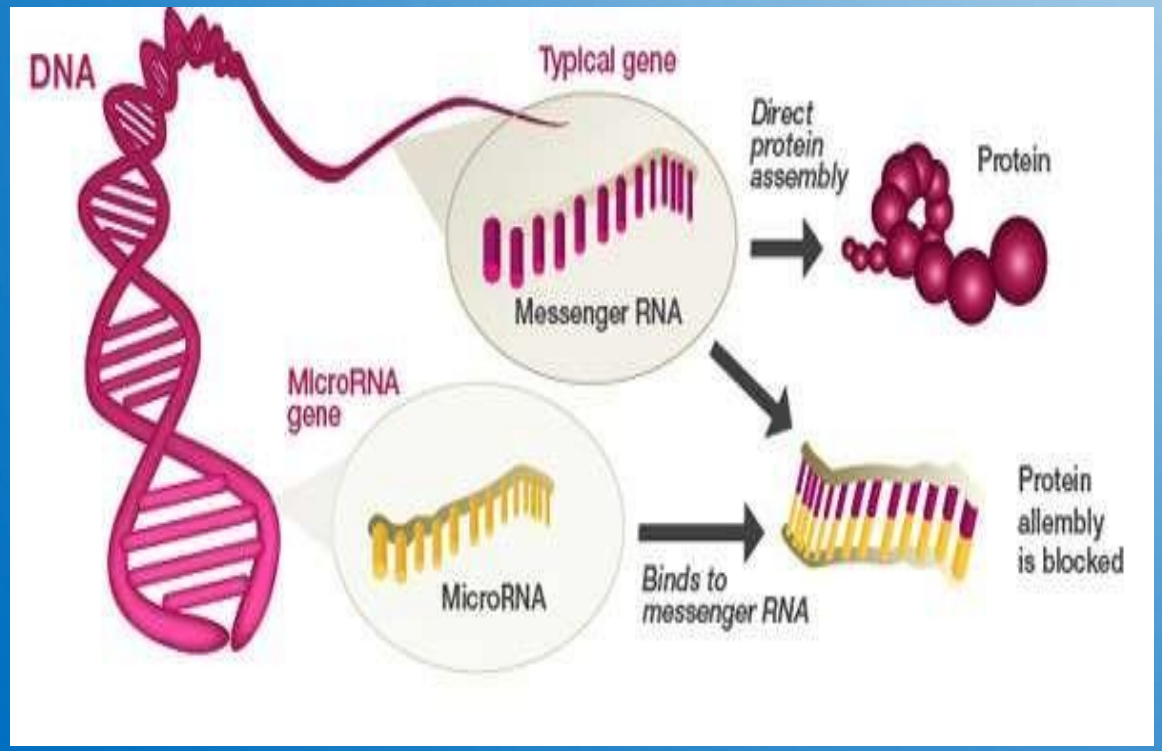




NON-CODING RNA (NCRNA)-ASSOCIATED GENE

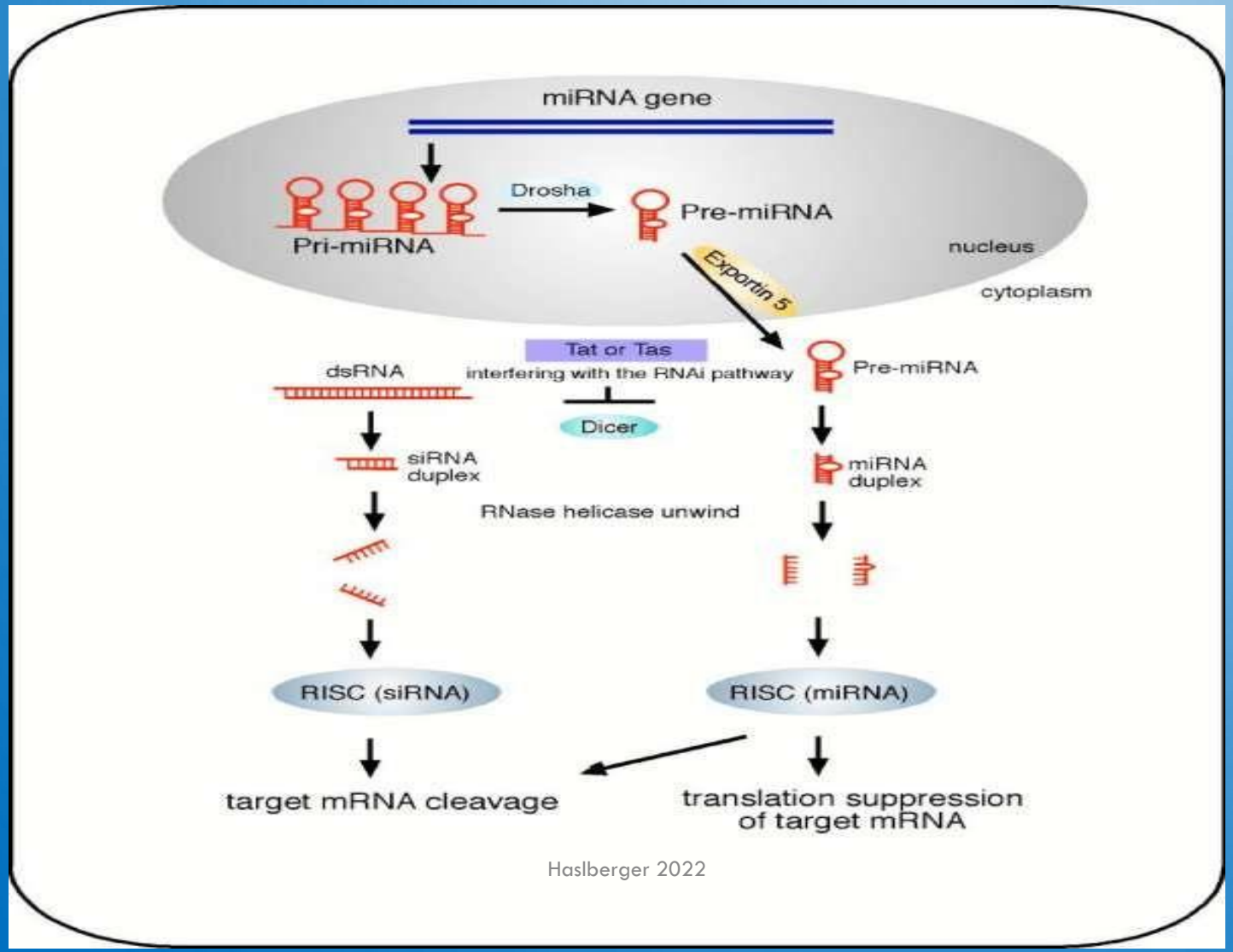
- miRNAs or ncRNA represent small RNA molecules encoded in the genomes of plants and animals. These highly conserved 22 nucleotides long RNA sequences regulate the expression of genes by binding to the 3'-untranslated regions (3'-UTR) of specific mRNAs. A growing body of evidence shows that miRNAs are one of the key players in cell differentiation and growth, mobility and apoptosis (programmed cell death).

RNA INTERFERENCE



- miRNAs regulate diverse aspects of development and physiology, thus understanding its biological role is proving more and more important. Analysis of miRNA expression may provide valuable information, as dysregulation of its function can lead to human diseases such as cancer, cardiovascular and metabolic diseases, liver conditions and immune dysfunction.

RNA INTERFERENCE



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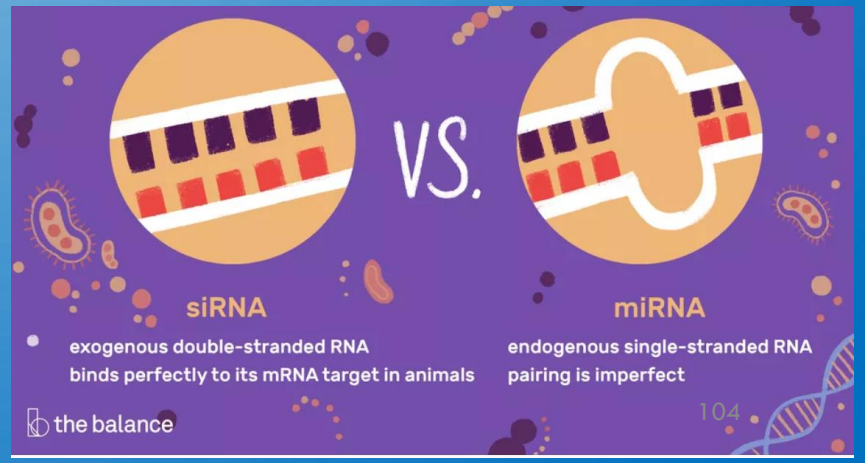
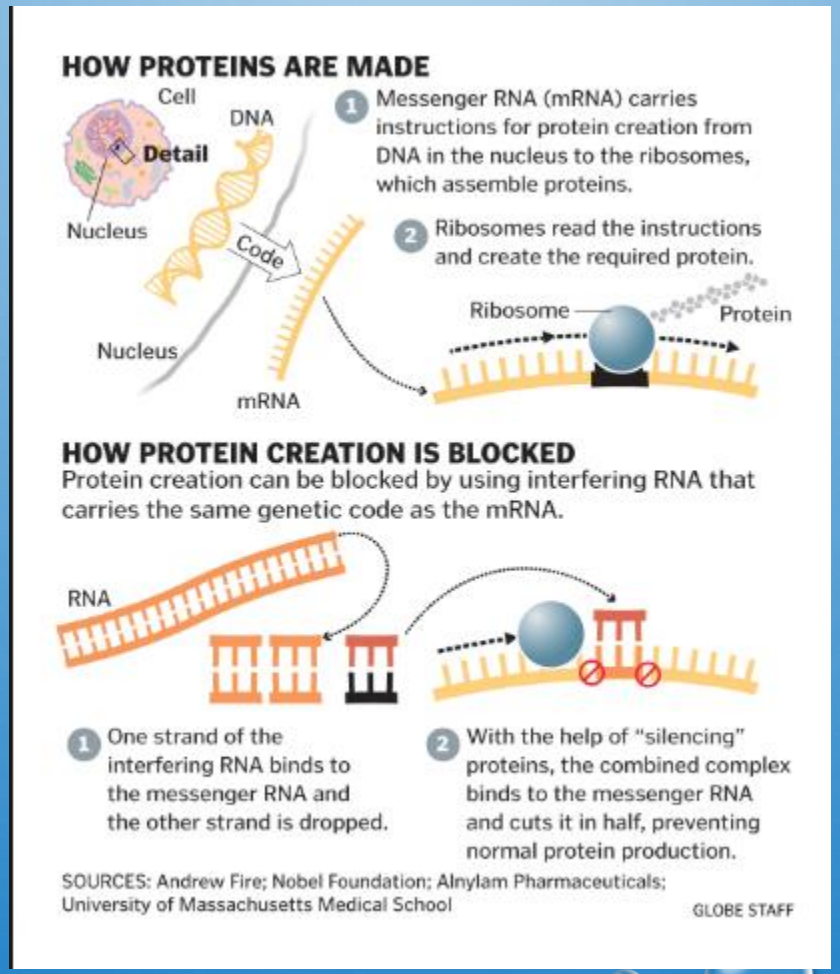
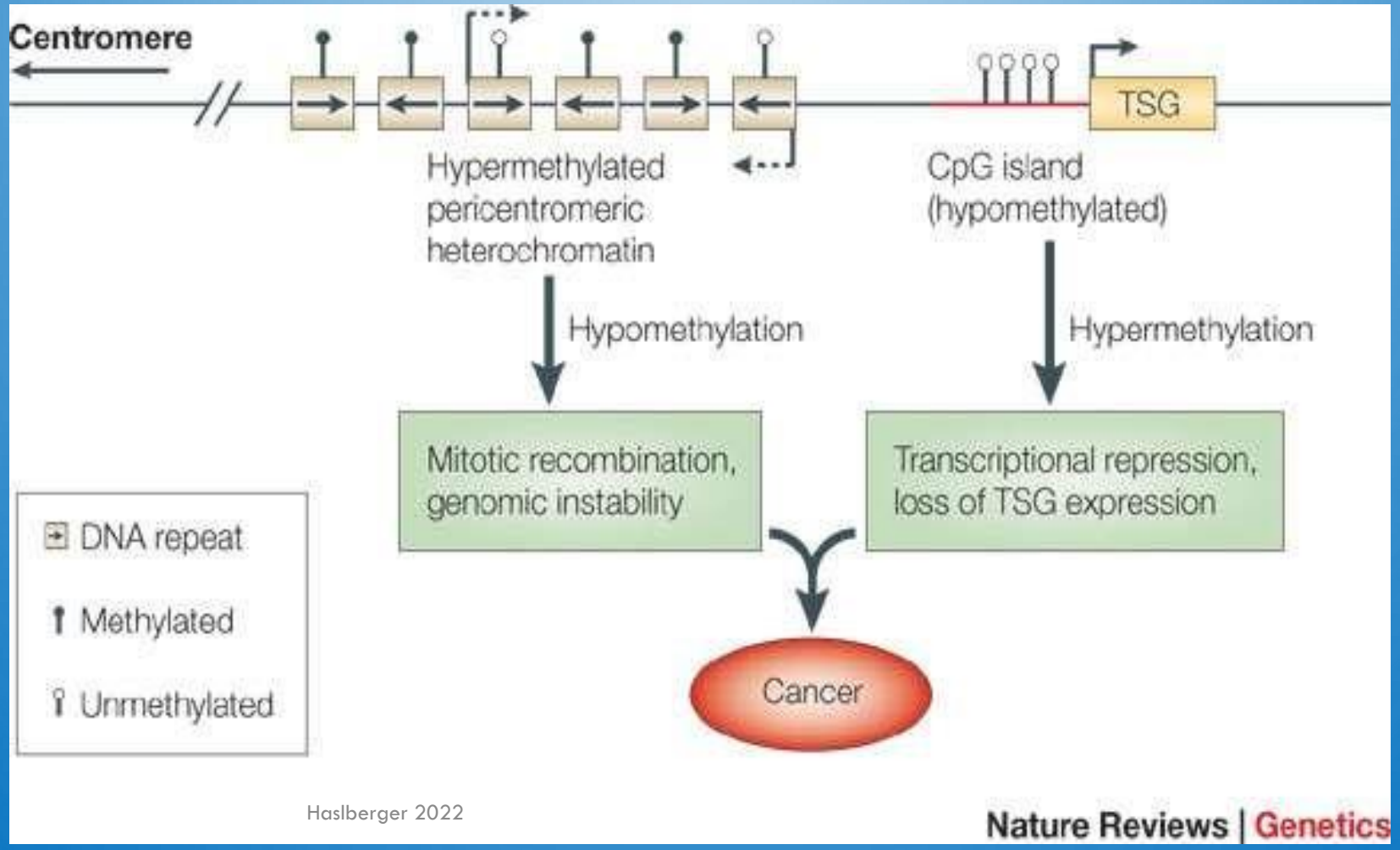


RNA INTEREFERENCE AND PROTEINS

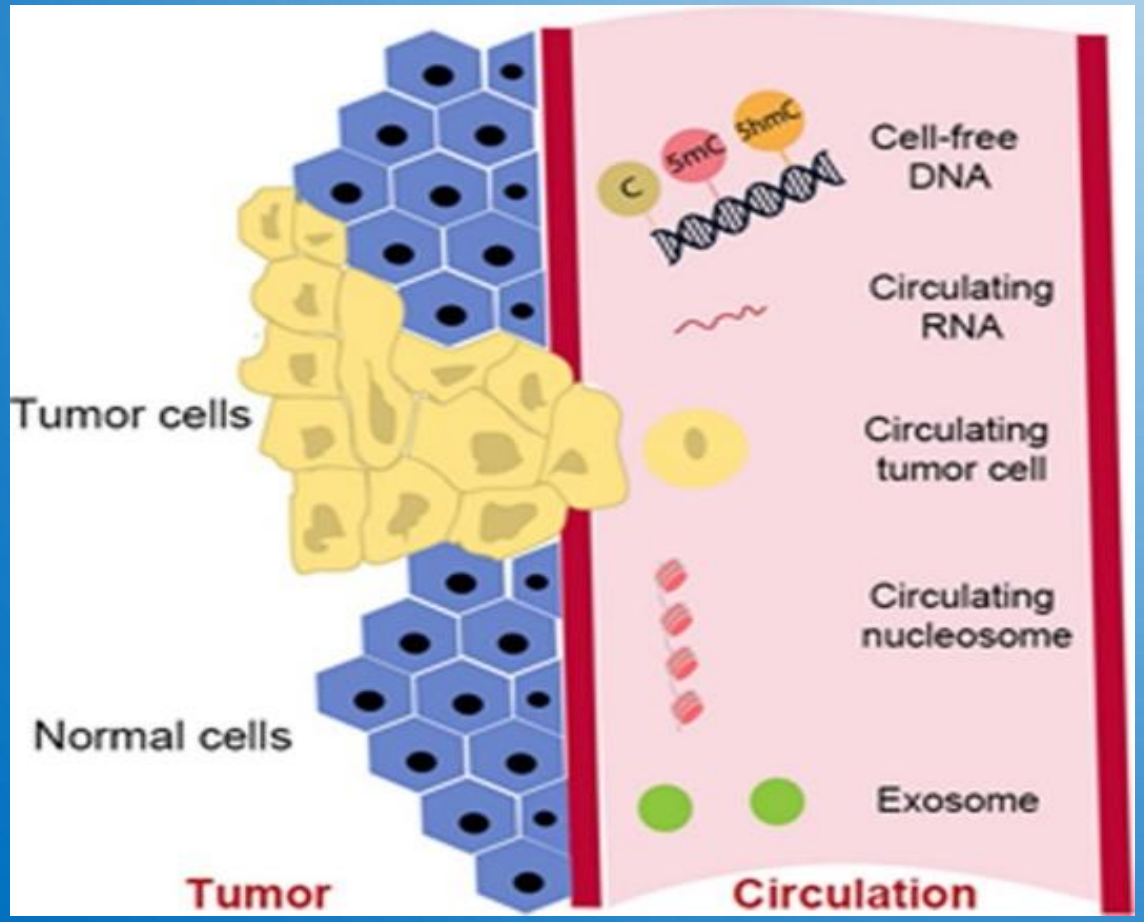


DNA METHYLATION AND CANCER



Haslberger 2022

PRECISION MEDICINE, ESPECIALLY CFDNA PRECISION NUTRITION



ORIGINAL ARTICLES
Epidemiology Biostatistics and Public Health - 2016, Volume 13, Number 2

The Relevance of Epigenetic Biomarkers for Breast Cancer and Obesity for Personalised Treatment in Public Healthcare: A Systematic Review

Andrea Goettler [1], Alexander Haslberger [2], Elena Ambrosino [3]

(1) Faculty of Health, Medicine & Life Sciences, University of Maastricht, 6229 ER Maastricht, The Netherlands
(2) Dep. for Nutritional Research, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
(3) Elena Ambrosino Institute of Public Health Genomics, Department of Genetics and Cell Biology, Research Institute GROW, Faculty of Health, Medicine & Life Sciences, University of Maastricht

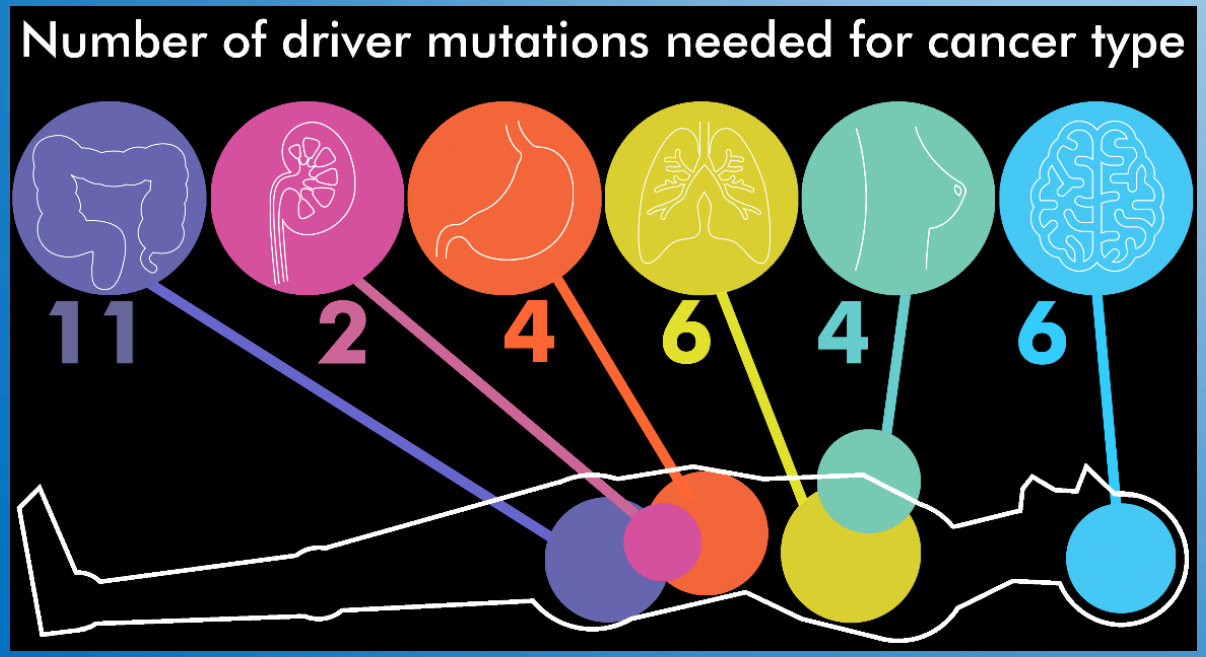
Introduction

Biomarkers and their impact on precision medicine

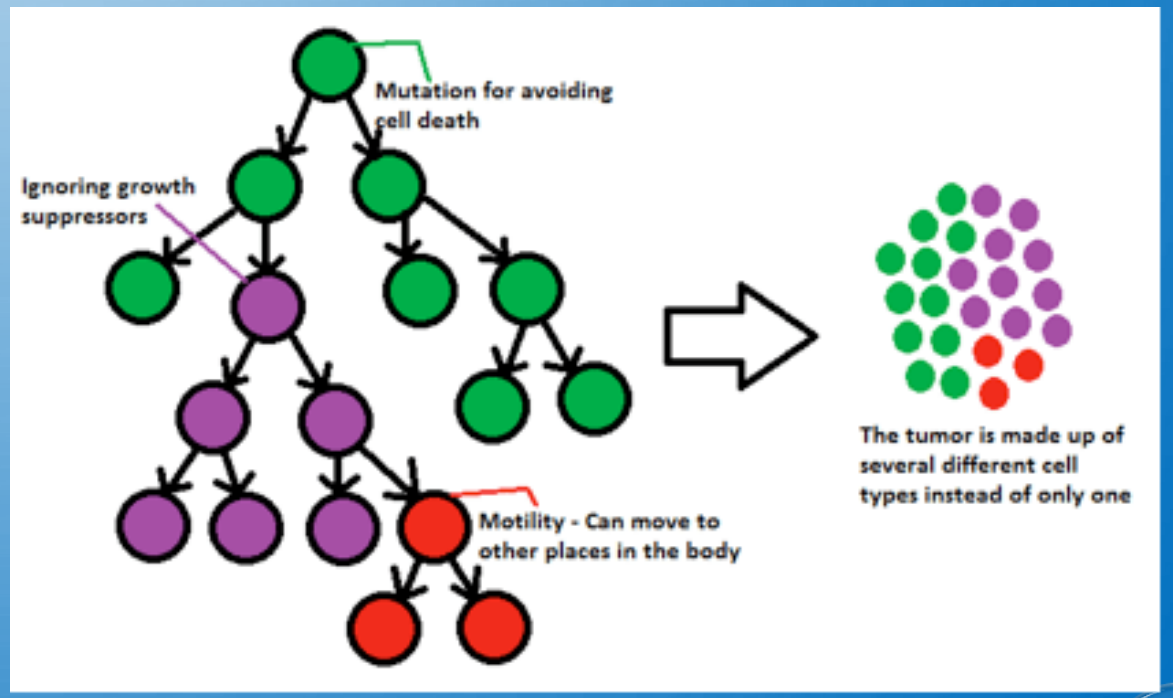
William Slikker Jr.
National Center for Toxicological Research, US-Food and Drug Administration, Jefferson, AR 72079, USA
Corresponding author: William Slikker Jr. Email: william.slikker@fda.hhs.gov

Experimental Biology and Medicine **2018; 3: 211–212. DOI: 10.1177/1535370217733426**

CELLS FROM THE SAME TUMOR COMPRISE GENETIC DIFFERENCES, ALREADY FROM TUMORIGENESIS

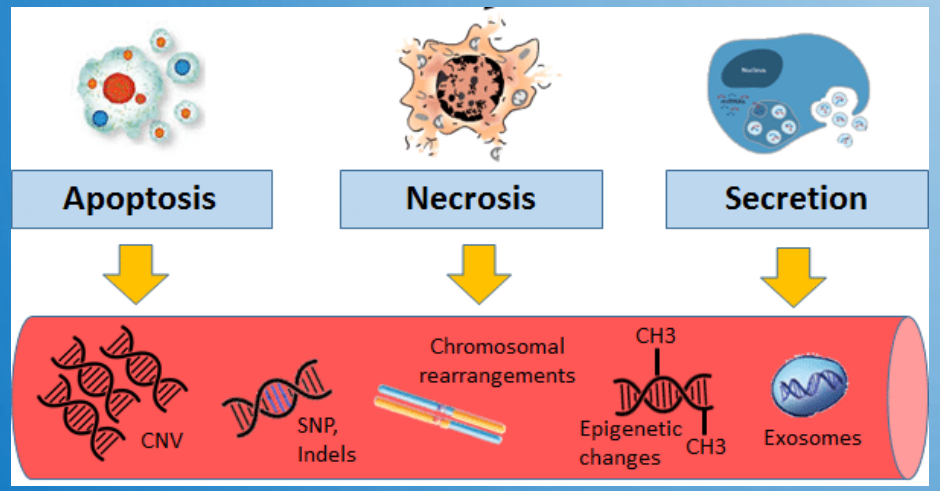


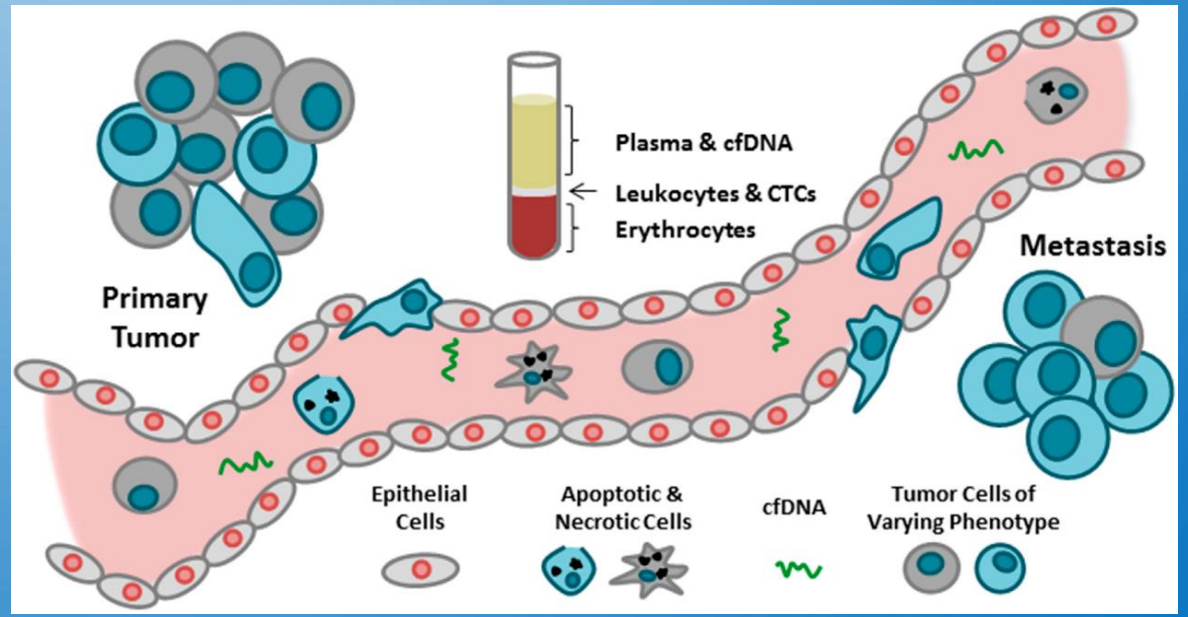
Mutations/ cell



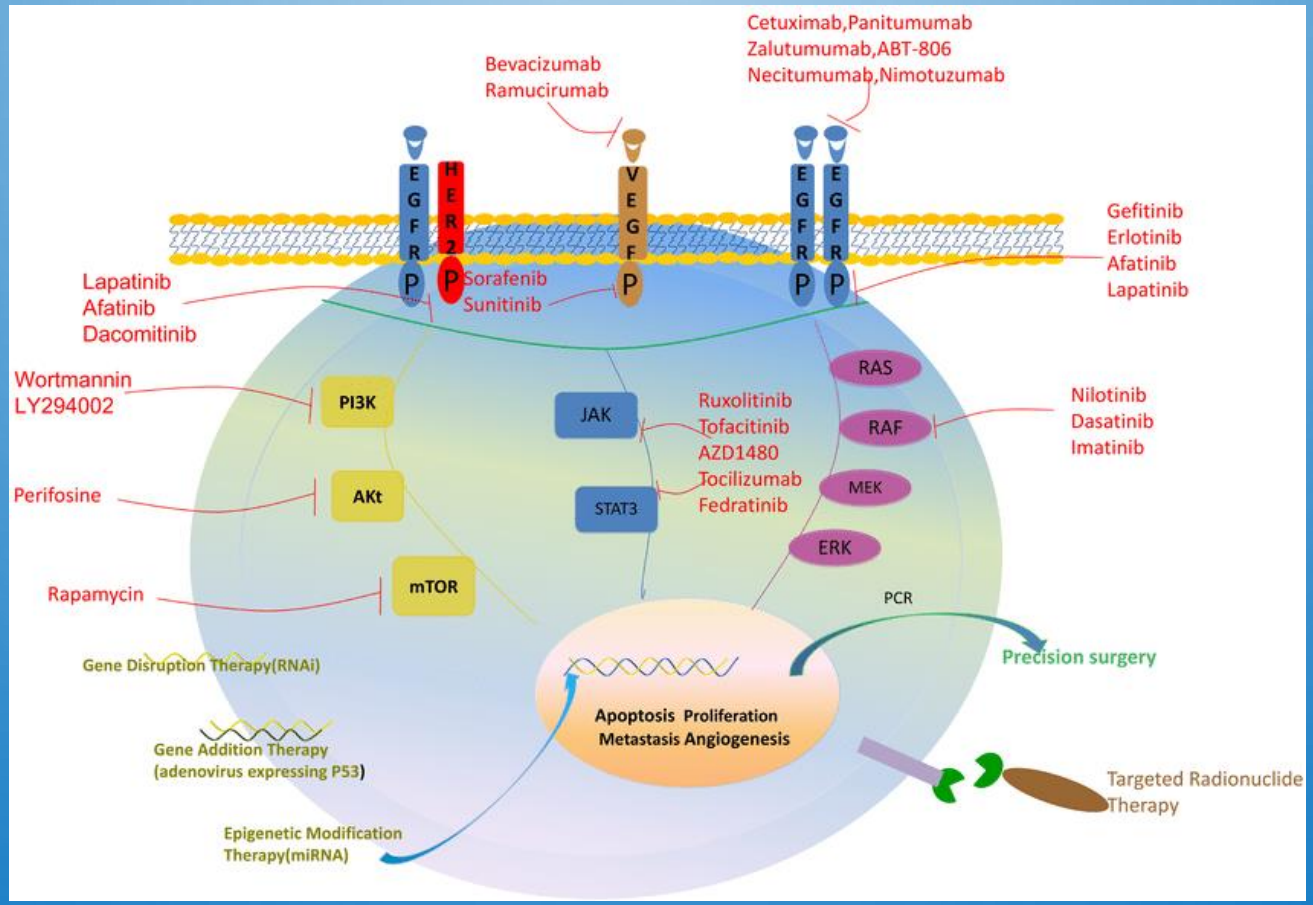
Heterogeneity : Mutation aquirence/tumor

POSSIBLE ANALYSIS USING CELL FREE DNA

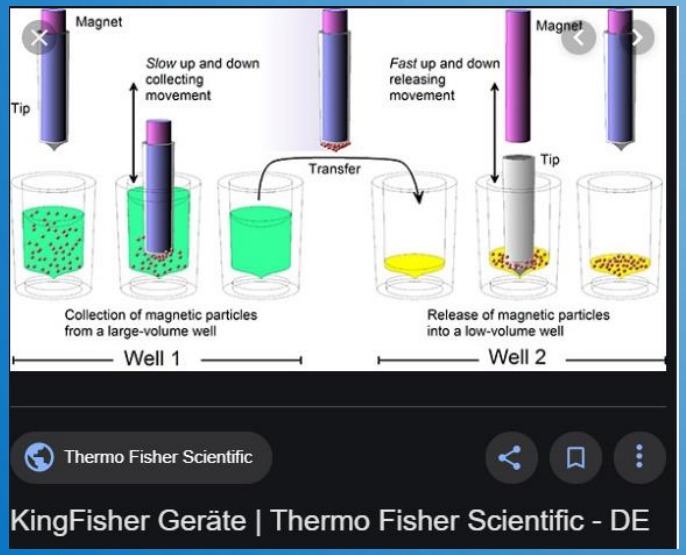


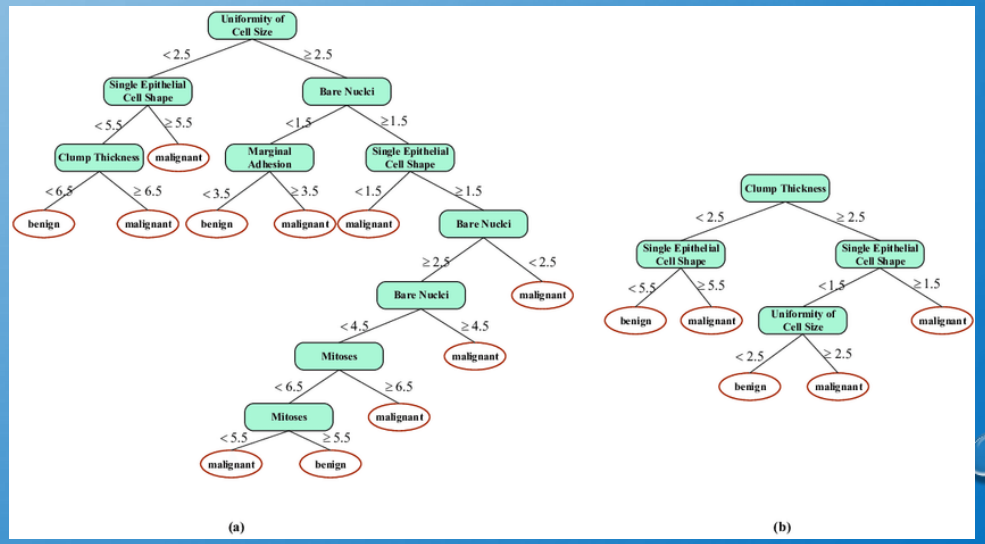


UPCOMING PRECISION MEDICINE; INTERVENTION ACCORDING TO ANALYSIS OF MUTATION, PATHWAYS



LIQUID BIOPSY APPROACH WILL RESULT IN EARLY DETECTION OF MAIN TUMORS USING ADVANCED, SENSITIVE METHODS AND ALGORITHM TO SPECIFY LIKELIHOOD AND STAGE OF CANCER





cancers

MDPI

Article

Comprehensive Approach to Distinguish Patients with Solid Tumors from Healthy Controls by Combining Androgen Receptor Mutation p.H875Y with Cell-Free DNA Methylation and Circulating miRNAs

Elena Tomeva [1], Olivier J. Switzeny [1], Clemens Heitzinger [2], Berit Hippe [1,3] and Alexander G. Haslberger [3,*]

1 HealthBioCare GmbH, A-1090 Vienna, Austria; et@healthbiocare.at (E.T.); switzeny@healthbiocare.at (O.J.S.); bh@healthbiocare.at (B.H.)
2 Center for Artificial Intelligence and Machine Learning (CAIML), TU Wien, A-1040 Vienna, Austria; clemens.heitzinger@tuwien.ac.at
3 Department of Nutritional Sciences, University of Vienna, A-1090 Vienna, Austria
* Correspondence: alexander.haslberger@univie.ac.at

Simple Summary: Blood-based tests for cancer detection are minimally invasive and could be useful for screening asymptomatic patients and high-risk populations. Since a single molecular biomarker is usually insufficient for an accurate diagnosis, we developed a multi-analyte liquid biopsy-based classification model to distinguish cancer patients from healthy subjects. The combination of cell-free DNA mutations, miRNAs, and cell-free DNA methylation markers improved the model's performance. Moreover, we demonstrated that the androgen receptor mutation p.H875Y is not only relevant in prostate cancer but had a strong predictive value for colorectal, bladder, and breast cancer. Our results, although preliminary, showed that a single liquid biopsy test could detect multiple cancer types simultaneously.

check for updates

Citation: Tomeva, E.; Switzeny, O.J.; Heitzinger, C.; Hippe, B.; Haslberger, A.G. Comprehensive Approach to Distinguish Patients with Solid Tumors from Healthy Controls by

CANCER EPIGENETICS

- A COMMON PARADIGM OF CANCER EPIGENETICS IS HYPERMETHYLATION OF CPG ISLAND OF TUMOR SUPPRESSOR GENE PROMOTER
- HYPERMETHYLATED PROMOTER DNA IS ASSOCIATED WITH VIRTUALLY EVERY TYPE OF HUMAN TUMOR
- WITH EACH TYPE OF TUMOR HAVING OWN SIGNATURE OF METHYLATED GENES

CANCER EPIGENETICS, EXAMPLES

Cancer	Methylated genes
Prostate	GSTP1
Renal	VHL
Colon and endometrial	MLH1 (mismatch repair gene)
Esophageal	APC

Glutathione S-transferases

Hippel–Lindau tumor suppressor

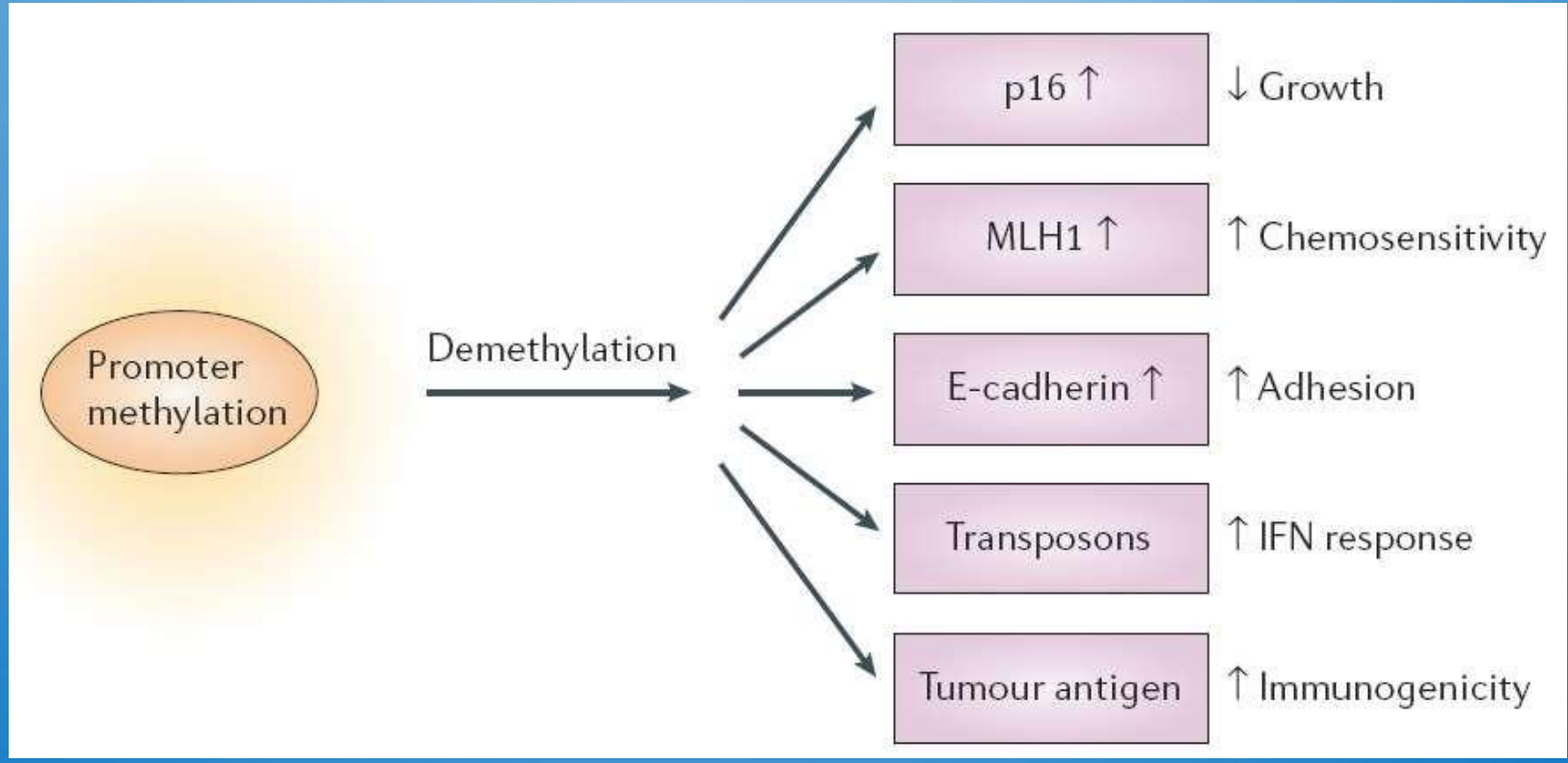
Tumor suppresssor

Cancer epigenetics, examples

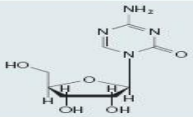
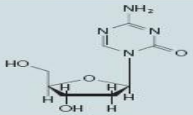
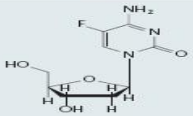
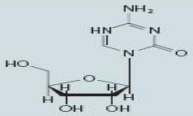
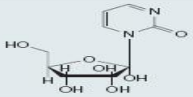
- Global hypomethylation: overall in 5-methylcytosine content in the genome
  - Found in premalignant and early stages of some neoplasm
  - Important in tumor progression

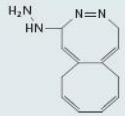
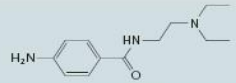
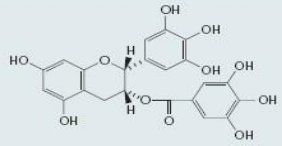
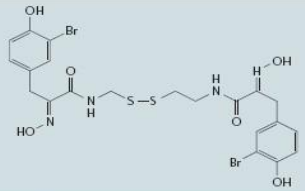
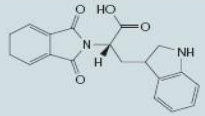
- Gene-specific hypomethylation:
  - Often affect promoter region of proto-oncogene and oncogene which are normally highly methylated

DEMETHYLATION IN CANCER THERAPY

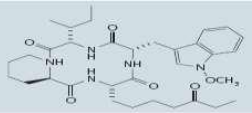
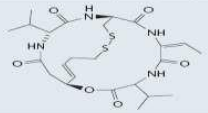
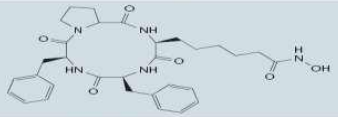
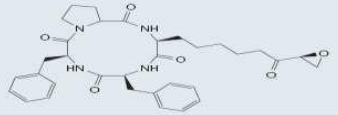
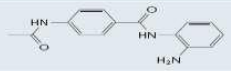
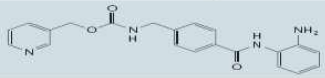


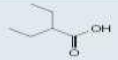
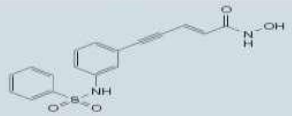
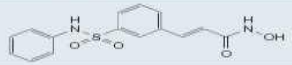
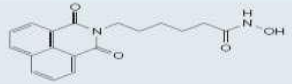
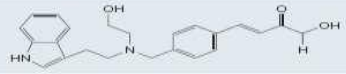
DANA METHYLATION MODULATION

Inhibitor	Structure	Dose range	Clinical trials	References
5-Azacytidine		µM	Phase I, II, III: haematological malignancies	51
5-Aza-2′-deoxycytidine		µM	Phase I, II, III: haematological malignancies; cervical, non-small-cell lung cancer	52–55,129,130
5-Fluoro-2′-deoxycytidine		µM	Phase I	47,66
5,6-Dihydro-5-azacytidine		µM	Phase I, II: ovarian cancer and lymphomas	65
Zebularine		µM–mM	Preclinical	16,74

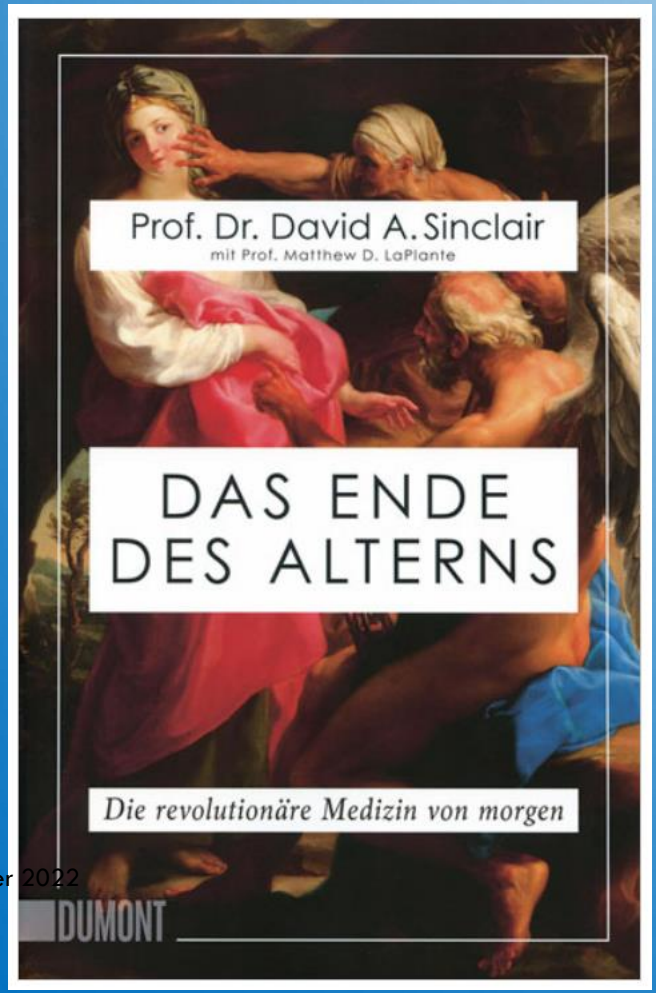
Inhibitor	Structure	Dose range	Clinical trials	References
Hydralazine		µM	Phase I: cervical cancer	86
Procainamide		µM	Preclinical	82–84
EGCG		µM	Preclinical	80
Psammaplin A		nM–µM	Preclinical	79
MG98	N/A	N/A	Phase I: advanced/ metastatic solid tumours	77–78
RG108		µM	Preclinical	75

HDAC INHIBITORS

Inhibitor	Structure	Dose range	Clinical trials
Cyclic tetrapeptides			
Apicidin		nM	Preclinical
Depsipeptide (FK-228, FR901228)		μM	Phase I, II: CLL, AML, T-cell lymphoma
TPX-HA analogue (CHAP)		nM	Preclinical
Trapoxin		nM	Preclinical
Benzamides			
CI-994 (N-acetyl dinaline)		μM	Phase I, II: solid tumours
MS-275		μM	Phase I, II: solid tumours and lymphoma

Inhibitor	Structure	Dose range	Clinical trials
Short-chain fatty acids			
Butyrate		mM	Phase I, II: colorectal
Valproic acid		mM	Phase I: AML, leukaemias
Hydroxamic acids			
m-Carboxy cinnamic acid bishydroxamic acid (CBHA)		μM	Preclinical
Oxamflatin		μM	Preclinical
PDX 101		μM	Phase I
Pyroxamide		nM	Preclinical
Scriptaid		μM	Preclinical
Suberoylanilide hydroxamic acid (SAHA)		μM	Phase I, II: haematological and solid tumours
Trichostatin A (TSA)		nM	Preclinical
LBH589	N/A	nM	Phase I
NVP-LAQ824		nM	Phase I

AGING A CURABLE DISEASE?



frontiers in Genetics

OPINION
published: 18 June 2015
doi: 10.3389/fgene.2015.00205

It is time to classify biological aging as a disease

Sven Bulterijs[1,2*], *Raphaella S. Hull*[3,4], *Victor C. E. Björk*[2,5] *and Avi G. Roy*[2,4,6]

[1] *Faculty of Science, Ghent University, Ghent, Belgium,* [2] *Heales vzw, Brussels, Belgium,* [3] *Biochemistry Department, University of Oxford, Oxford, UK,* [4] *The Biogerontology Research Foundation, London, UK,* [5] *Institutionen för Biologisk Grundutbildning, Uppsala University, Uppsala, Sweden,* [6] *Institute for Translational Medicine, School of Science, University of Buckingham, Buckingham, UK*

If they could turn back time: how tech billionaires are trying to reverse the ageing process

Jeff Bezos and Peter Thiel are pouring huge sums into startups aiming to keep us all young – or even cheat death. And the science isn't as far-fetched as you might think

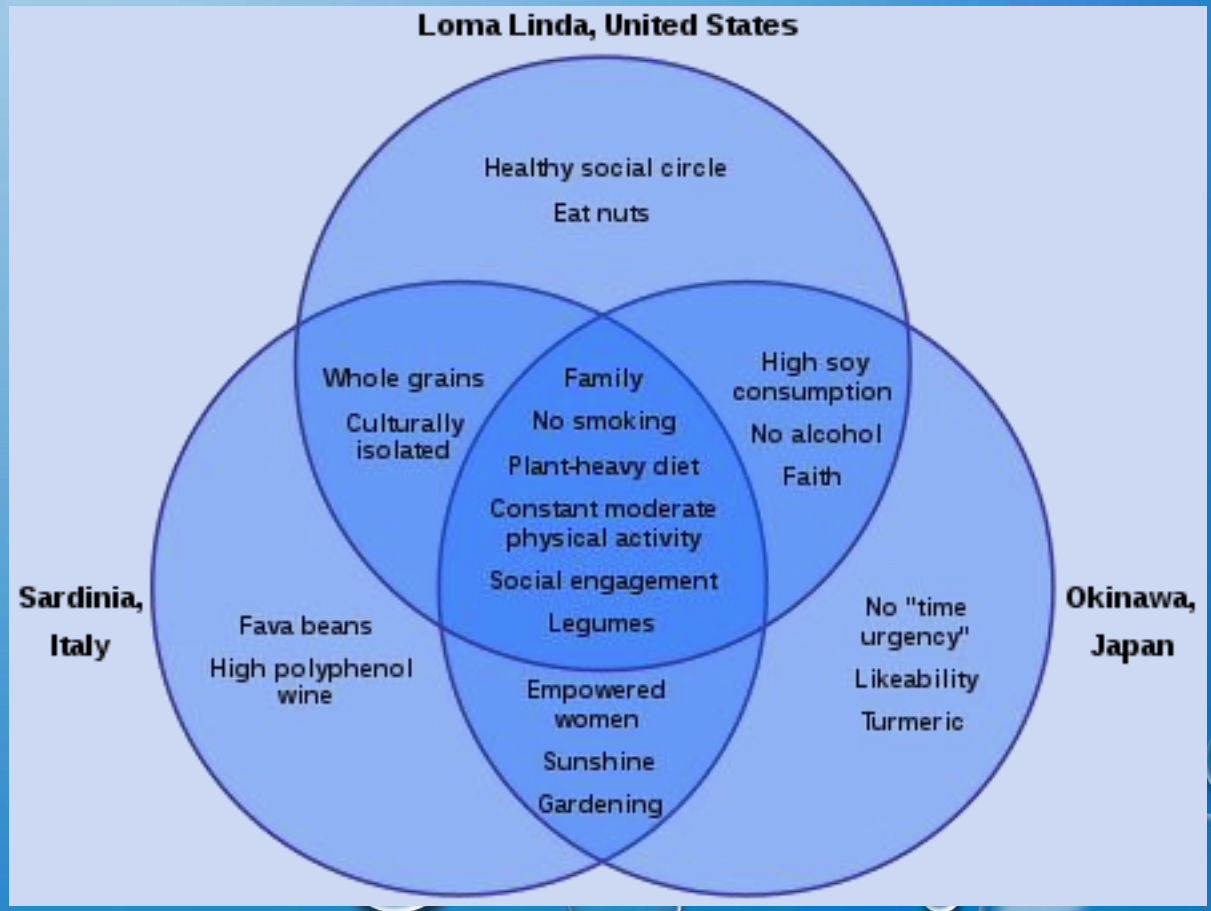
BLUEZONES

Blaue Zonen sind Regionen der Welt in denen Menschen viel länger als der Durchschnitt leben sollen. Das Konzept wird von Dan Buettner vertreten und wurde erstmals im November 2005 im Magazin National Geographic in der Titelgeschichte „The Secrets of a Long Life“ von Buettner vorgestellt.

Buettner identifizierte fünf Regionen, die er als „Blaue Zonen“ betrachtet: Okinawa (Japan), Sardinien (Italien), die Nicoya-Halbinsel (Costa Rica), Ikaria (Griechenland) und unter den Siebenten-Tags-Adventisten in Loma Linda, Kalifornien.

Er gibt eine Erklärung, basierend auf Daten und Beobachtungen aus erster Hand, warum diese Bevölkerungs-gruppen gesünder und länger leben.

VON DEN BLUEZONES LERNEN WIR PERSÖNLICHE, REGIONAL SPEZIFISCHE MASSNAHMEN GEGEN VORZEITIGES ALTERN, ALTERS-BEDINGTE ERKRANKUNGEN, ZENTRAL: BIOAKTIVE MOLEKÜLE



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Die Menschen in den Blauen Zonen haben gemeinsame Lebensstil-Merkmale, die zu ihrer Langlebigkeit beitragen. Sechs gemeinsamen Merkmale der Menschen in Okinawa, Sardinien und den Blauen Zonen von Loma Linda:

- Familie – wichtiger als andere Anliegen
- Nicht rauchen
- Pflanzenbasierte Ernährung – der Großteil der verzehrten Nahrung stammt aus Pflanzen.
- Ständige moderate körperliche Aktivität – ein untrennbarer Bestandteil des Lebens.
- Soziales Engagement – Menschen jeden Alters sind sozial aktiv und in ihre Gemeinschaften integriert.
- Hülsenfrüchte – häufig konsumiert

Buettner: Faktoren die den Lebensstil der Menschen in den blauen Zonen behandeln:

- Mäßige, regelmäßige körperliche Aktivität.
- Lebensinhalt.
- Stressabbau.
- Mäßige Kalorienzufuhr.
- Pflanzenbasierte Ernährung.
- Mäßiger Alkoholkonsum; überwiegend Wein.
- Engagement in der Spiritualität oder Religion.
- Engagement im Familienleben.
- Engagement im gesellschaftlichen Leben.

BLUEZONES FUER SPEZIELLE ERKRANKUNGEN

BLUE ZONES®

ARTICLES RECIPES COMMUNITIES SPEAKING LIFE ACTIVATE PRESS

Prevent Alzheimer's Disease with 4 Brain-Boosting Habits

If you ask the very old in the blue zones region of Ikaria how they live to be 100, they might say it's the leisurely pace of island life, the ocean breeze, the wine consumed with friends, wild herbal tea, or perhaps, as one Ikarian woman put it, "We just forget to die." Their extreme longevity is a combination of many lifestyle habits, leading them to experience a life virtually free from age-related diseases, including dementia, which affects more than 5 million people in the United States.

While there is currently no cure and no single silver bullet to prevent dementia and Alzheimer's disease, there is a combination of many simple lifestyle factors that can help you live a longer,

STRATEGIEN GEGEN DAS VERGESSEN

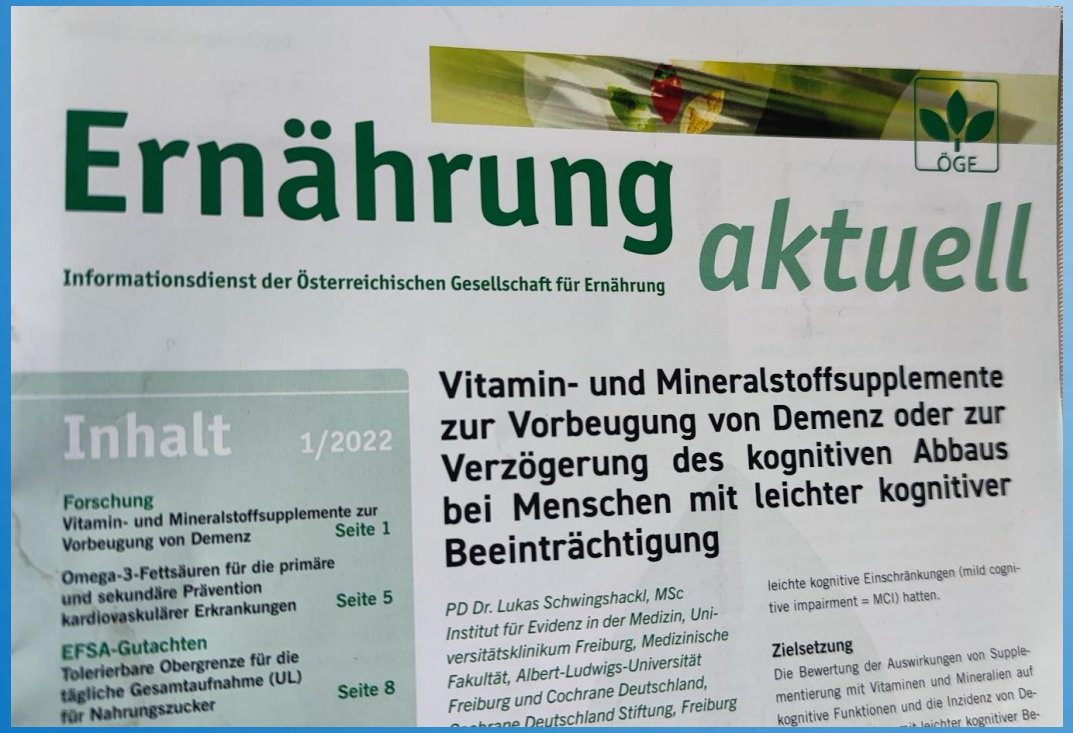
Become a Master (in just about anything!)
Learn a language, pick up an instrument, take a class, or find a new hobby. Challenging yourself to master new skills can trigger pathways that help you maintain cognitive function into old age. No matter your education or income, learning something new, reading the newspaper, or even watching YouTube videos to learn how to garden can protect you from a decline in cognitive ability.

Drink Moderately
Your weekly happy hour is good for more than just your social circle. Studies show moderate drinkers have a lower chance of mortality and an increased chance of maintaining cognitive abilities into old age. Red wine, particularly Cannonau from Sardinia, is a great choice due to its high resveratrol content.

Eat Like You're Greek
Similar to the traditional Mediterranean diet, Ikarians eat wild greens, beans, nuts, seeds, fruits, whole grains, and olive oil. Many of these foods are high in folate, which has been shown to improve cognitive processes. Olive oil, nuts, and seeds

Say "Om"
Chronic stress leads to inflammation and is the foundation for every age-related disease, including Alzheimer's and dementia. Centenarians in the blue zones regions of the world have effective ways to manage stress on a daily basis. For Sardinians, this means a glass of wine and a chat with friends at the end of the day.

ALZHEIMER, VITAMIN, MINERALSTOFFE ;-(



Ernährung aktuell

Informationsdienst der Österreichischen Gesellschaft für Ernährung

ÖGE

Inhalt 1/2022

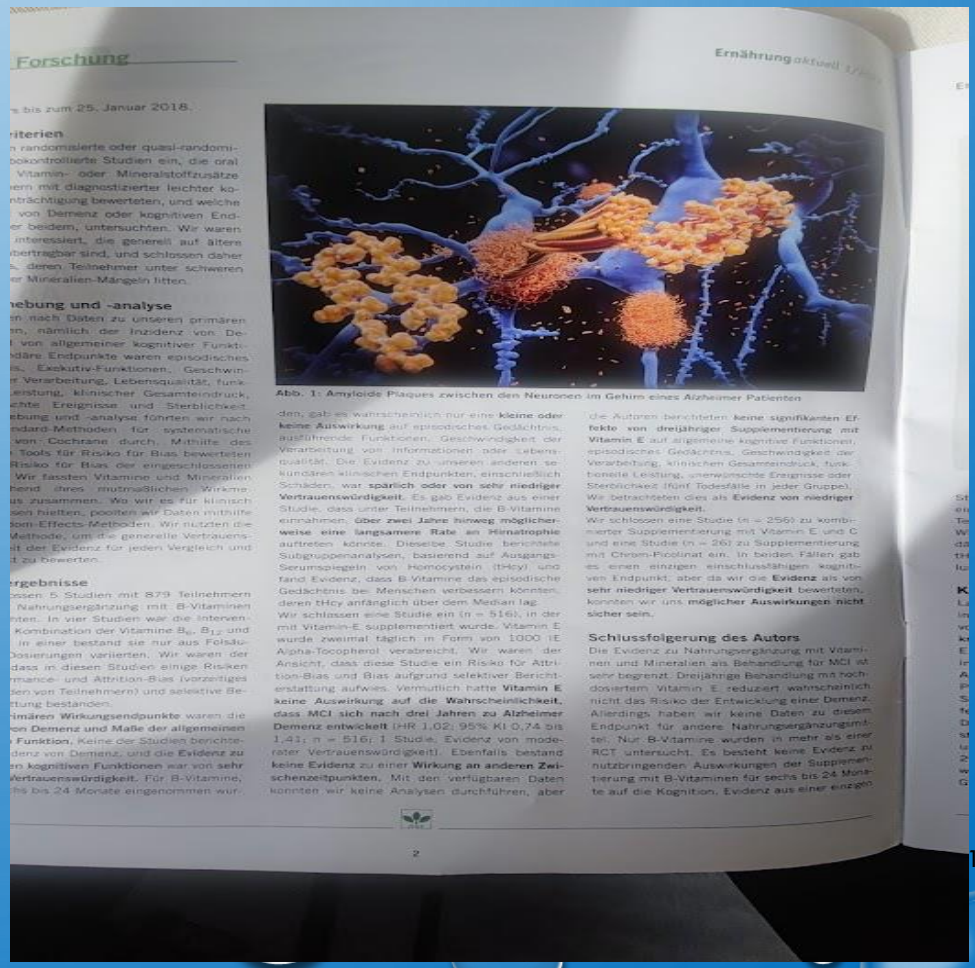
Vitamin- und Mineralstoffsupplemente zur Vorbeugung von Demenz oder zur Verzögerung des kognitiven Abbaus bei Menschen mit leichter kognitiver Beeinträchtigung

PD Dr. Lukas Schwingshackl, MSc
Institut für Evidenz in der Medizin, Universitätsklinikum Freiburg, Medizinische Fakultät, Albert-Ludwigs-Universität Freiburg und Cochrane Deutschland, Cochrane Deutschland Stiftung, Freiburg

leichte kognitive Einschränkungen (mild cognitive impairment = MCI) hatten.

Zielsetzung

Die Bewertung der Auswirkungen von Supplementierung mit Vitaminen und Mineralien auf kognitive Funktionen und die Inzidenz von De-



Forschung

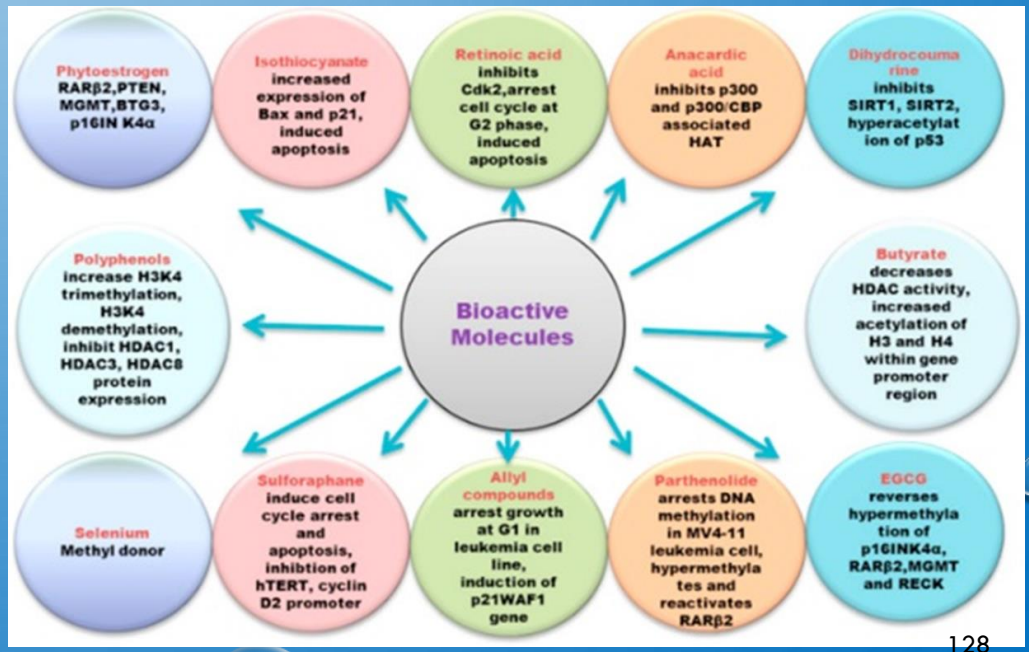
Ernährung aktuell

Abb. 1: Amyloide Plaques zwischen den Neuronen im Gehirn eines Alzheimer Patienten

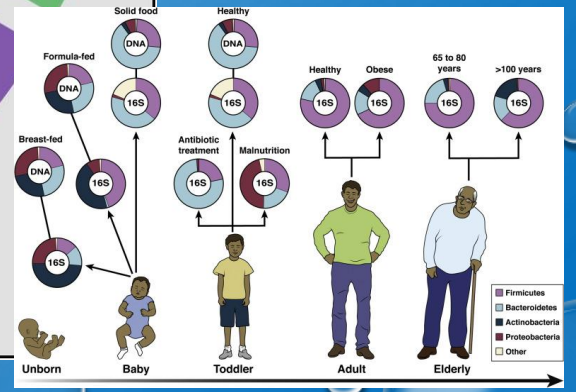
Schlussfolgerung des Autors

Die Evidenz zu Nahrungsergänzung mit Vitaminen und Mineralien als Behandlung für MCI ist sehr begrenzt. Dreijährige Behandlung mit hochdosiertem Vitamin E reduziert wahrscheinlich nicht das Risiko der Entwicklung einer Demenz. Allerdings haben wir keine Daten zu diesem Endpunkt für andere Nahrungsergänzungsmittel. Nur B-Vitamine wurden in mehr als einer RCT untersucht. Es besteht keine Evidenz zu nutzbringenden Auswirkungen der Supplementierung mit B-Vitaminen für sechs bis 24 Monate auf die Kognition. Evidenz aus einer einzigen

WENN NICHT SPURENELEMENTE, VITAMINE : VIELLEICHT BIOAKTIVE MOLEKÜLE ?



HALLMARKS OF AGING



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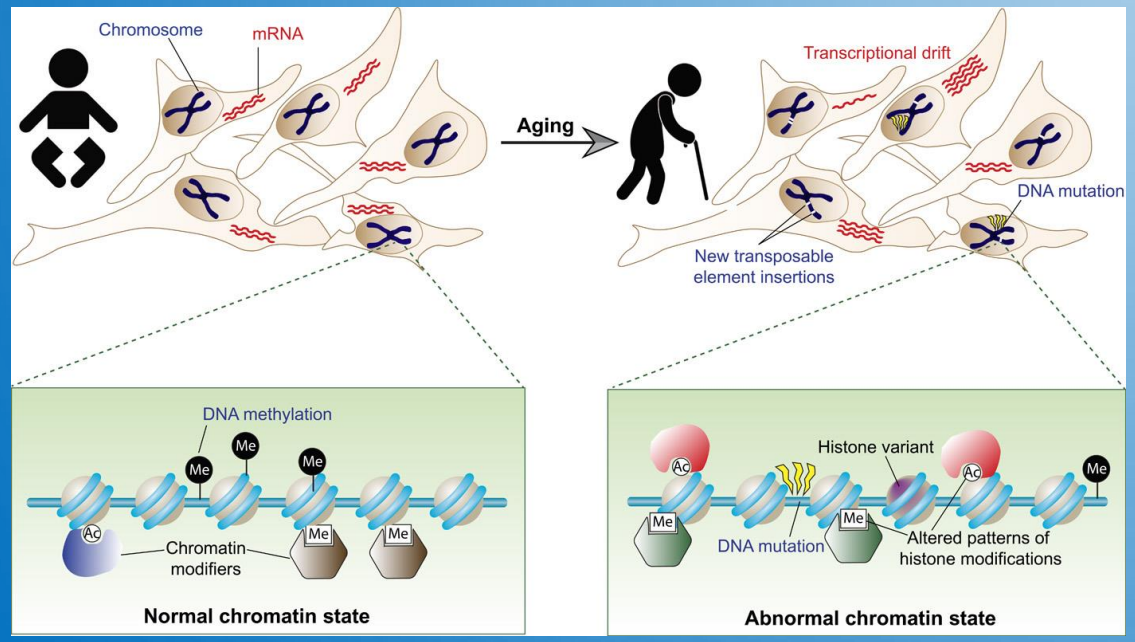
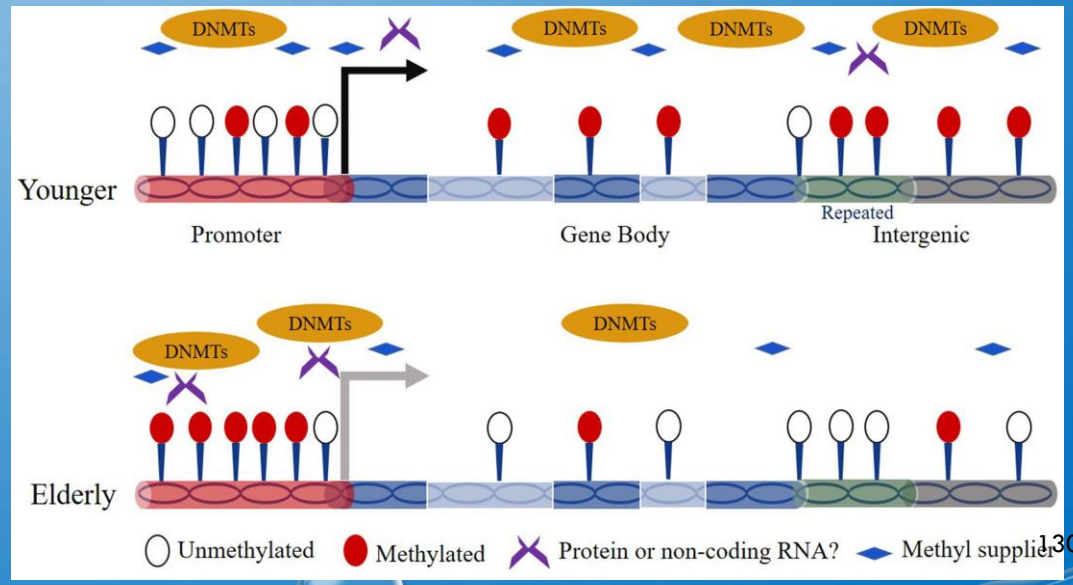
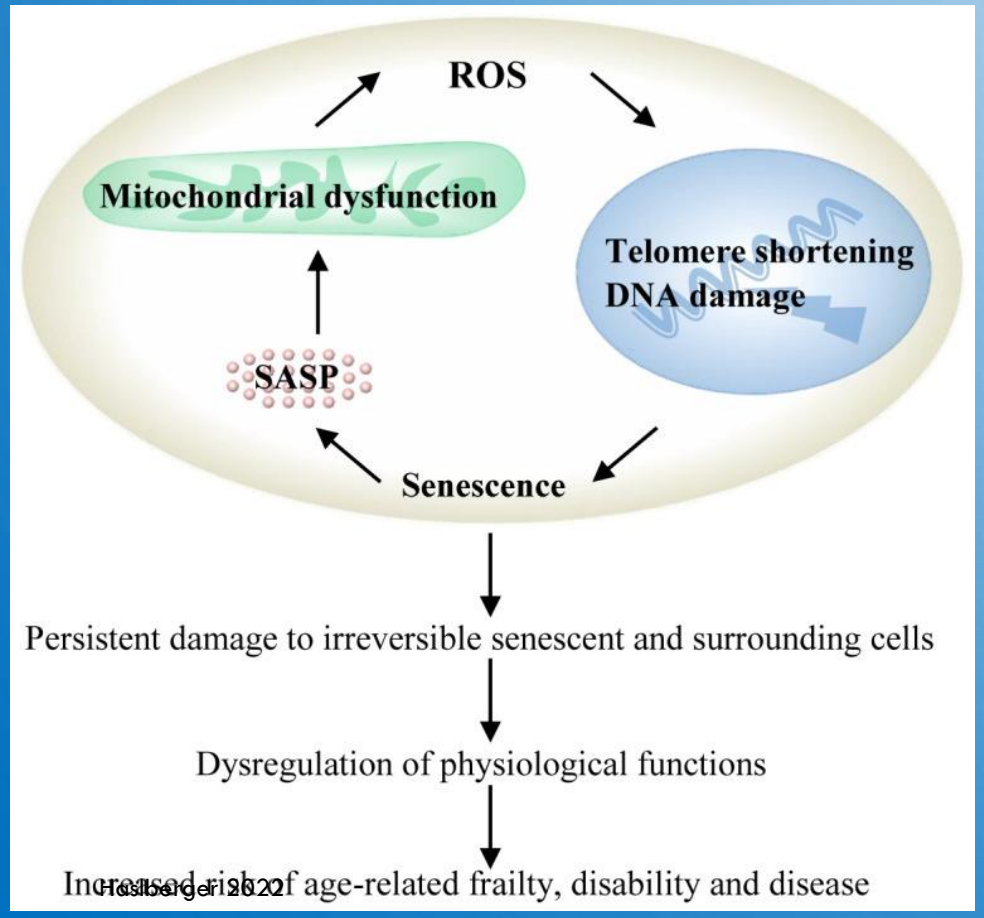
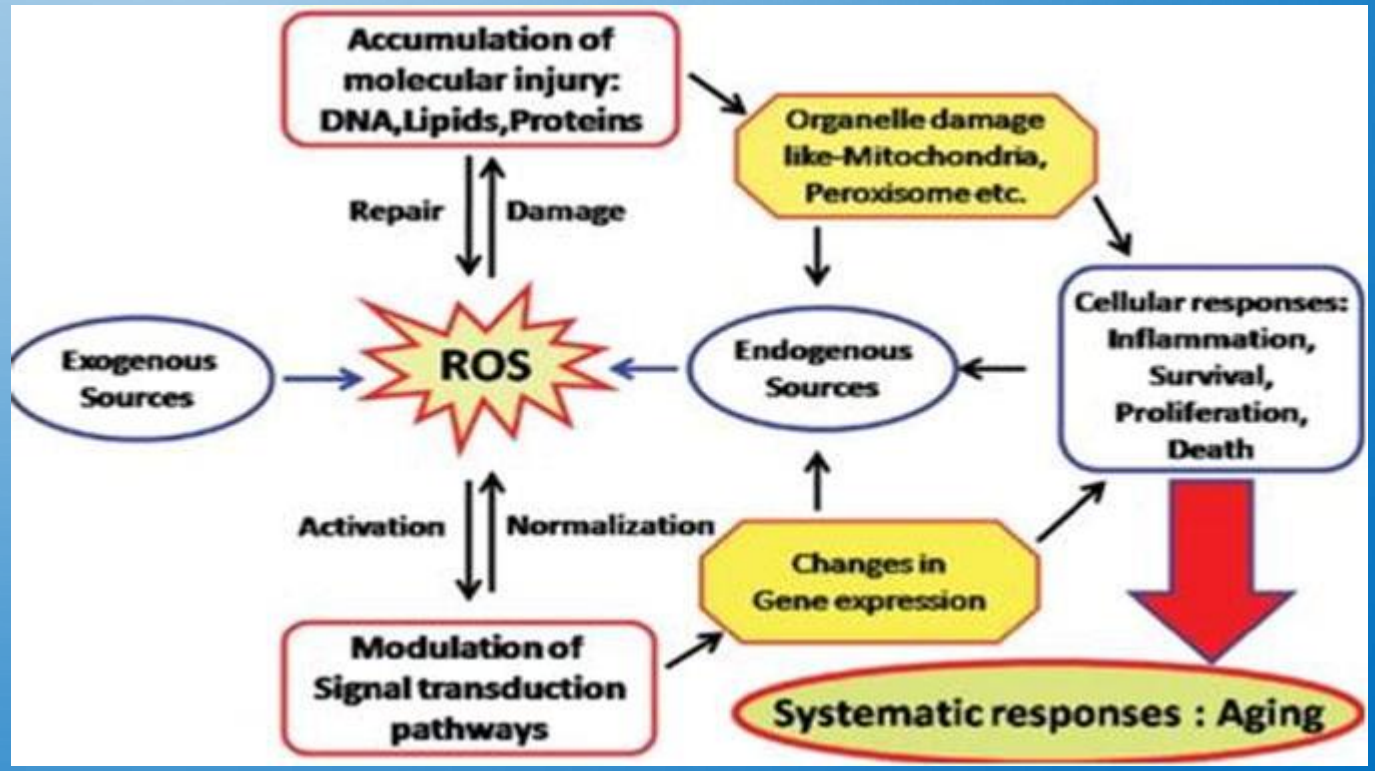
AGING, OLD THEORIES, CHROMATIN INSTABILITY



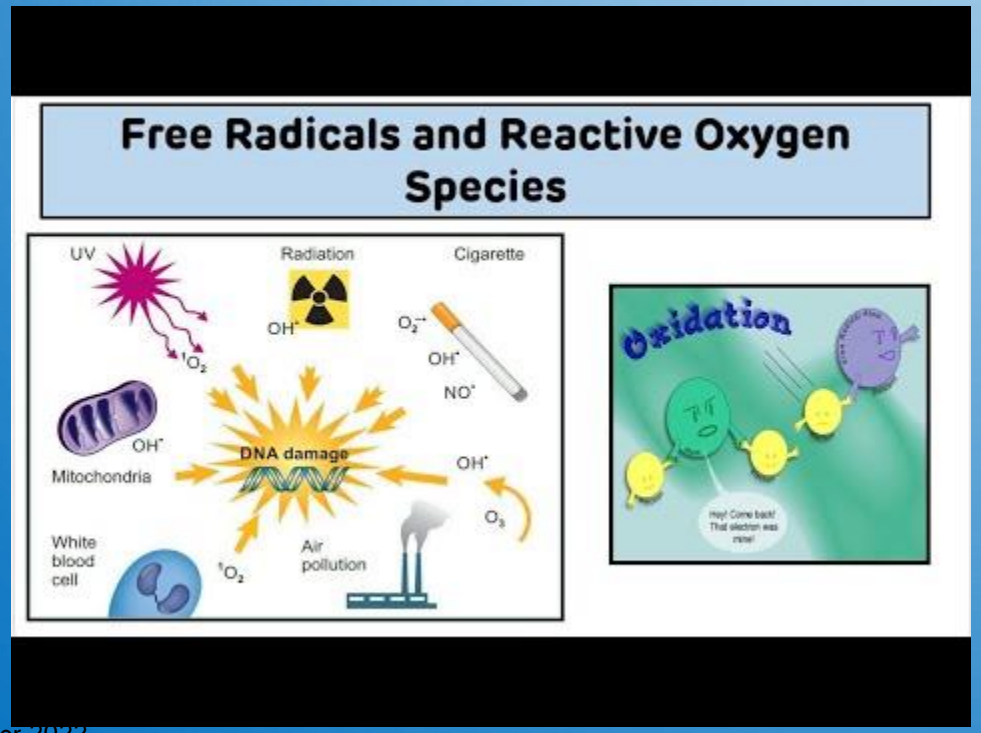


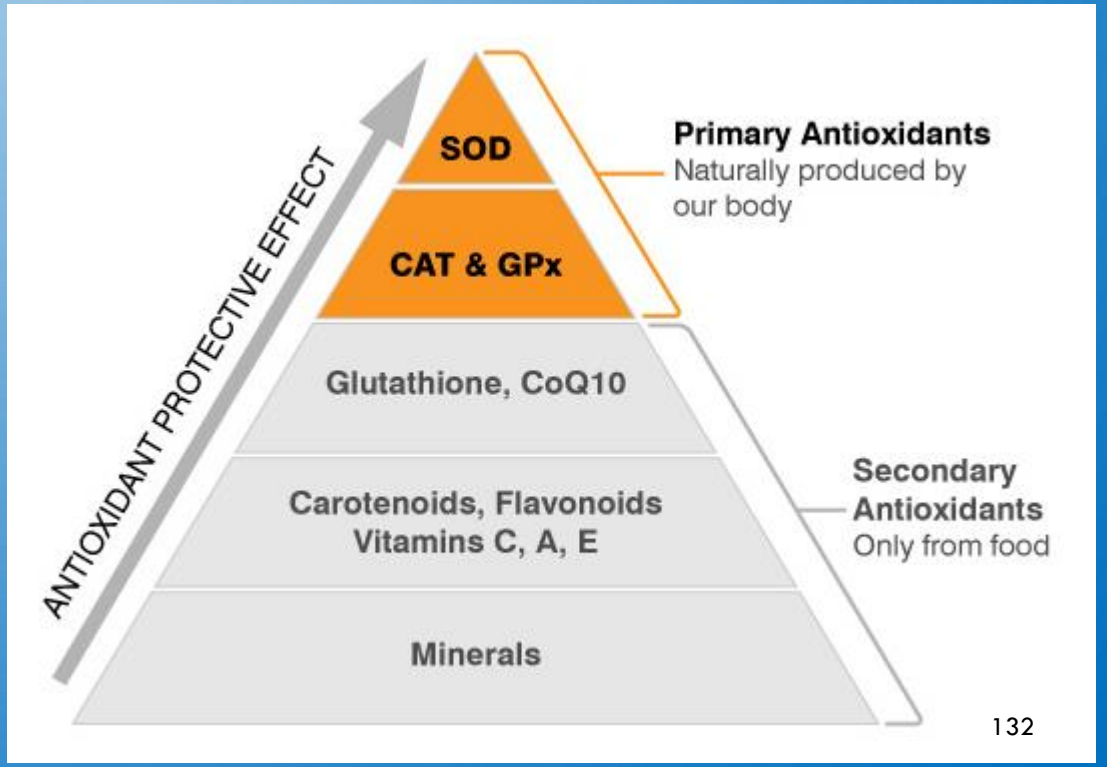
ROS OXYDATION: TELOMERE, MITOCHONDRIA



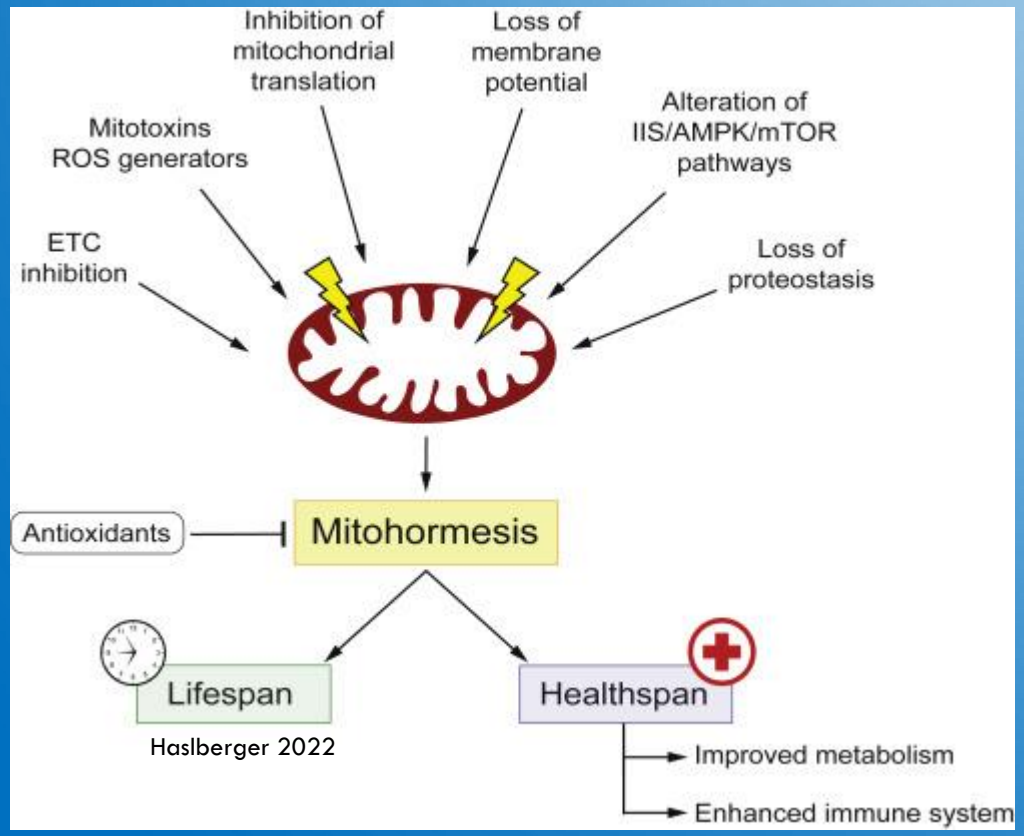


OXYDATION, ROS





MITOHORMESIS, LOW ROS



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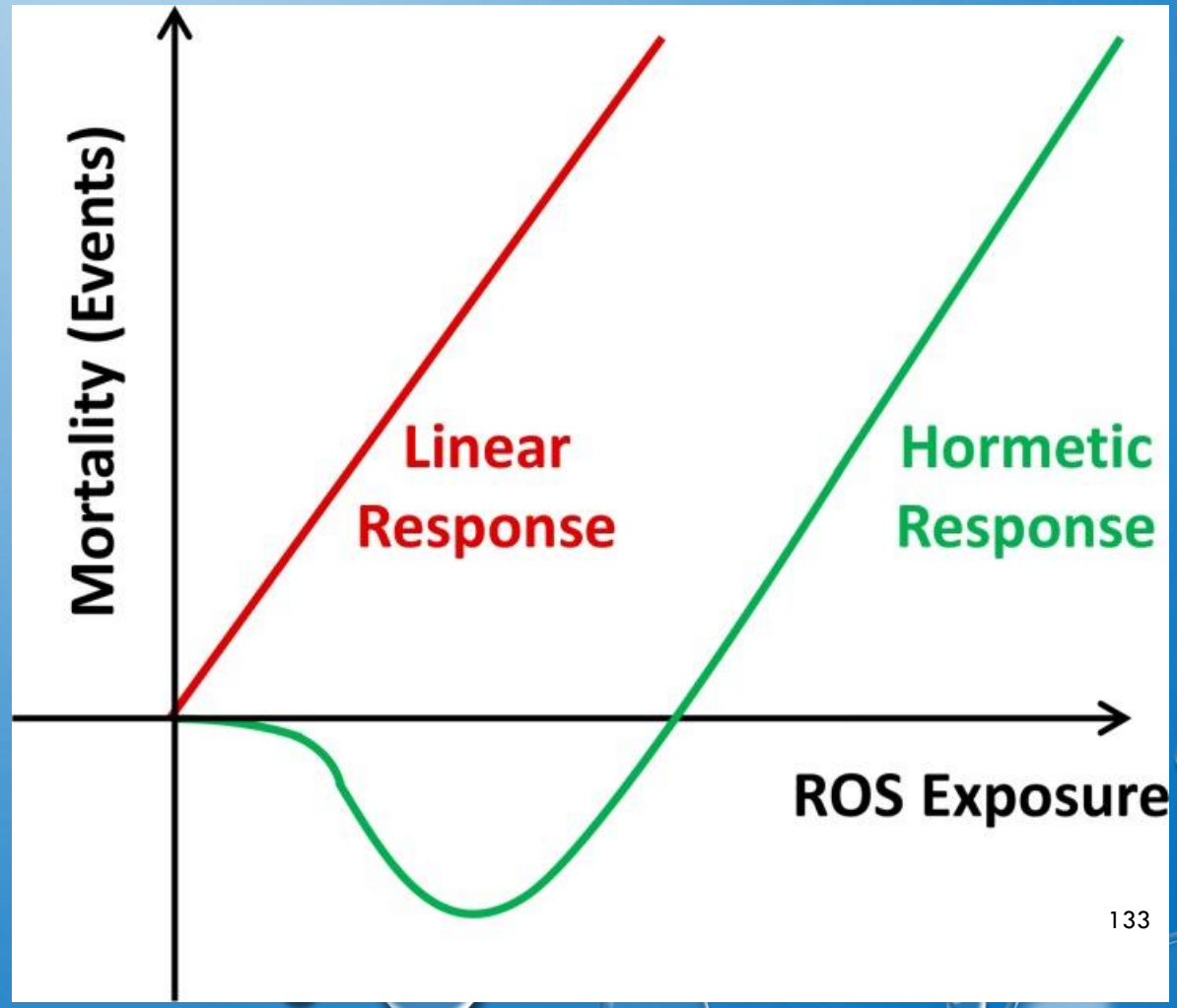
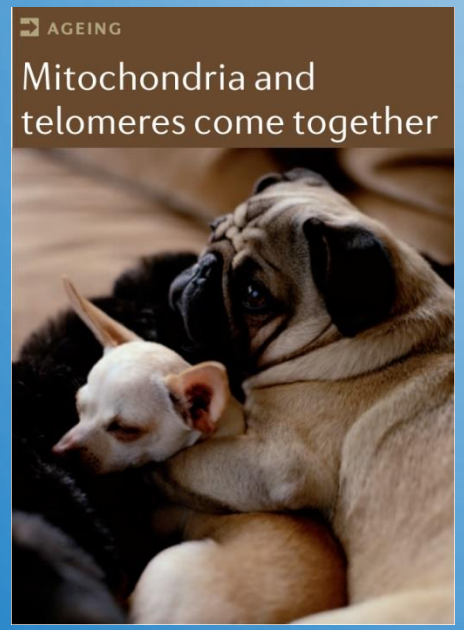


AGEING: NATURE: TELOMERS AND GENOTOXIC STRESS ?



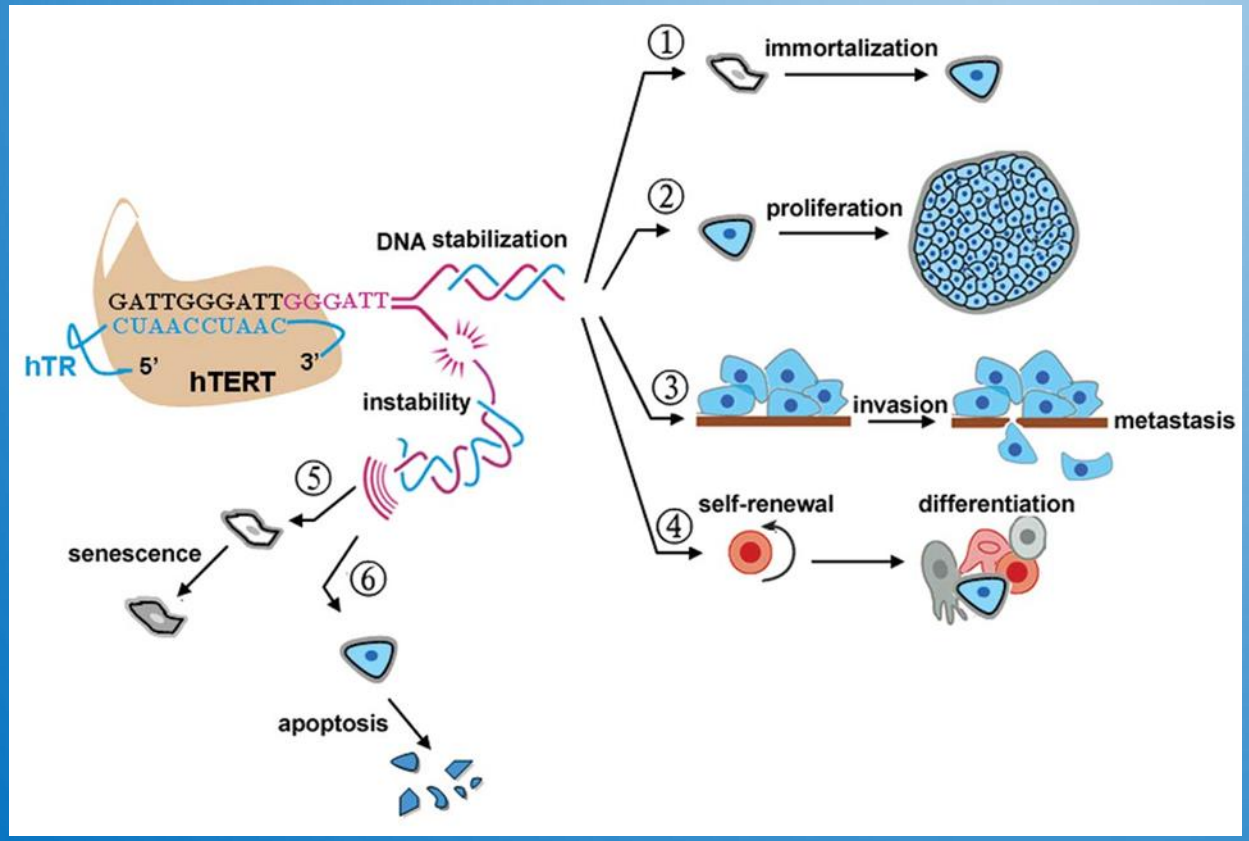
ORIGINAL RESEARCH PAPER Sahin, E. *et al.* Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* **470**, 359–365 (2011)

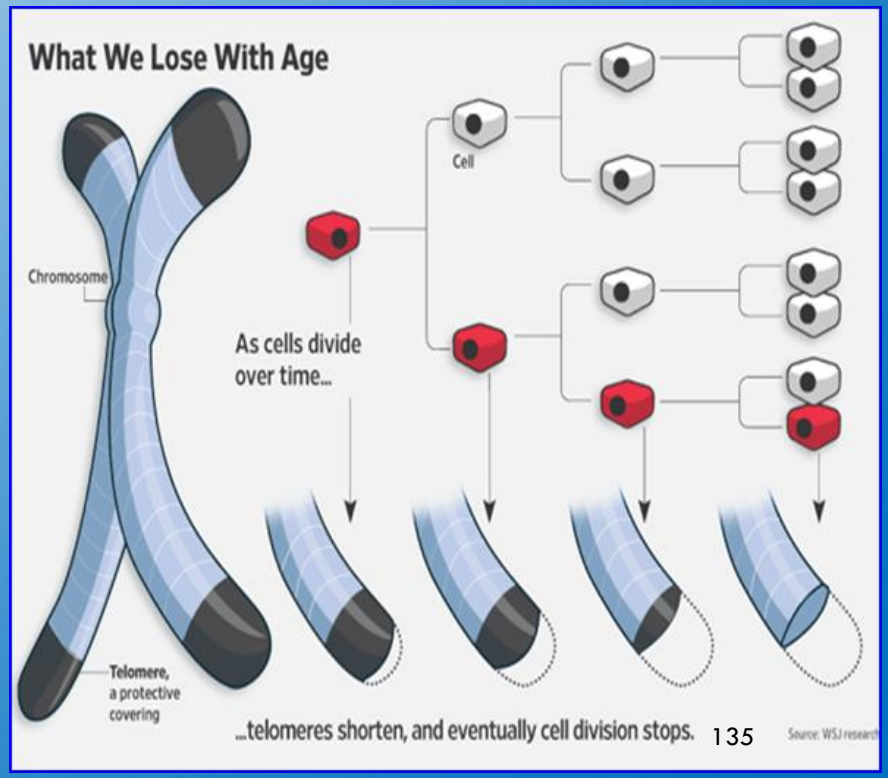
> telomere dysfunction can lead to defects in mitochondrial biology

There are mixed views as to what makes us age: one hypothesis proposes that ageing is caused by accumulating genotoxic stress provoked by the progressive loss of telomeres, which leads to replicative senescence and apoptosis, whereas another postulates that ageing is the result of progressive mitochondrial malfunction. A study by DePinho and colleagues now brings these two theories together by identifying a direct molecular link between telomere and mitochondrial dysfunction.

In highly proliferative tissues, age-related telomere decline is associated with telomere dysfunction and

TELOMERS, IMMORTALISATION





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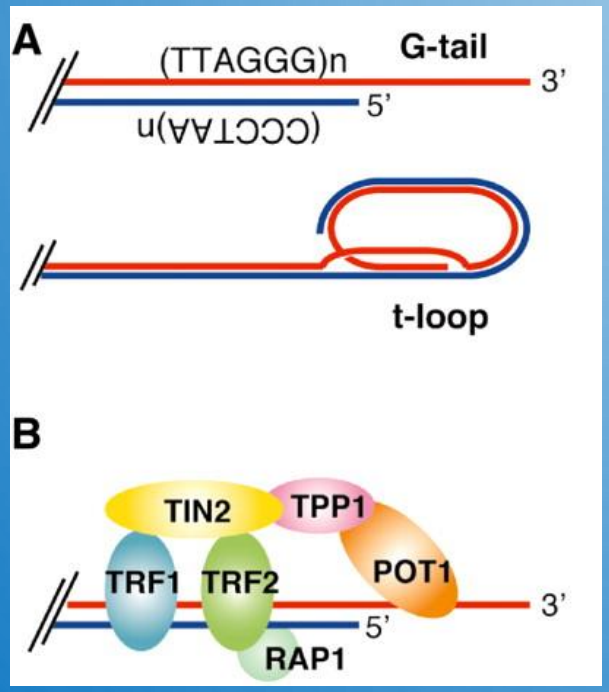
Telomere Structure und Function



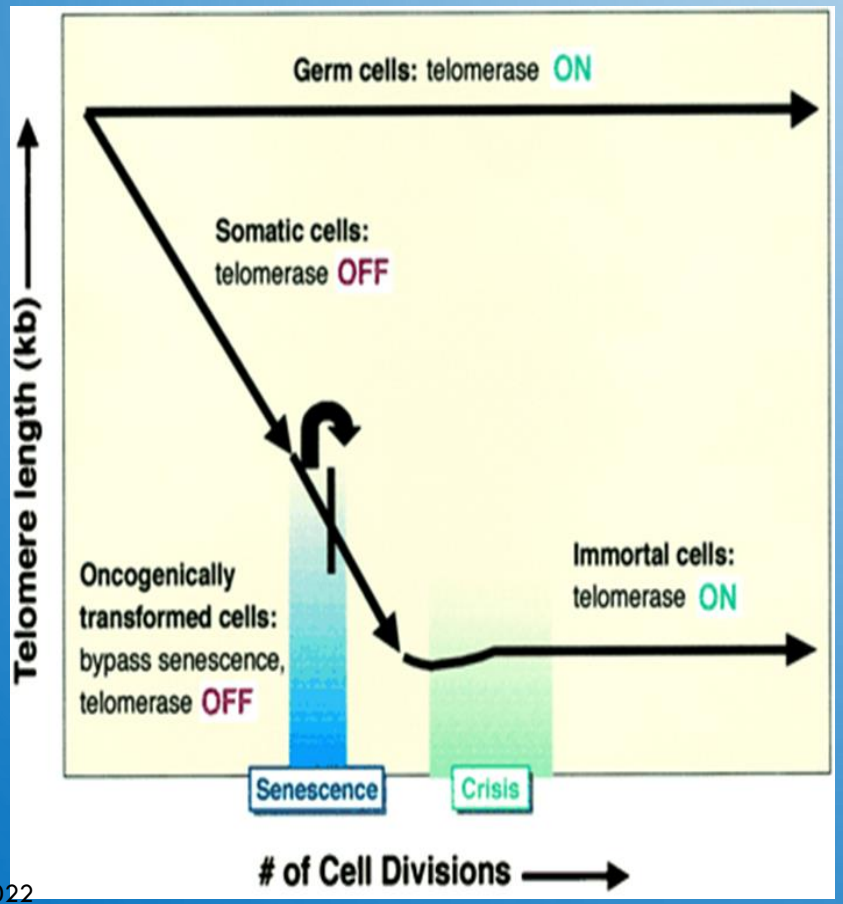
Consist of repeat sequences and associated proteins

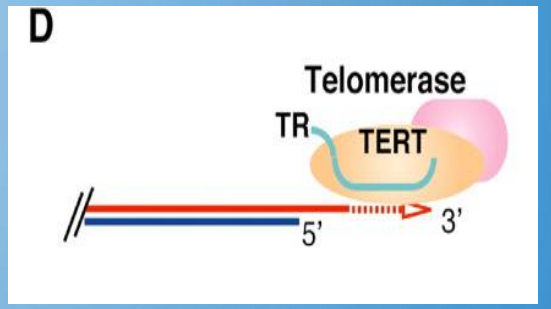
Cap the ends of chromosomes - protection against end-end-fusions, recombinations, degradation

Essential for chromosomal integrity

Nabetani A , and Ishikawa F J Biochem 2011;149:5-14

Telomerase, TERT



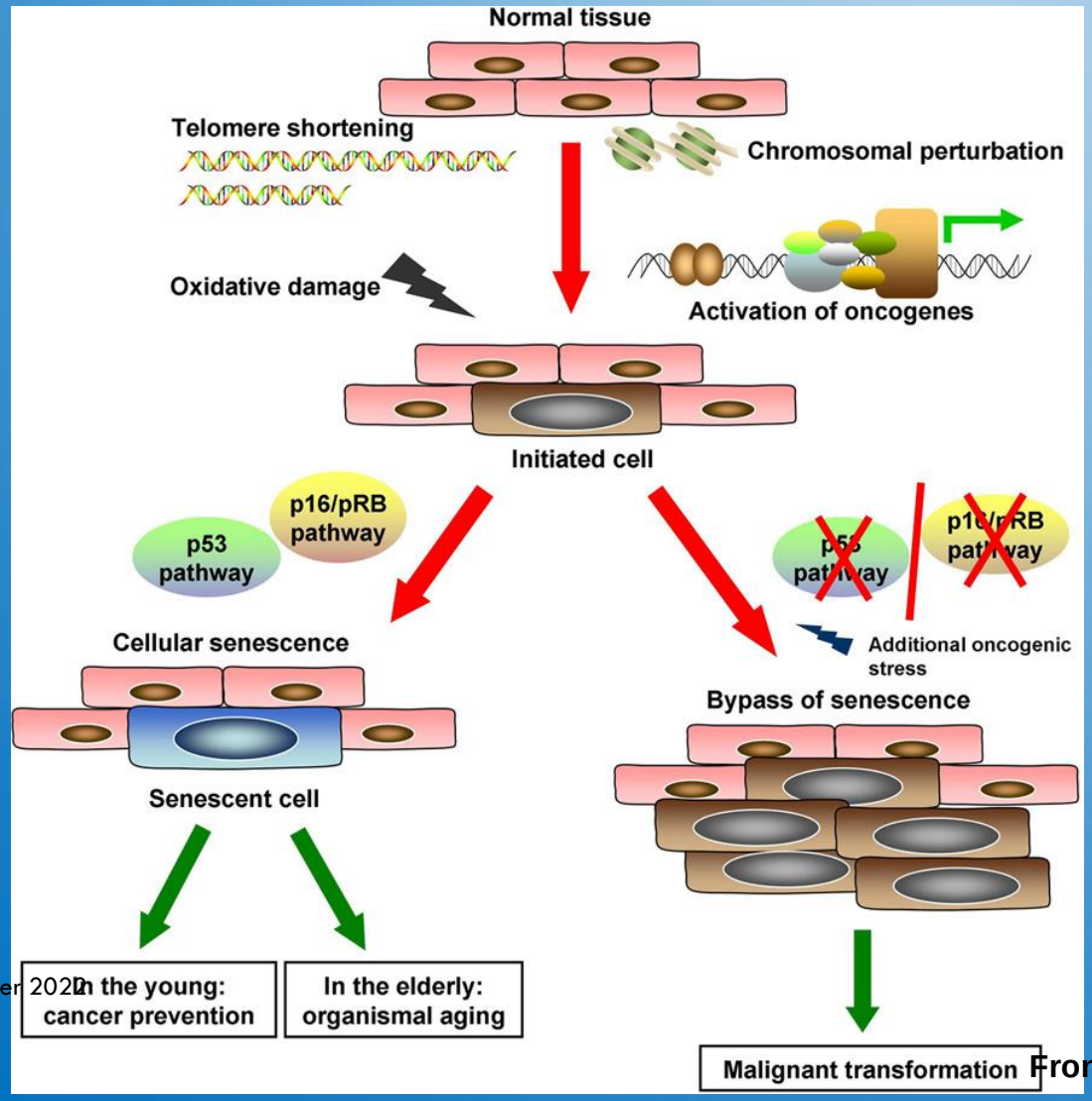


Composed of RNA subunits (hTR)
Reverse transcriptase catalytic subunit (hTERT)

Telomerase elongates telomeres which are shortened after each replication cycle

Journal of clinical oncology, Vol 18, Issue 13(Huly), 2000: 2626-2634

ROS: TELOMERE SHORTENING, SENESCENCE



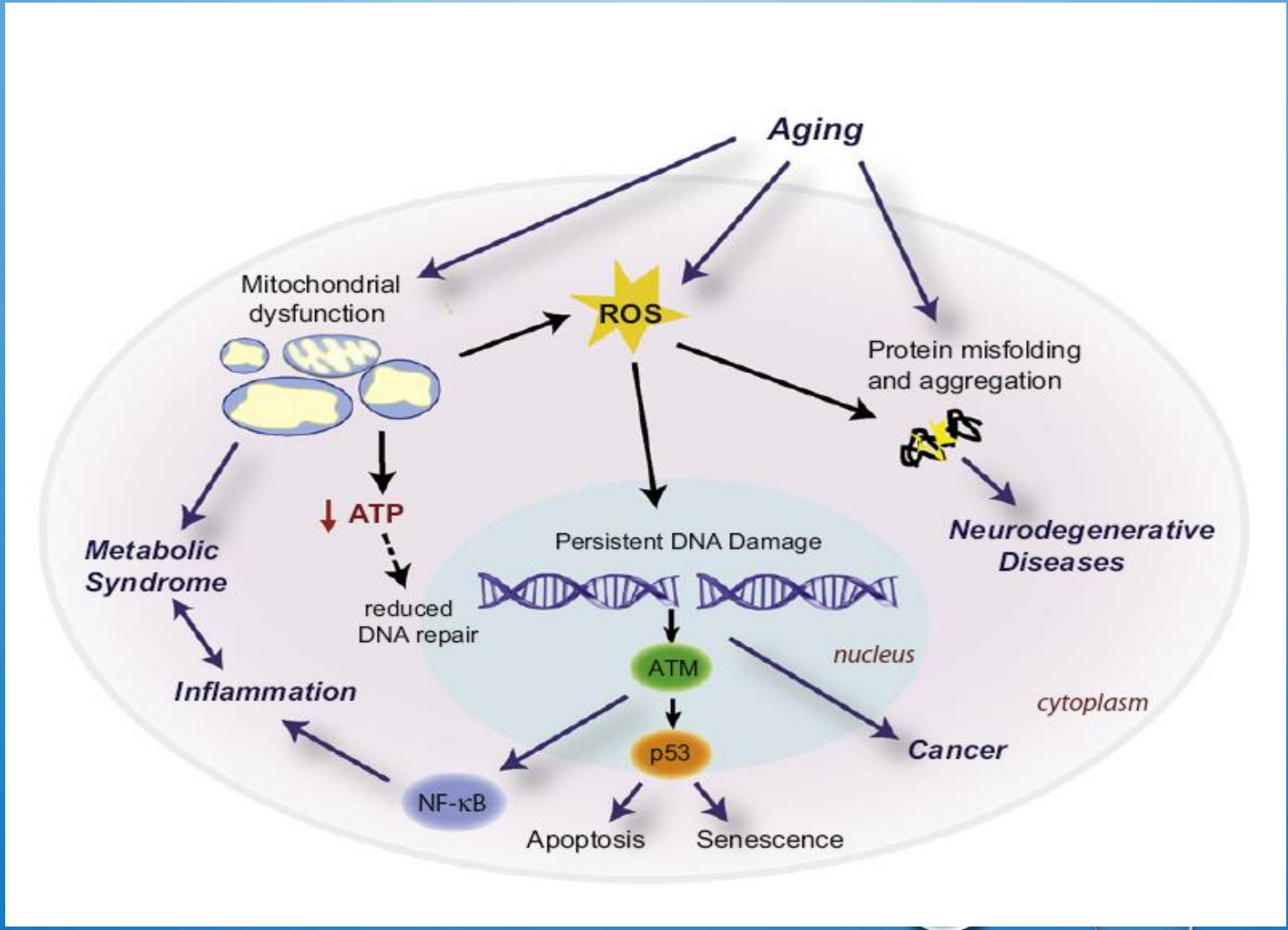
Frontiers in Bioscience 14, 4044-4057, January 1, 2009

METHODS FOR TELOMERE ANALYSIS

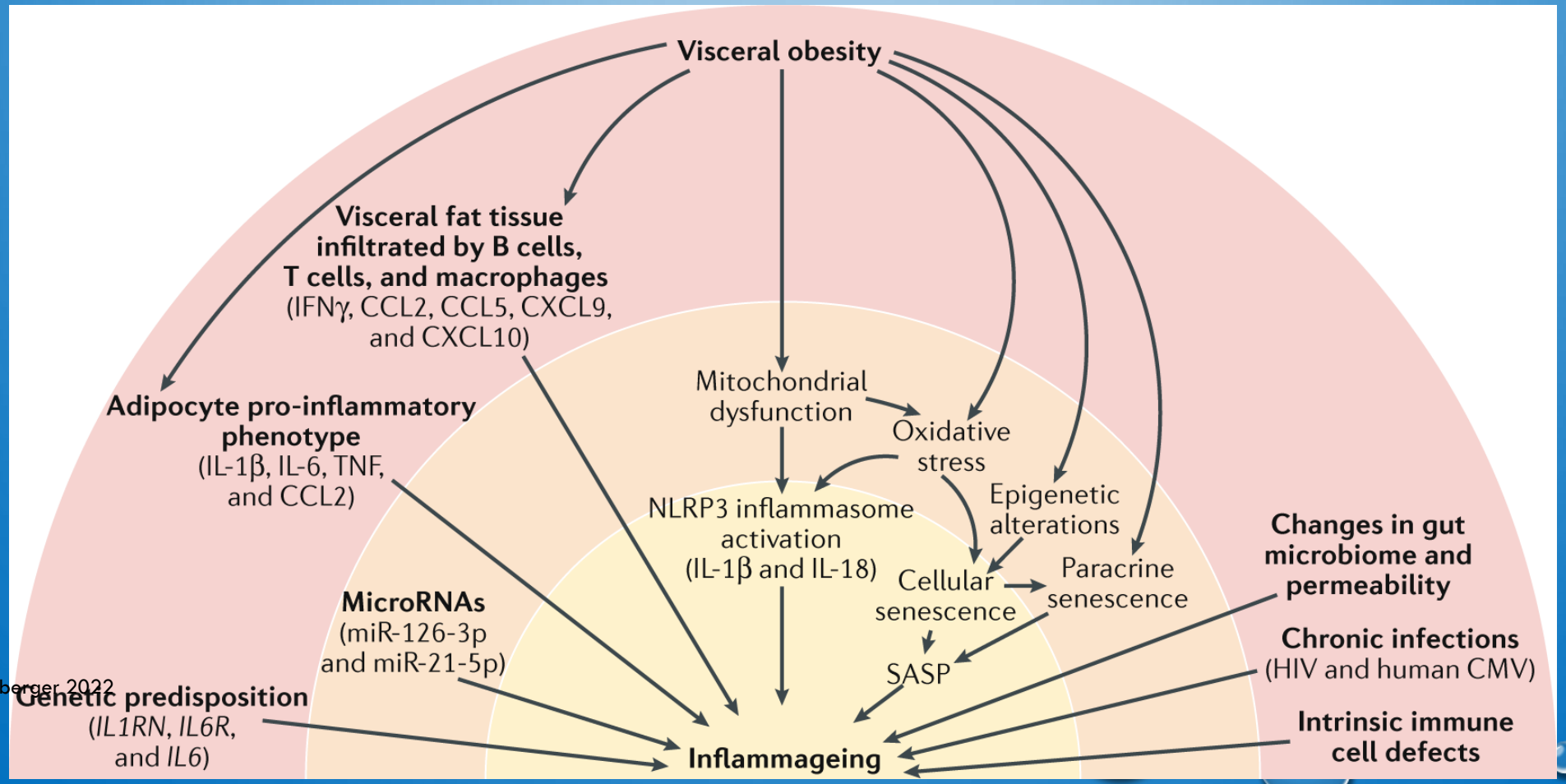
Table 1. Summary of the advantages and drawbacks of the main telomere length measurement methods

Method	Approach	Advantages	Drawbacks
Telomere Restriction Fragment (TRF)	Southern blot hybridization using probes against telomere repeats.	-Well known and widely used technique. -It has no special requirements in terms of reagents or equipment .	-Difficult to quantify. -Requires many cells (~106). -Provides and estimate of the average telomere length per sample -Subtelomeric polymorphism.
Telomere measurement by quantitative PCR	It measures the ratio of telomere repeat copy number to single copy gene copy number.	-Simple -Fast -Scalable to achieve a high throughput (HT) of samples.	-It quantifies the average telomere length per sample and cannot quantify individual telomeres.
Flow FISH	Based on the determination of telomere fluorescence in individual interphase cells using fluorescence-activated cell sorting (FACS) technology.	-Simple -Amenable to automatization, -Quantitative, reproducible, and accurate.	-Restricted to isolated cells, and cell suspensions. -Requires expensive and technical demanding system. -Not many samples (<20) are processed and analyzed at the same time. -It quantifies the average telomere length per cell.
Metaphases quantitative FISH	Based on the use of digital fluorescence microscopy to determine telomere fluorescence after hybridization of metaphase spreads with a fluorescent PNA telomeric probe.	-Permits the measurement of telomere length at each individual chromosome end. -Allows quantification of the number of "signal-free ends" (<0.15 kb) -High accuracy.	-Labor-intensive and time consuming (week/s) -Requires expensive and technical demanding system. -External calibration (from auf to kb) -Many controls required to avoid inter/intra-session variability. -Very few samples are analyzed at the same time.
Single Telomere Length Analysis (STELA)	It is a ligation PCR-based method.	-It requires no specialized equipment. - It requires very limited starting material	-It is usually restricted to several well characterized chromosome ends: XpYp, 2p, 11q and 17p. -It is limited in the analysis of long telomeres (typically >20kb). -Labor intensive and low throughput.

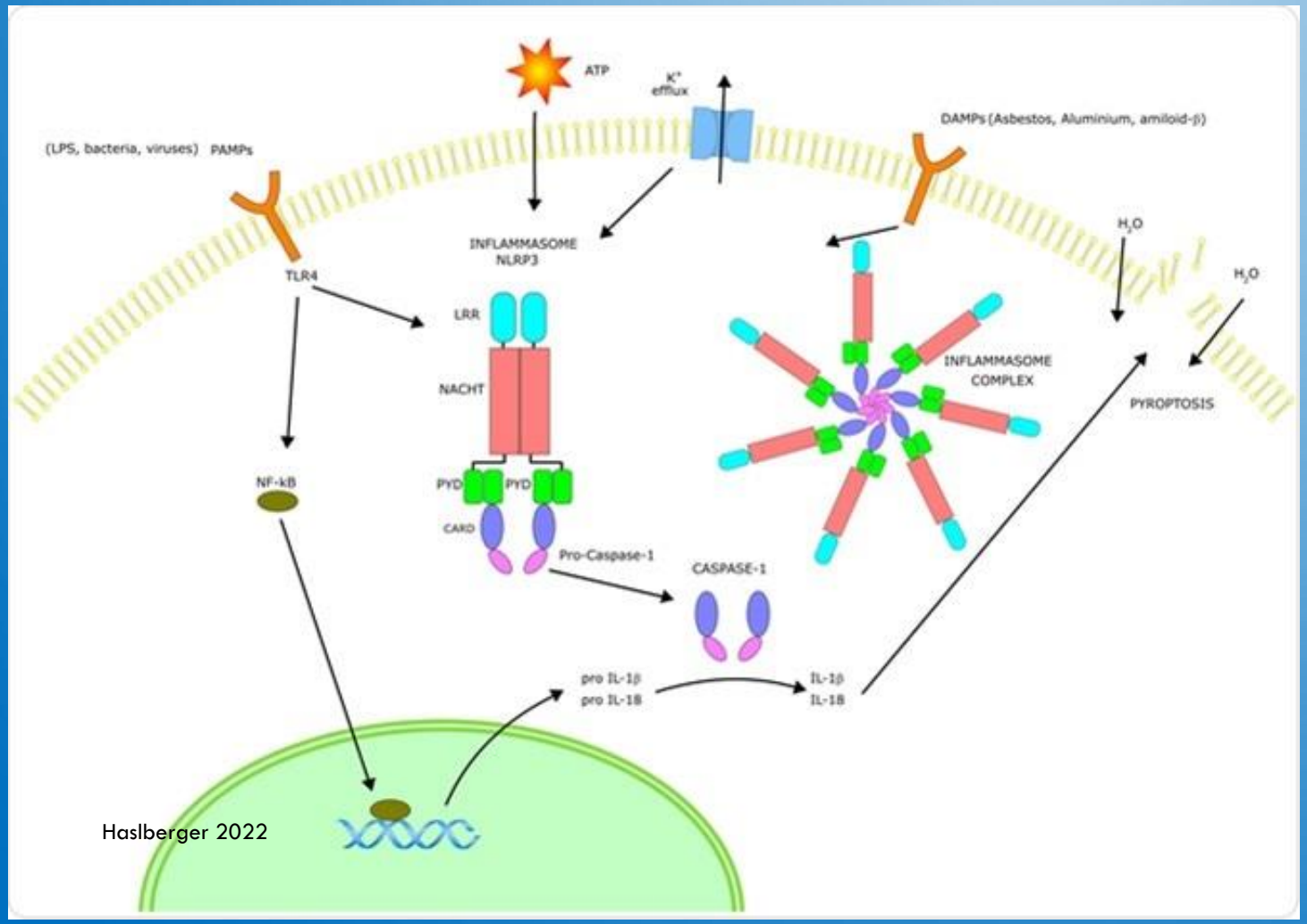
AGEING, INFLAMMATION AND DNA DAMAGE



INFLAMMAGEING: CHRONIC INFLAMMATION IN AGEING, CARDIOVASCULAR DISEASE, AND FRAILTY



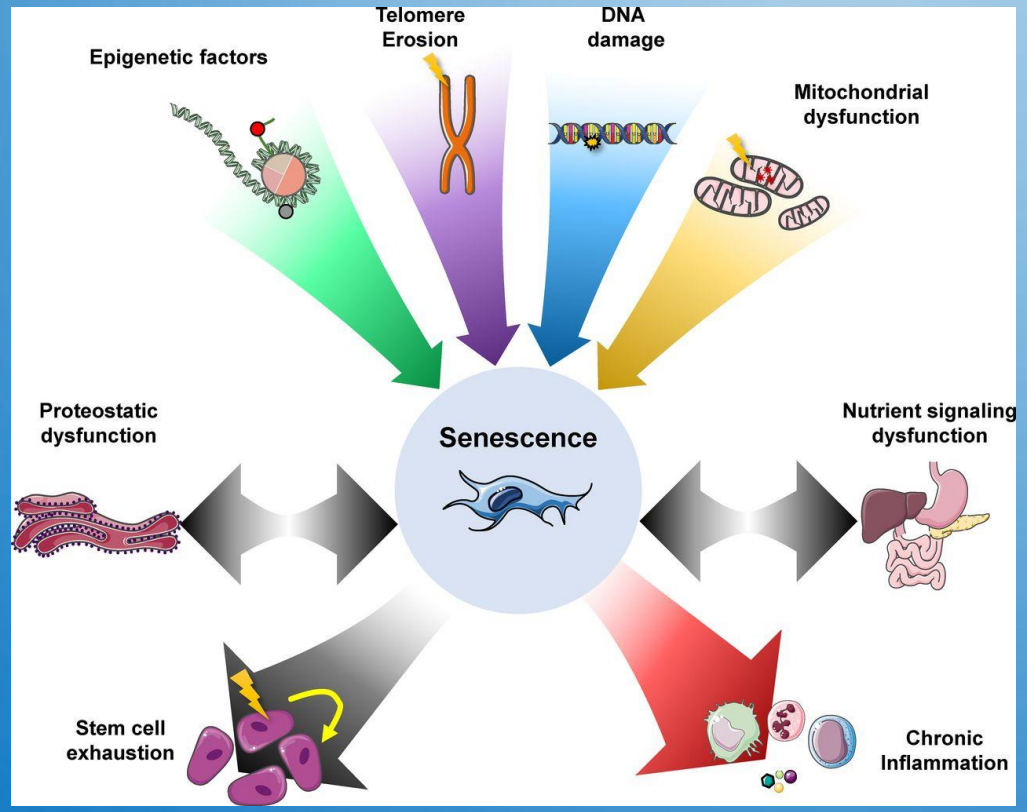
INFLAMMASOME



The inflammasomes are **innate immune system receptors and sensors that regulate the activation of caspase-1 and induce inflammation in response to infectious microbes and molecules derived from host proteins**

AGING MECHANISMS AND SENESCENCE

„IN GENERAL SENESCENCE CAN BE BENEFICIAL, THUS ELIMINATING DAMAGED CELLS, WHEREAS AN ACCUMULATION CAN BE DETRIMENTAL"

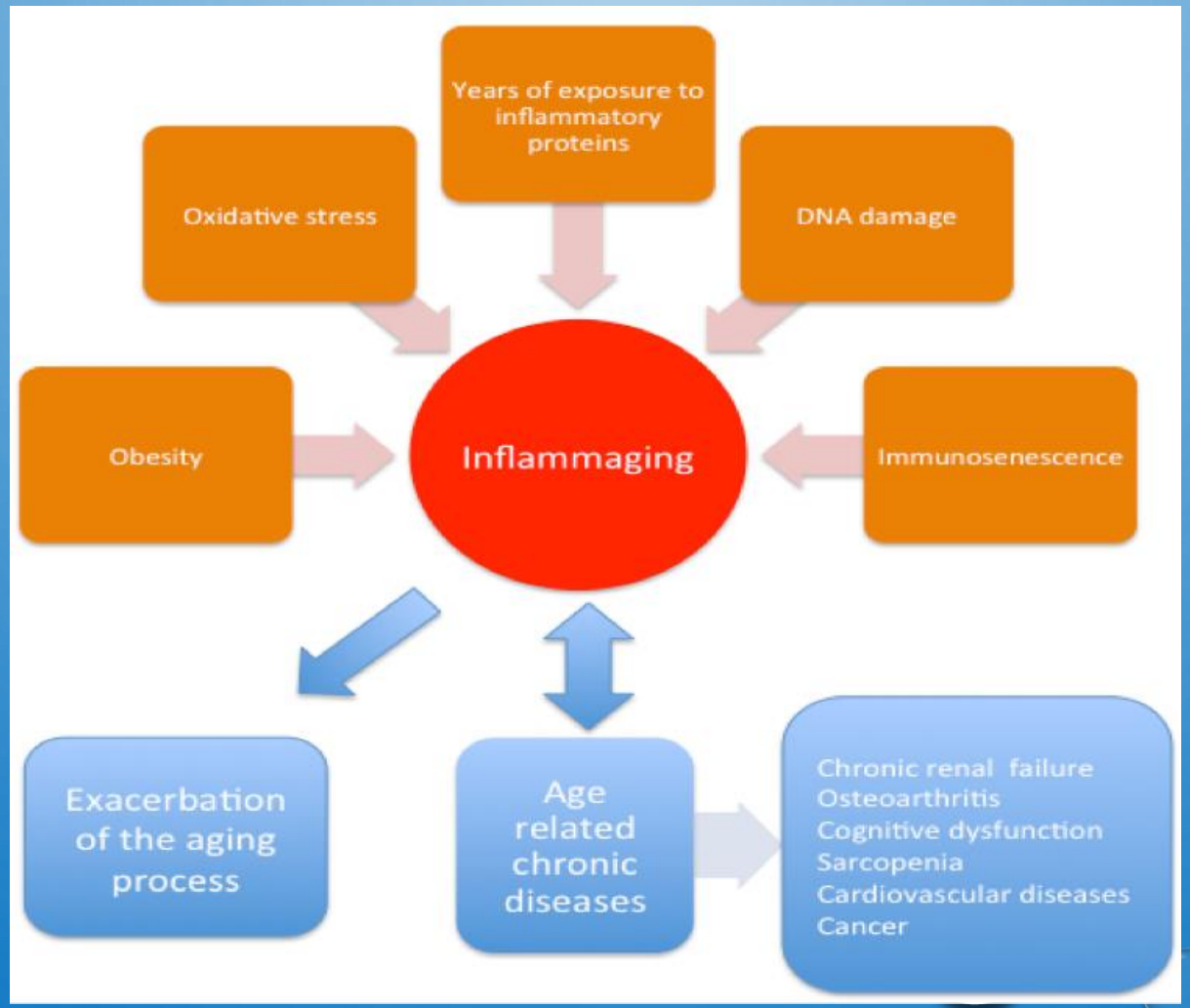


Senescence : The good, the bad, the carefully regulated

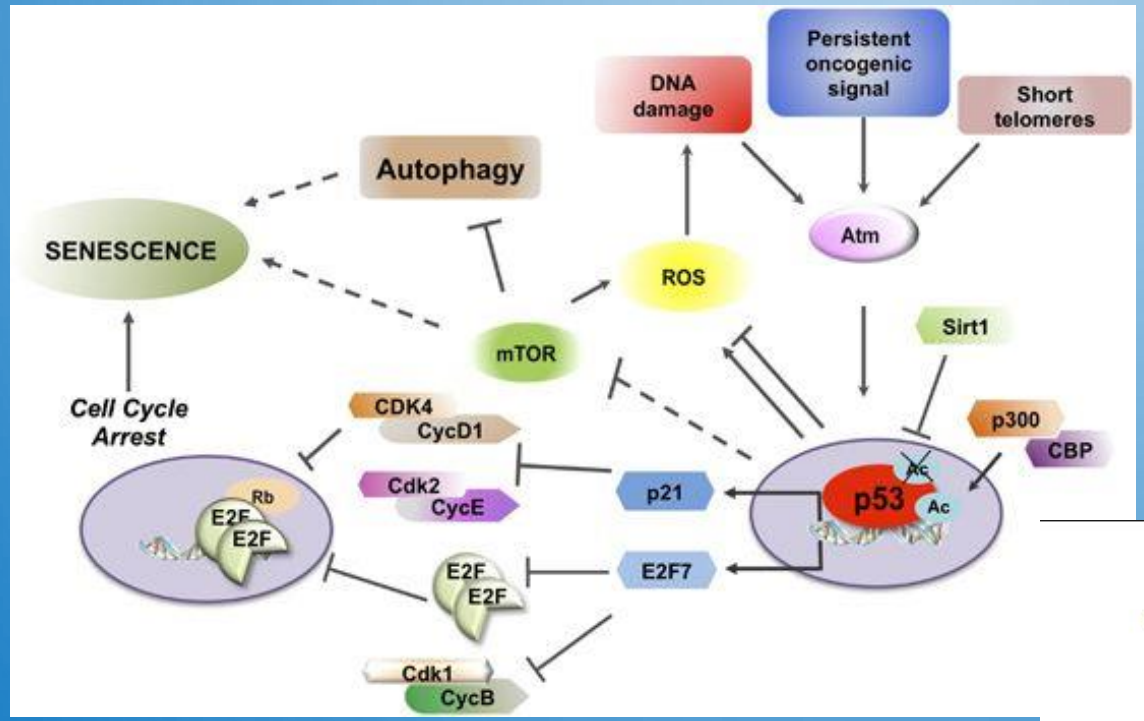
replicative senescence, DNA damage induced senescence, stress induced senescence and oncogene induced senescence

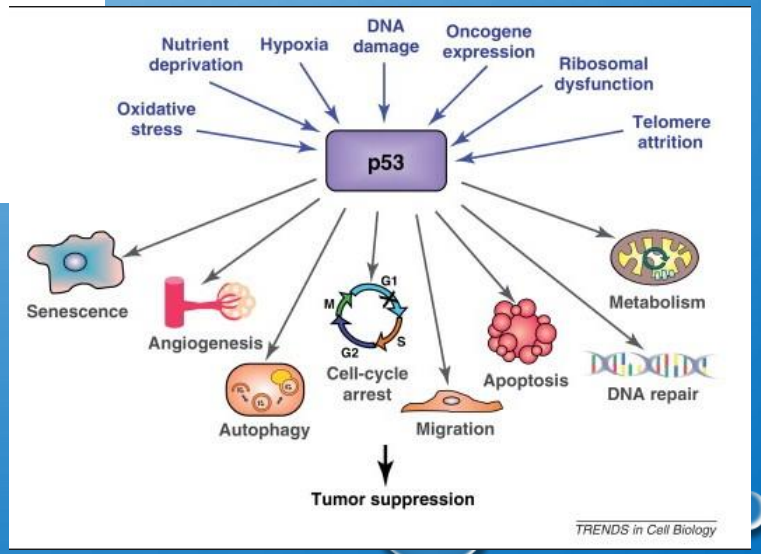
Domhnall McHughand Jesús Gil, JCB 2017

INFLAMM-AGEING IN CENTER OF AGEING AND MANY COMPLEX DISEASES E.G. OBESITY



SENESCENCE INVOLVED PATHWAYS: SIRT AND MTOR PATHWAY; P53-HSP70-AUTOPHAGY; NRF2-ROS, HSP90-STRESS, CDKS,…

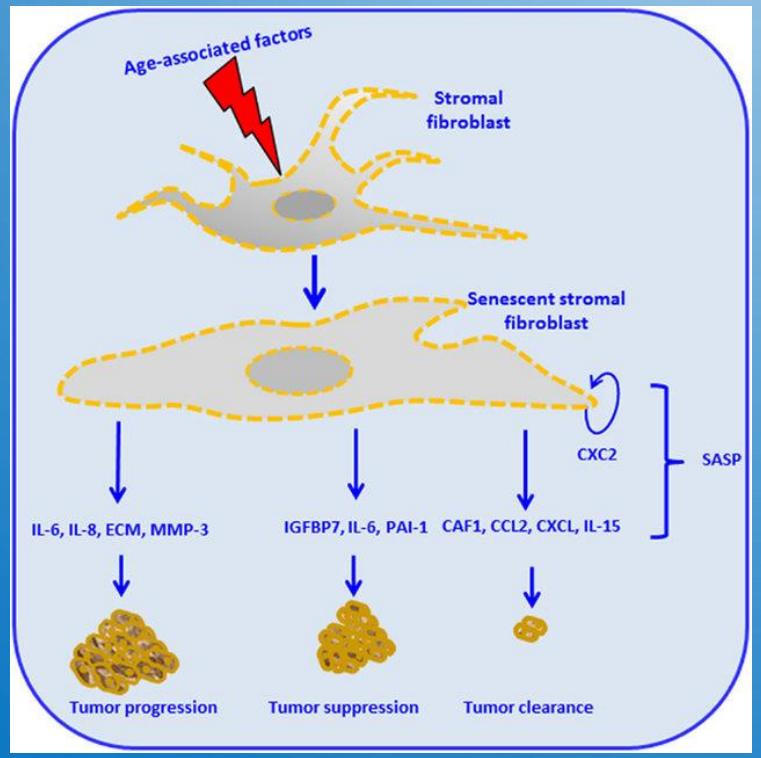




Senescence is a cellular program that induces a stable growth arrest chromatin remodeling, metabolic reprogramming, increasedautophagy, and the implementation of a complex proinflammatory secretome. first identified by Hayflick and Moorhead (1961)

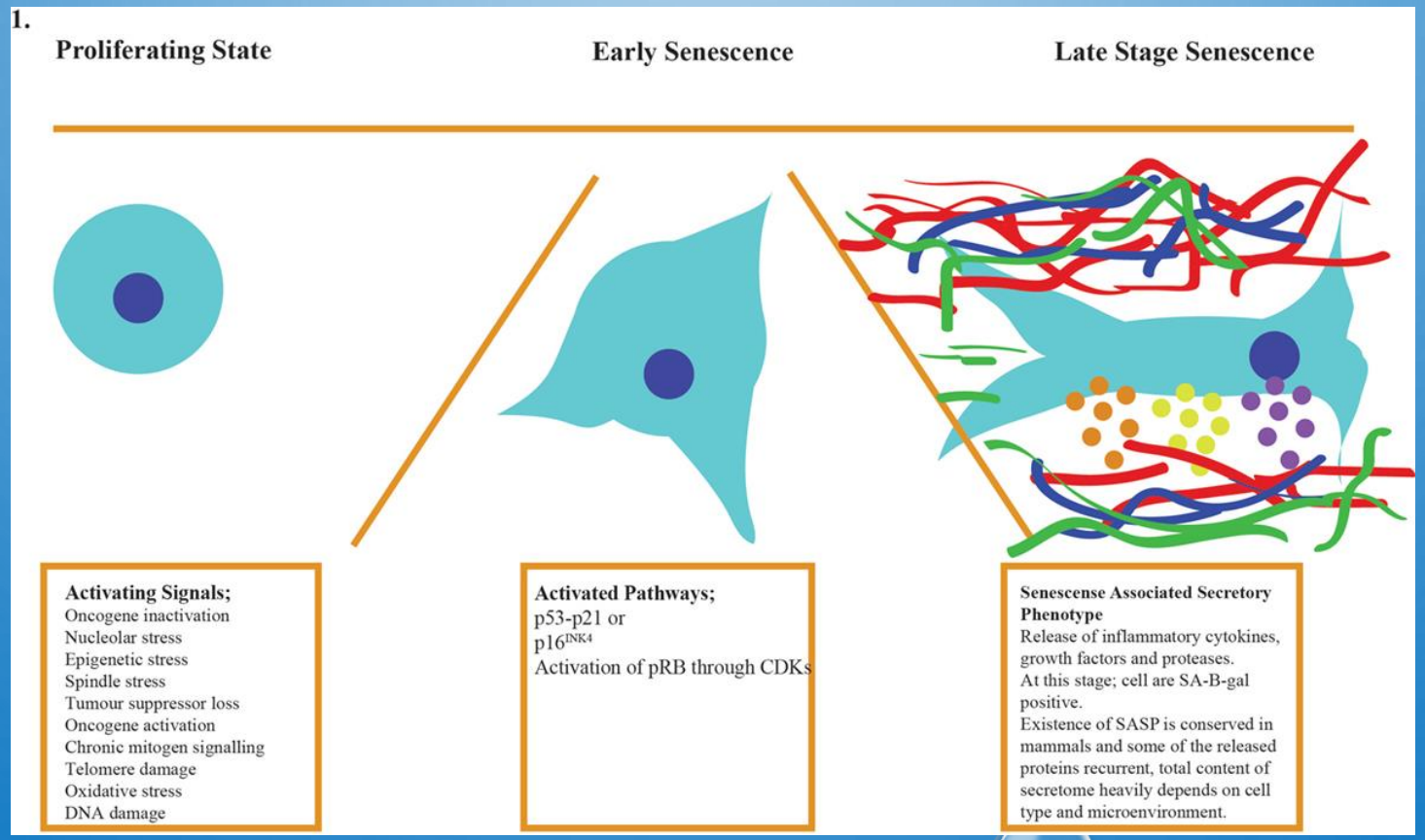
SENESCENCE AND THE SENESCENCE ASSOCIATED SECRETORY PATHWAY

Senescent cells negatively affect their surrounding tissue by losing their cell specific functionality and by secreting a pro-tumorigenic and pro-inflammatory mixture of growth hormones, chemokines, cytokines and proteases, termed the **senescence-associated secretory phenotype (SASP)**

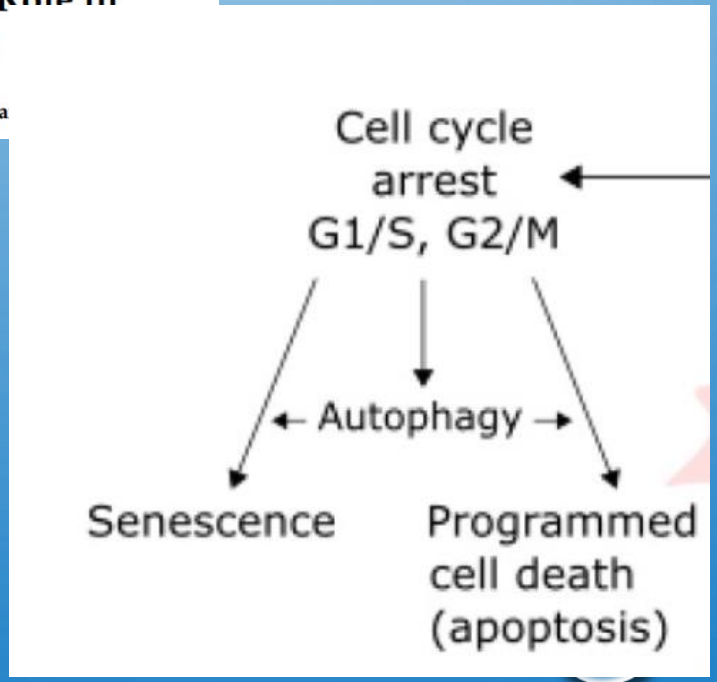


SASP recruits immune cells to eliminate senescent cells but also contributes to inflammaging

THE SEQUENCE OF SENESCENCE UNTIL BETA-GAL POSITIVE



BALANCED REGULATION BETWEEN SENESCENCE,CELL CYCLE ARREST, AUTOPHAGY AND APOPTOSIS



(and mitophagy ?)

EPIGENETIC REGULATION OF SENESCENCE: CPG METHYLATION, HISTONE MODIFICATION AND MIRNAS

frontiers in Genetics

REVIEW
published: 26 September 2017
doi: 10.3389/fgene.2017.00138

Epigenetic Regulation of Cellular Senescence and Aging

*Corinne Sidler, Olga Kovalchuk and Igor Kovalchuk**

Review Article

MicroRNA Regulation of Oxidative Stress-Induced Cellular Senescence

Huaije Bu, Sophia Wedel, Maria Cavinato, and Pidder Jansen-Dürr

Institute for Biomedical Aging Research and Center for Molecular Biosciences Innsbruck (CMBI), Universität Innsbruck, Innsbruck, Austria

Correspondence should be addressed to Huaije Bu; huajie.bu@uibk.ac.at

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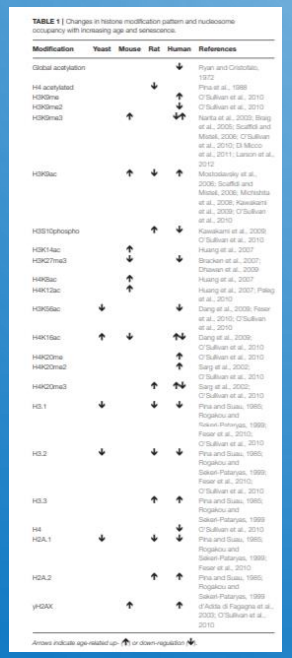


TABLE 1 | Changes in histone modification pattern and nucleosome occupancy with increasing age and senescence.

Modification	Yeast	Mouse	Rat	Human	References
Global acetylation				↓	Ryan and Cristofalo, 1972
H4 acetylated			↓		Pina et al., 1988
H3K9me				↑	O'Sullivan et al., 2010
H3K9me2				↓	O'Sullivan et al., 2010
H3K9me3		↑		↑↓	Narita et al., 2003; Braig et al., 2005; Scaffidi and Misteli, 2006; O'Sullivan et al., 2010; Di Micco et al., 2011; Larson et al., 2012
H3K9ac		↑	↓	↑	Mostoslavsky et al., 2006; Scaffidi and Misteli, 2006; Michishita et al., 2008; Kawahara et al., 2009; O'Sullivan et al., 2010
H3S10phospho			↑	↓	Kawahara et al., 2009; O'Sullivan et al., 2010; Huang et al., 2007
H3K14ac		↑			Bracken et al., 2007; Dhawan et al., 2009
H3K27me3		↓		↓	Huang et al., 2007
H4K8ac		↑			Huang et al., 2007; Pelegi et al., 2010
H4K12ac		↑			Dang et al., 2009; Feser et al., 2010; O'Sullivan et al., 2010
H3K56ac	↓			↓	Dang et al., 2009; O'Sullivan et al., 2010
H4K16ac	↑	↓		↑↓	O'Sullivan et al., 2010
H4K20me				↑	O'Sullivan et al., 2010
H4K20me2				↑	Sarg et al., 2002; O'Sullivan et al., 2010
H4K20me3			↑	↑↓	Sarg et al., 2002; O'Sullivan et al., 2010
H3.1	↓		↓	↓	Pina and Suau, 1985; Rogakou and Sekeri-Pataryas, 1999; Feser et al., 2010; O'Sullivan et al., 2010
H3.2	↓		↓	↓	Pina and Suau, 1985; Rogakou and Sekeri-Pataryas, 1999; Feser et al., 2010; O'Sullivan et al., 2010
H3.3			↑	↑	Pina and Suau, 1985; Rogakou and Sekeri-Pataryas, 1999
H4				↓	O'Sullivan et al., 2010
H2A.1	↓		↓	↓	Pina and Suau, 1985; Rogakou and Sekeri-Pataryas, 1999; Feser et al., 2010
H2A.2			↑	↑	Pina and Suau, 1985; Rogakou and Sekeri-Pataryas, 1999
γH2AX		↑		↑	d'Adda di Fagagna et al., 2003; O'Sullivan et al., 2010

Arrows indicate age-related up- (↑) or down-regulation (↓).

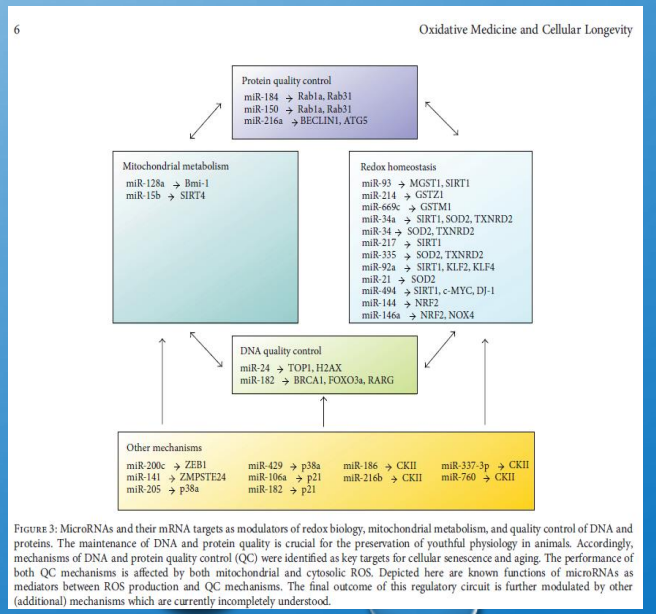
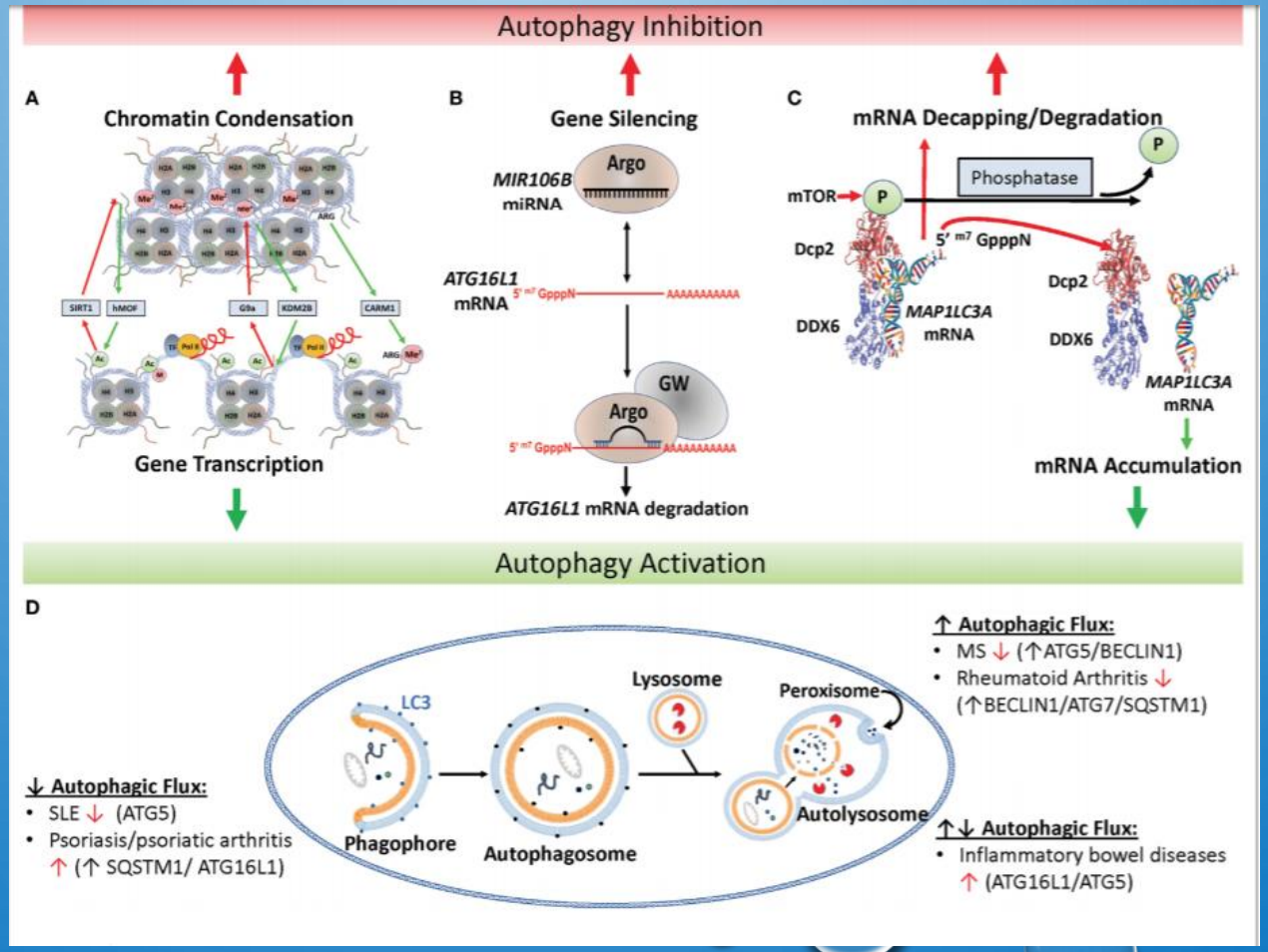


FIGURE 3: MicroRNAs and their mRNA targets as modulators of redox biology, mitochondrial metabolism, and quality control of DNA and proteins. The maintenance of DNA and protein quality is crucial for the preservation of youthful physiology in animals. Accordingly, mechanisms of DNA and protein quality control (QC) were identified as key targets for cellular senescence and aging. The performance of both QC mechanisms is affected by both mitochondrial and cytosolic ROS. Depicted here are known functions of microRNAs as mediators between ROS production and QC mechanisms. The final outcome of this regulatory circuit is further modulated by other (additional) mechanisms which are currently incompletely understood.

AUTOPHAGY IS REGULATED EPIGENETICALLY



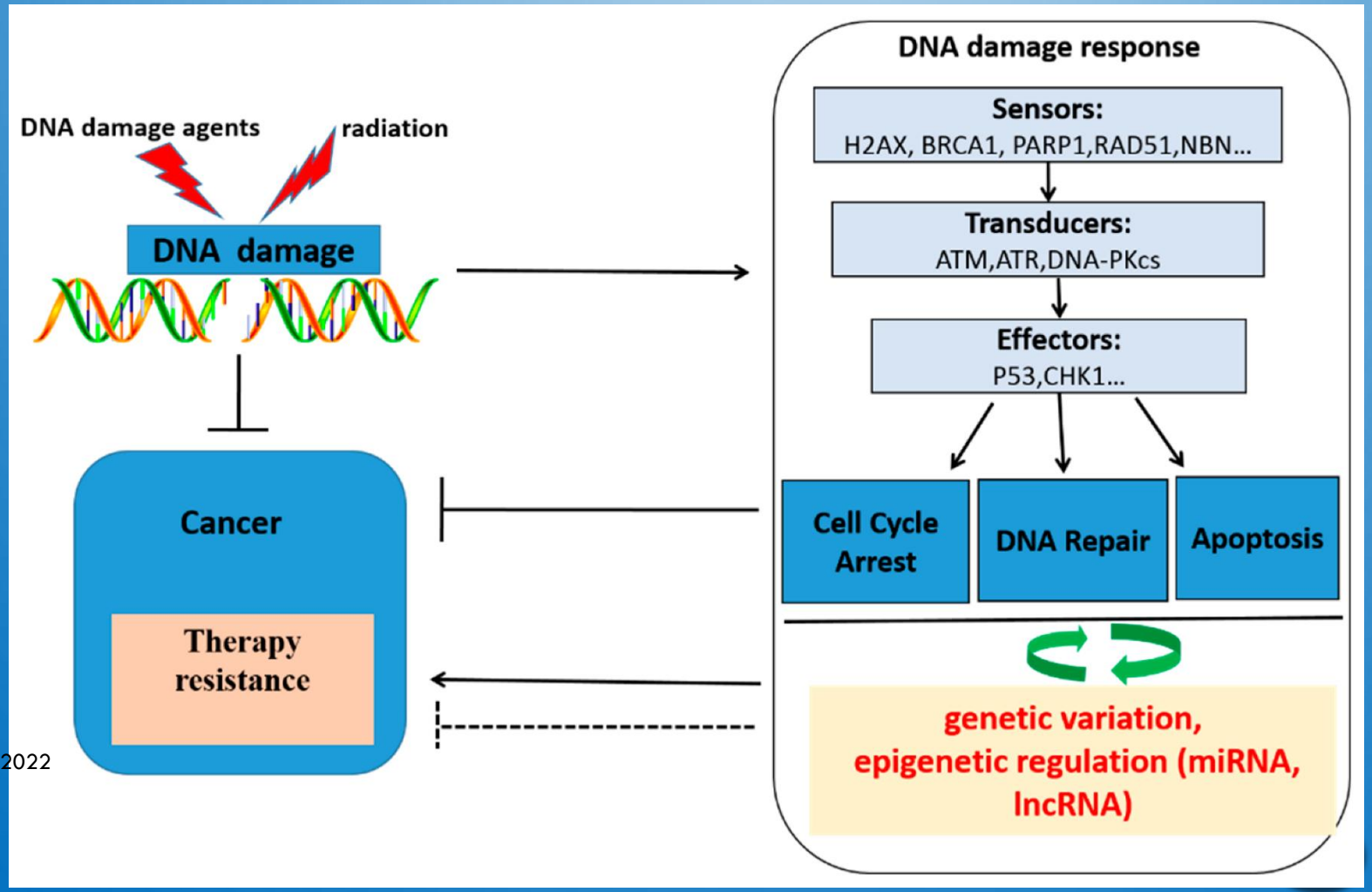
EPIGENETICS AND AUTOPHAGY

TABLE 1 | Epigenetic regulators associated with autophagy and immunity.

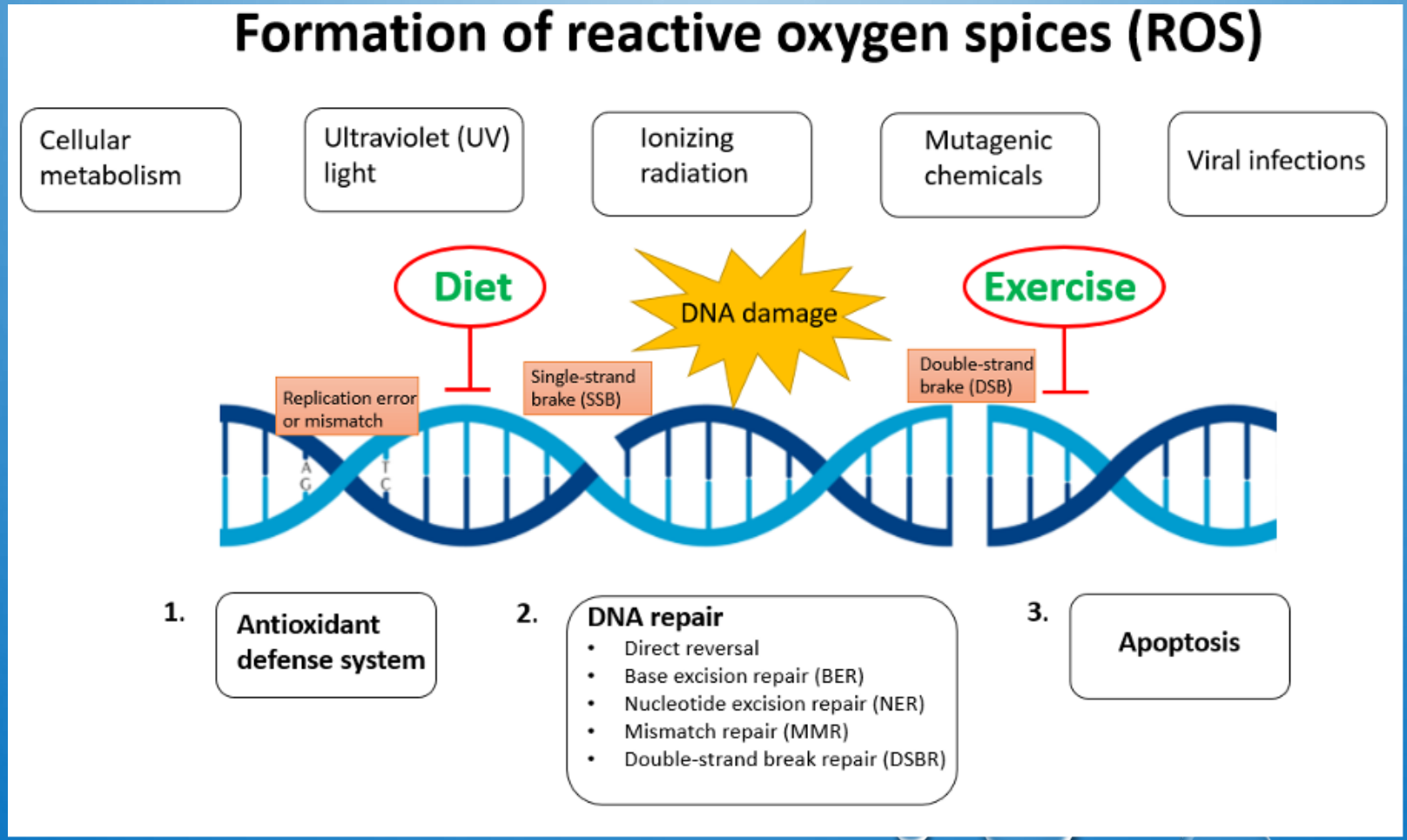
Histone modification

Histone modification	Regulator	Effect on autophagy	Immune phenotype	Disease implicated	Reference
H3K9Ac	SIRT6	↑ATG5	Inhibition of NOTCH/NF-κB signaling	Proteinuric kidney disease	(50–52)
H4K16Ac (H1.2 variant)	SIRT1/HDAC1	↑Autophagy	Inflammation	Diabetic retinopathy	(53)
H3K9me	HIF-1α, KDMs	↑BNIP3	Reactive oxygen species response	Traumatic brain injury/tumors	(51, 54)
H3R17me2	TFEB/co-activator-associated arginine methyltransferase 1	↑ATG14	Myeloid differentiation, SWI/SNF	Unknown	(39, 55, 56)
H4R3me2	C/EBPβ/PRMT5	Unknown	IL-8, TNFα expression	Unknown	(57)
Multiple	HDAC6	SQSTM1 autophagic clearance	Interferon response pathway	Viral/bacterial clearance	(58, 59)
Histone deacetylase inhibitors (HDACi)					
Drug	**Regulator**	**Effect on autophagy**	**Immune phenotype**	**Diseases treated with HDACi**	**Reference**
Vorinostat	HDACs	↑Autophagosome formation (ATG5)	Viral myocarditis	Cutaneous T-cell lymphoma	(60)
Vorinostat	HDACs	Unknown	CD4 and CD8 tumor immunity	Metastatic colorectal cancer	(61)
Vorinostat	HDACs	↑Autophagy (ATG5)	NF-κB signaling, VSV oncolysis	See diseases treated above	(62)
Tubastatin A	HDAC6	↑Autophagy (ATG7)	TNFα, IL-6 cisplatin toxicity	Acute kidney injury/pancreatic cancer	(49, 63)
Panobinostat	HDACs	↑Autophagy (LC3)	Lymphocyte tumor killing, TNFα	Hodgkin lymphoma/multiple myeloma	(64, 65)
Multiple	HDACs	↑Autophagic flux (ULK1/ATG7)	Reverse HIV-1 latency	Peripheral T-cell lymphoma	(66)
Multiple	HDACs	↓Autophagy (ATG7)	Apoptosis induction	DS-AMKL (proposed)	(67)
microRNA (miRNA) regulation of autophagy					
miRNA		**Effect on autophagy**	**Immune phenotype**	**Disease implicated**	**Reference**
miR-30a		↓BECN1 (↓autophagy)	Unknown	Cancer	(68)
miR-30b		↓Autophagy (↓ATG12, BECN1)	Intracellular survival of *Helicobacter pylori*	Cancer	(69, 70)
miR-106b, miR-93		↓Autophagy (↓ATG16L1)	Defects in bacterial clearance, inflammation	Crohn's disease	(71)
miR-142-3p		↓ATG16L1	Intestinal inflammation	Crohn's disease	(72)
miR-30c, miR-130a		↓Autophagy (↓ATG5, ATG16L1)	Invasive *Escherichia coli*, NF-κB activation, inflammation	Crohn's disease	(73)
miR-196		↓IRGM (↓autophagy)	Mitochondrial function, ineffective *Mycobacterium tuberculosis* (*Mtb*) and *E. coli* control	Crohn's disease	(74, 75)
miR-210		↓Bcl-2	HIF-1α pathways, hypoxia-induced apoptosis, TH_{17} differentiation	Traumatic brain injury	(76, 77)
miR-21		↓IL-12p35, ↓Bcl-2	NF-κB activation, impaired anti-mycobacterial T cell responses	*Mtb* infection, asthma	(78, 79)
miR-17, -20, -93, -106		↓SQSTM1	Elevated P-ERK levels, enhanced hematopoiesis	Acute myeloid leukemia	(80)
miR-155, -31		↓PPP2R5A (↓autophagy)	↓JAK-STAT ↑WNT-SHH, Th2 polarization	Mycobacteria, *Shigella*, *Listeria* infection	(81)
miR-UL148d (HCMV)		↓ERN1 (↓autophagy)	Inhibition of apoptosis, impaired anti-viral response	HCMV infection	(82)
miR-1303		↓ATG2B (↓autophagy)	Suppression of mycobacteria-induced autophagy, ↓TNF-α	*Mtb* infection	(83)
miR-471-5p		↓LC3, ↓ATG12, ↓BECN1	LC3-associated phagocytosis, apoptotic germ cells	Male infertility	(84)
miR-155		↓ATG3 (↓autophagy)	Suppression of anti-*Mtb* dendritic cell response	*Mtb* infection	(85)
miR-155		↓RHEB (↑autophagy)	Enhanced killing of intracellular *Mtb*	*Mtb* infection	(86)

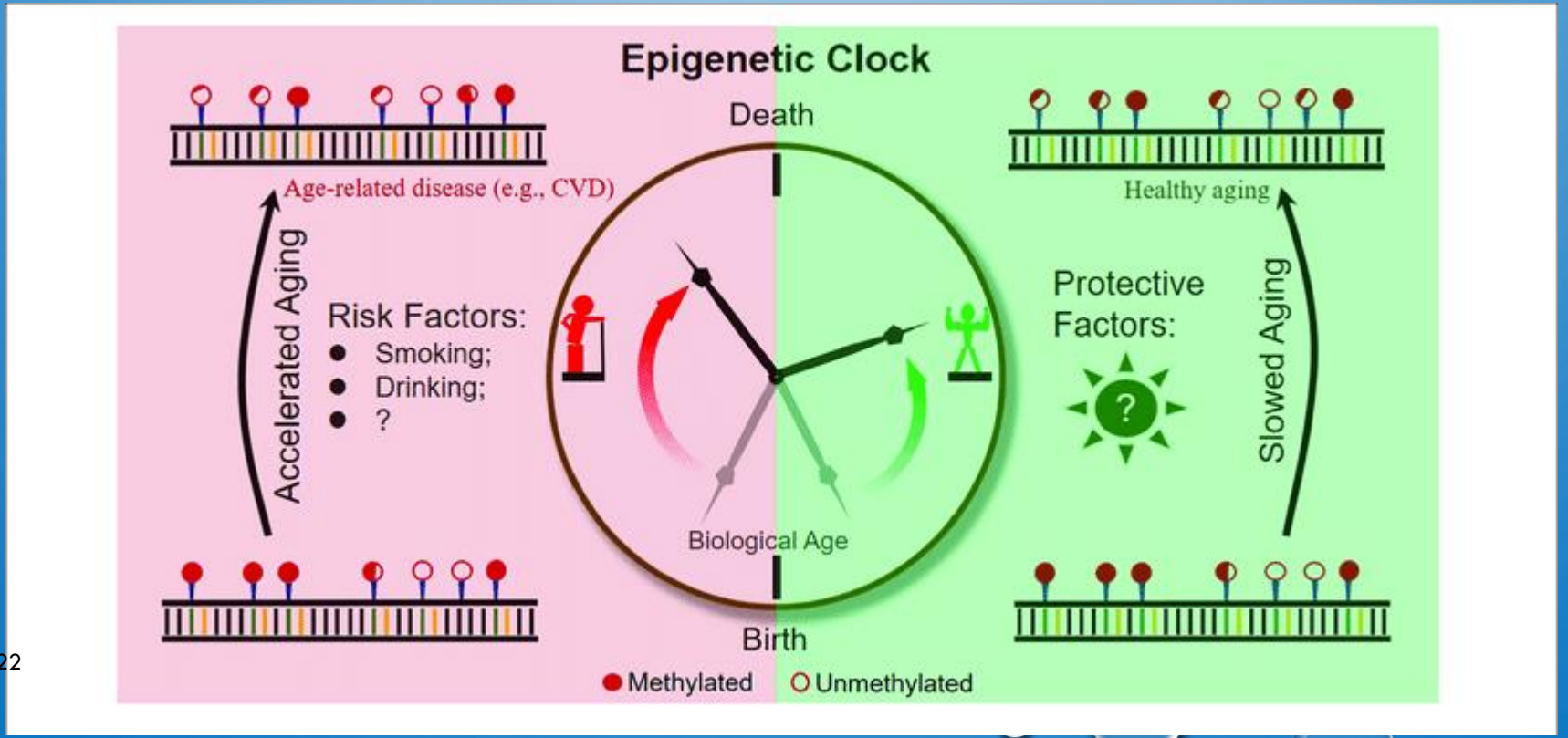
EPIGENETICS REGULATES DNA REPAIR



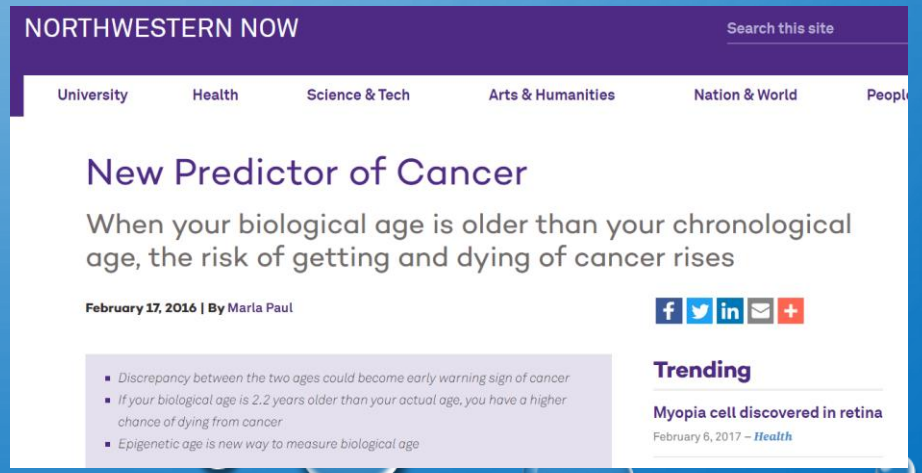
DNA BREAKS, REPAIR



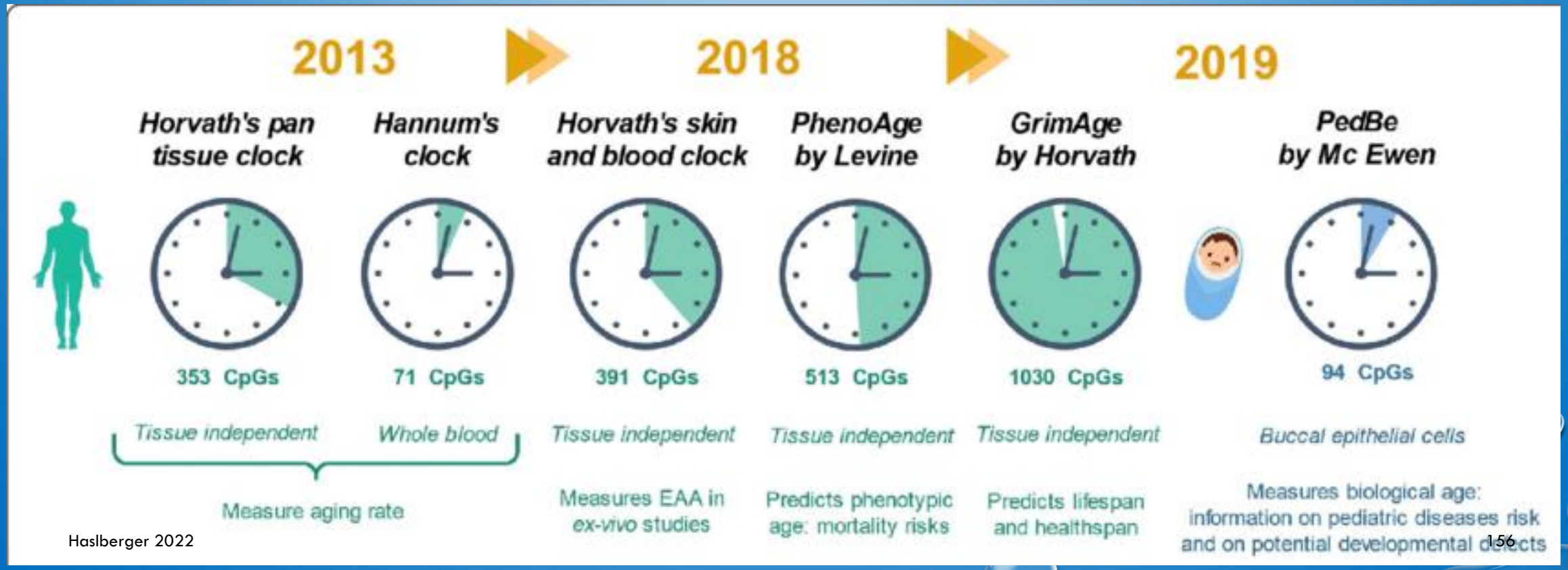
AGING AND CPG METHYLATION, THE EPIGENETIC CLOCK



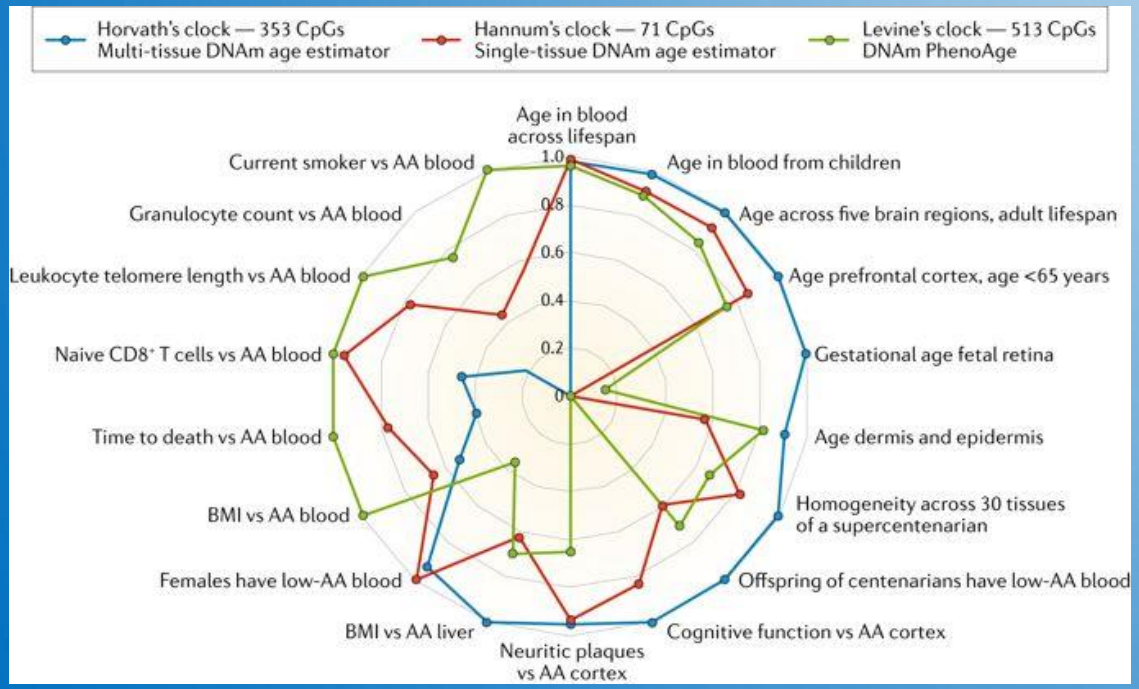
BIOLOGICAL AGE: NICE TO KNOW OR BIOLOGICAL RELEVANCE? E.G. RISK FOR COMPLEX DISEASES

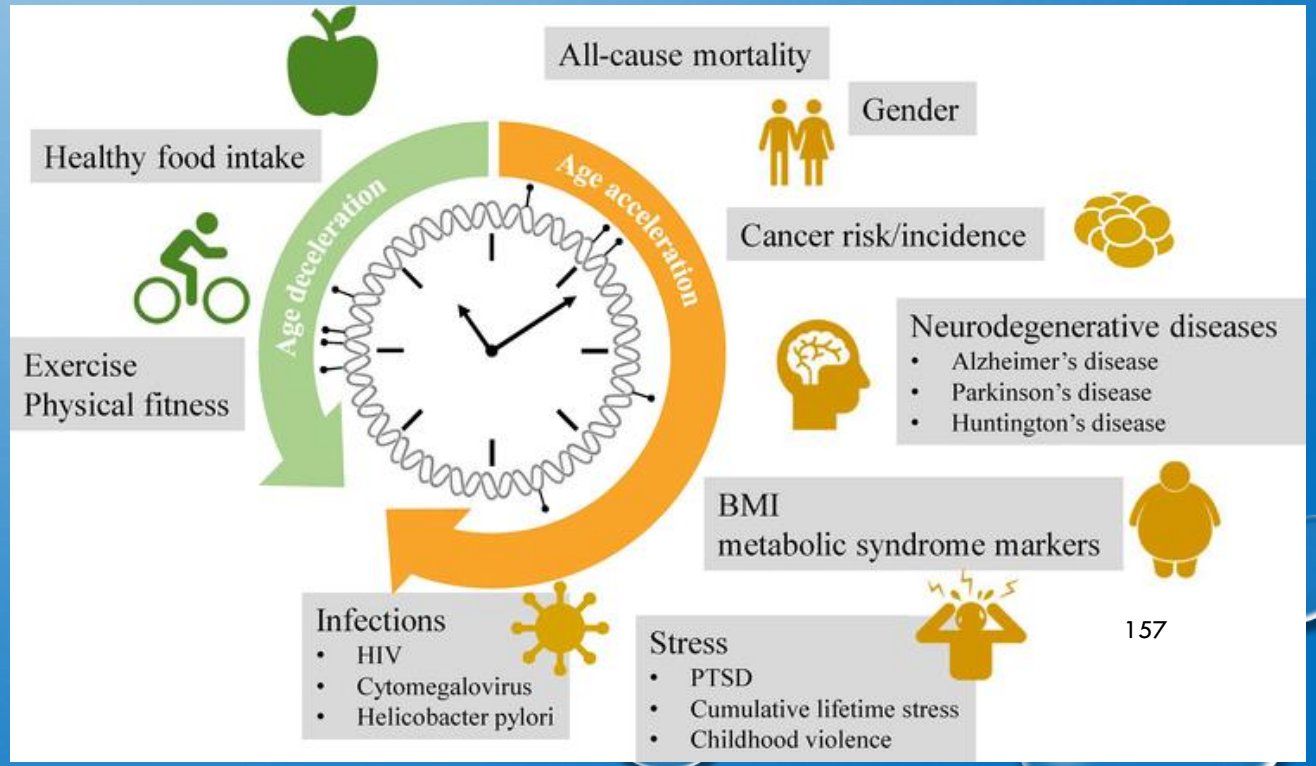


CLOCKS


2013
2018
2019
Horvath's pan tissue clock
Hannum's clock
Horvath's skin and blood clock
PhenoAge by Levine
GrimAge by Horvath
PedBe by Mc Ewen
353 CpGs
71 CpGs
391 CpGs
513 CpGs
1030 CpGs
94 CpGs
Tissue independent
Whole blood
Tissue independent
Tissue independent
Tissue independent
Buccal epithelial cells
Measure aging rate
Measures EAA in ex-vivo studies
Predicts phenotypic age: mortality risks
Predicts lifespan and healthspan
Measures biological age: information on pediatric diseases risk and on potential developmental defects

CLOCKS AND PREDICTION OF MORTALITY

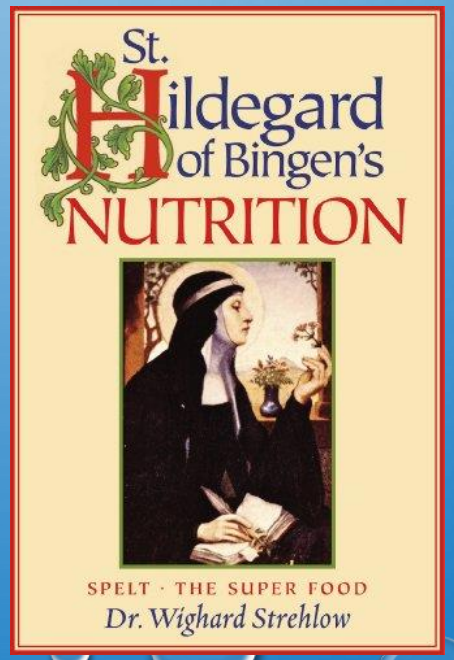




NUTRIEPIGENETICS

NUTRITION FOODS

Nutrition is the biochemical and physiological process by which an organism uses food to support its life.	Hippocrates, **"Let food be thy medicine, and let medicine be thy food"**



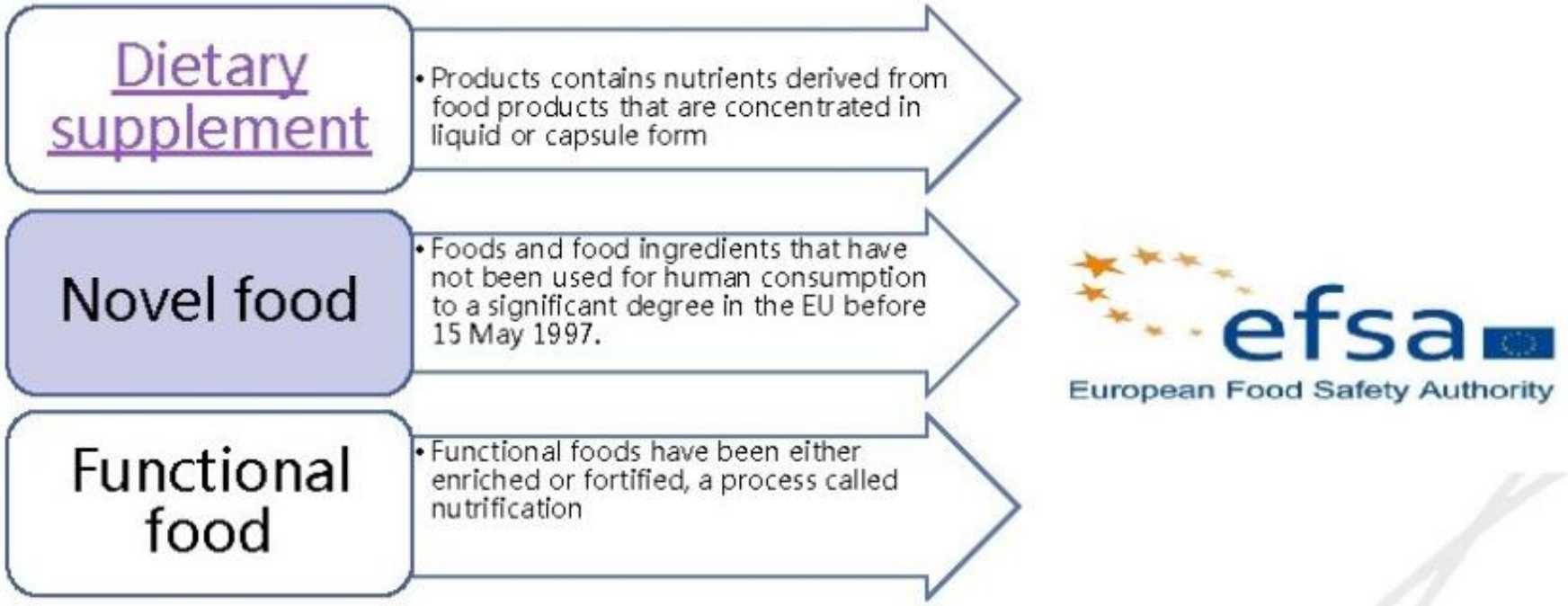
Dinkel ist das Hildegard-Getreide schlechthin.

Sie schätzte das Korn für seine warmen, kräftigen und fetten Eigenschaften. Dinkel sei zudem sehr mild und sorge für ein gutes Blut und Fleisch. Heute wissen wir, dass Dinkel eine tolle Alternative zum klassischen Weizen ist. Er gilt als robuster und weniger schadstoffbelastet im Vergleich zum konventionellen Weizen. Der Dinkelanbau ist weniger auf künstliche Dünger und Pestizide angewiesen, außerdem schützt seine besonders dicke Getreidehülse (Spelze) das Korn gut vor schädlichen Einflüssen.

Knoblauch ist laut Hildegard von Bingen roh, frisch und in Maßen zu verzehren.

Hält man sich an diese Regeln, soll die pikante Knolle das Blut erwärmen und gut für die Augen sein. Dem Knoblauch wird heutzutage auch eine besonders antibiotische und antioxidative Wirkung zugeschrieben. Also darf er doch gerne auf dem Teller landen – sollten wir es mit dem Verzehr nicht übertreiben und ihn maßvoll essen – wie Hildegard empfiehlt. Dann bleiben uns und unserem Umfeld auch die knoblauchtypischen Körperausdünstungen erspart.

EFSA


Dietary supplement
• Products contains nutrients derived from food products that are concentrated in liquid or capsule form
Novel food
• Foods and food ingredients that have not been used for human consumption to a significant degree in the EU before 15 May 1997.
Functional food
• Functional foods have been either enriched or fortified, a process called nutrification
efsa
European Food Safety Authority

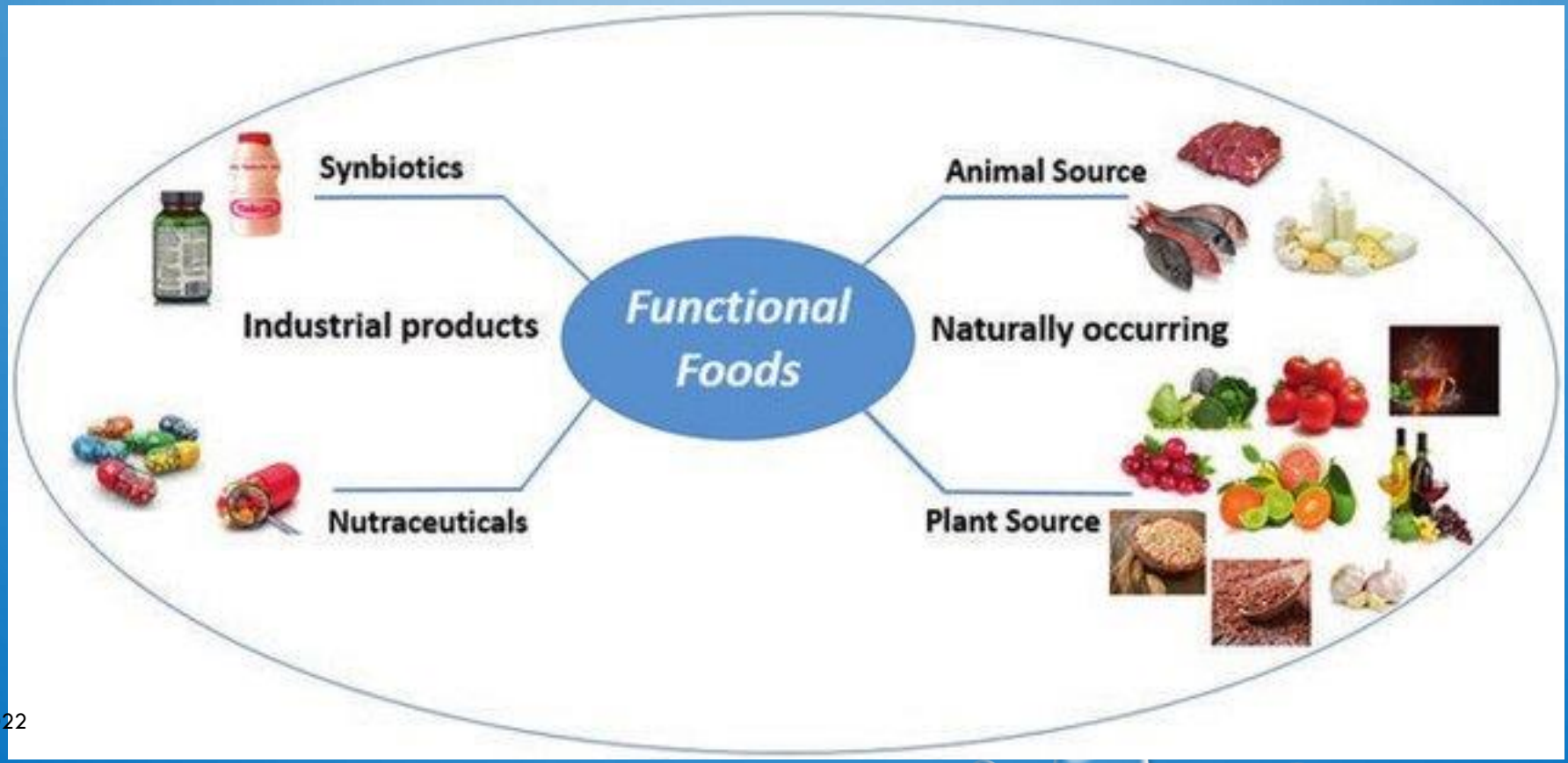
Novel food

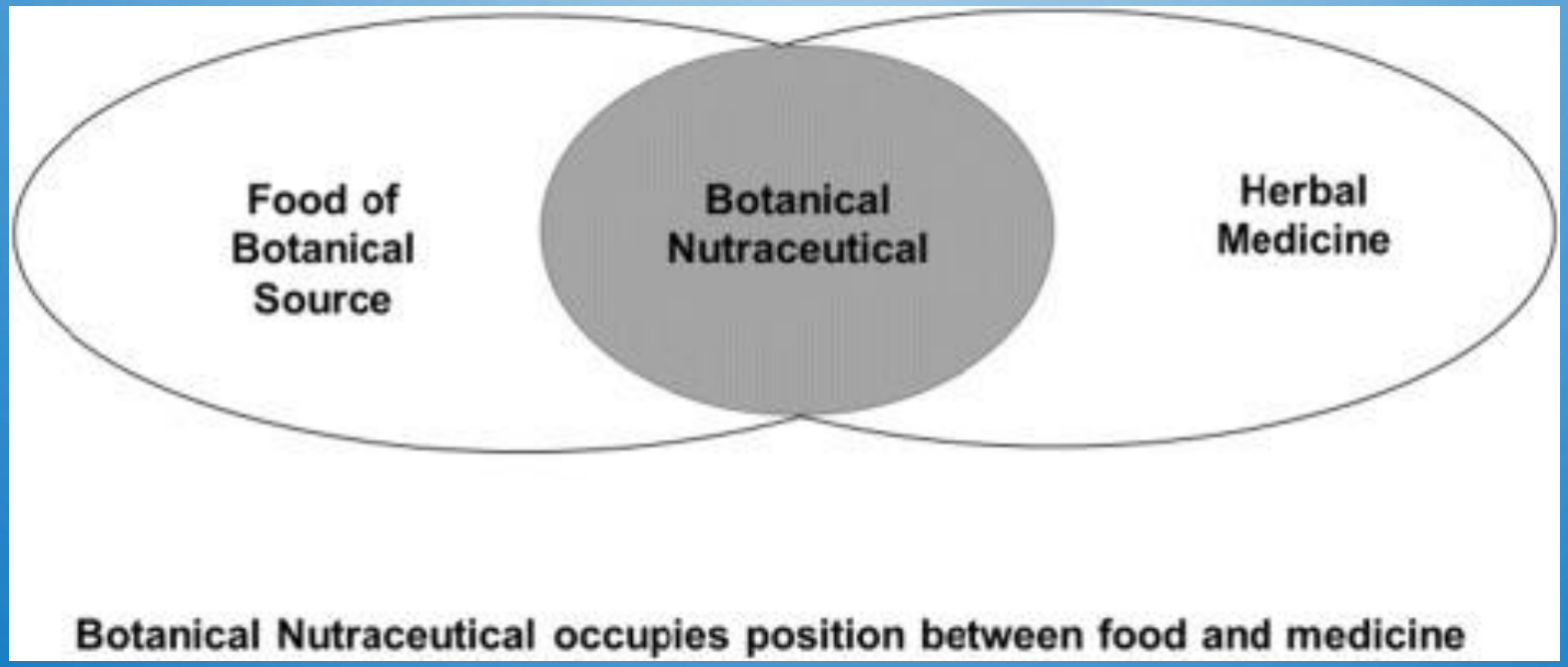
- Foods and food ingredients
  - with a new or intentionally modified primary molecular structure (eg, fat substitutes);
  - consisting of microorganisms, fungi or algae, or can be isolated from this (for example, microalgae oil);
  - consisting of plants or isolated (eg phytosterols), and isolated from animals food ingredients.

INTRODUCTION

- Functional foods are defined as “any food and food ingredients that may provide health benefit beyond the traditional nutrition that it contains”.
- **Japan** was the first country to recognize functional foods as a separate category when in **1991** it introduced the **FOSHU (Foods for Specific Health Use)** system to evaluate health claims.
- FSSAI issues Gazette notification for regulations on Nutraceuticals, Functional Foods, Novel Foods and others on 23 December 2016.

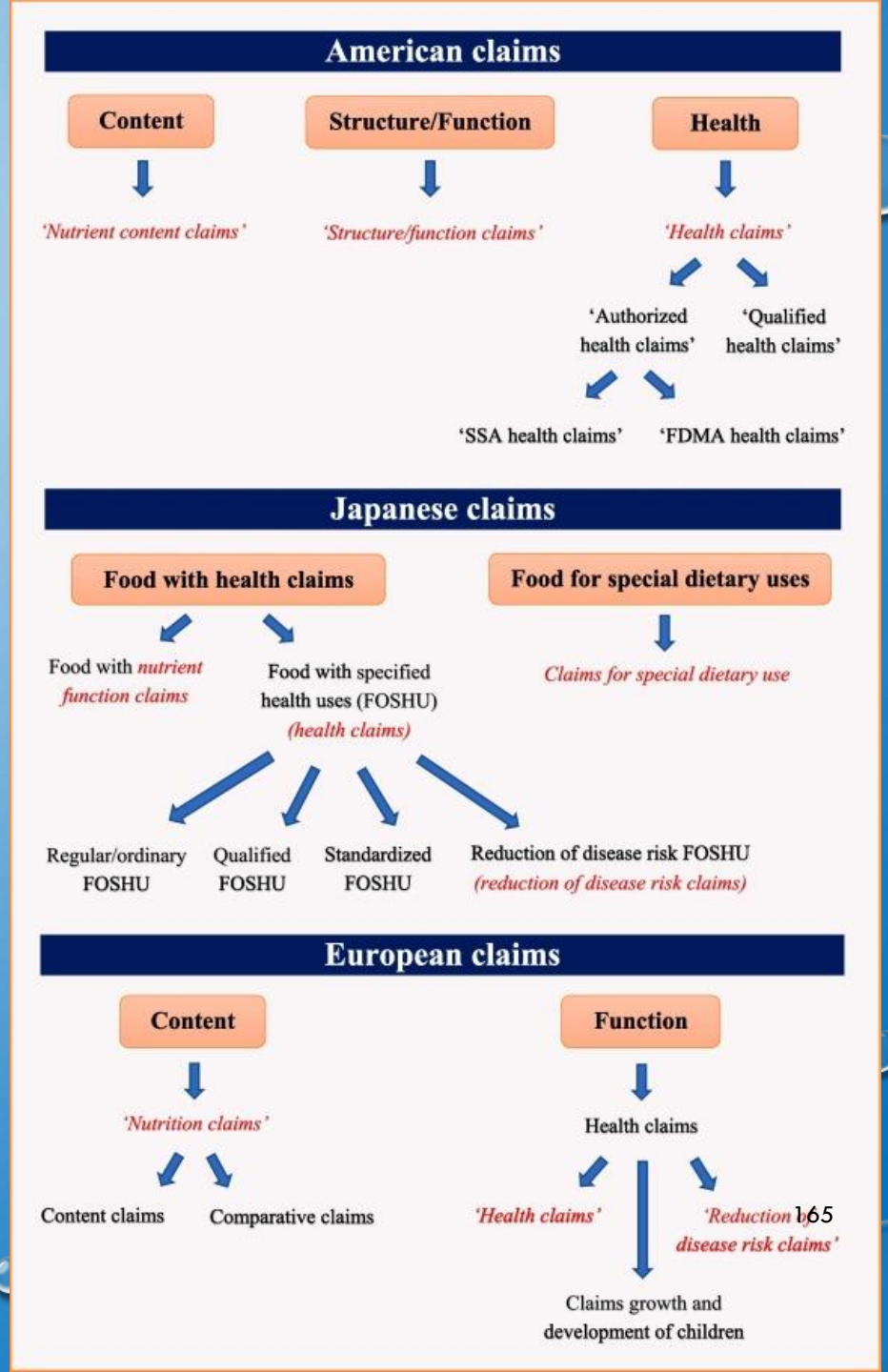
FUNCTIONAL FOOD





Botanical Nutraceutical occupies position between food and medicine

FUNCTIONAL FOODS AND HEALTH CLAIMS



EPIGENETIC DIETS FOR PREVENTION AND CO- THERAPY ?

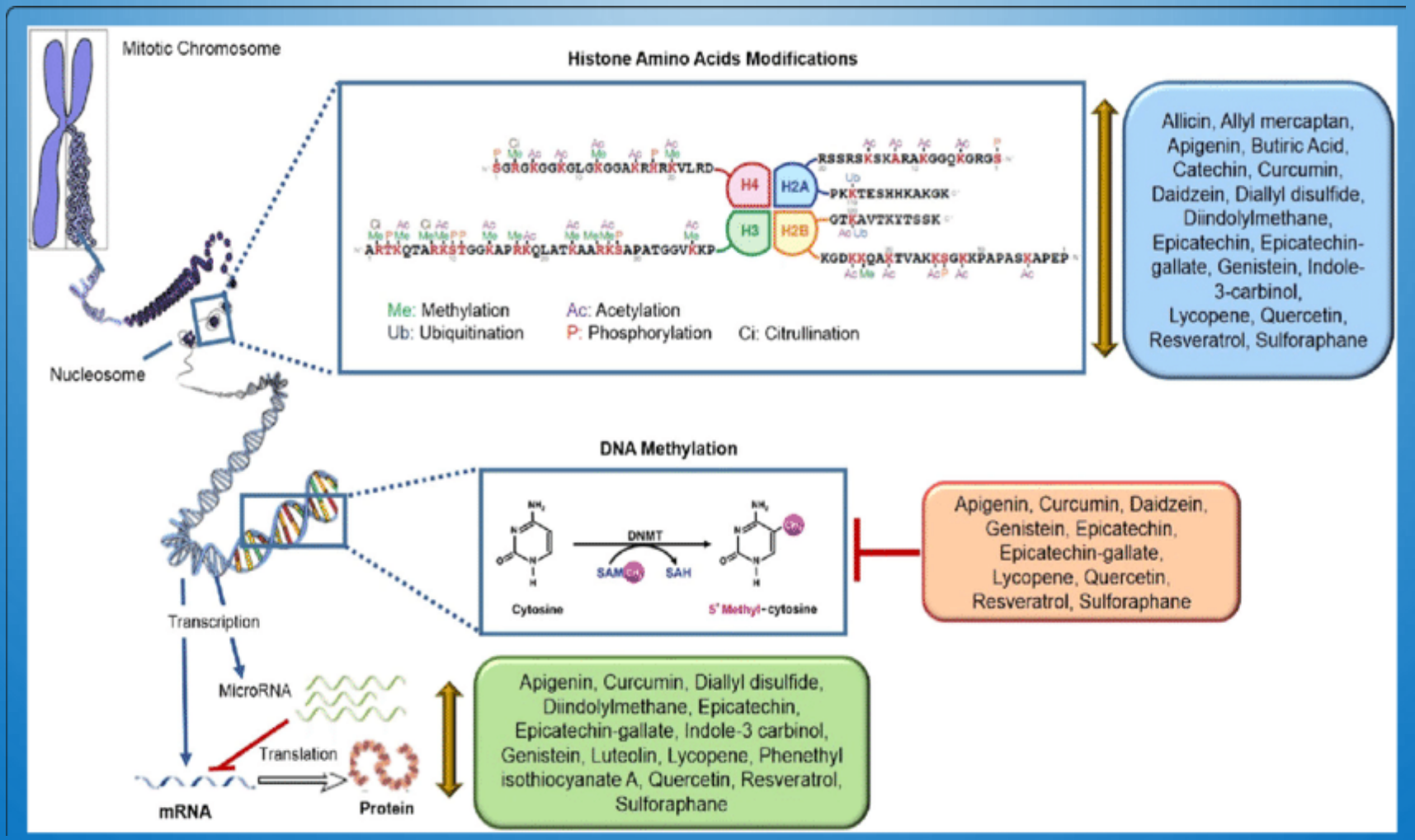
Diet and Epigenetics

Examples of dietary ingredients with epigenetic and chromatin remodeling properties

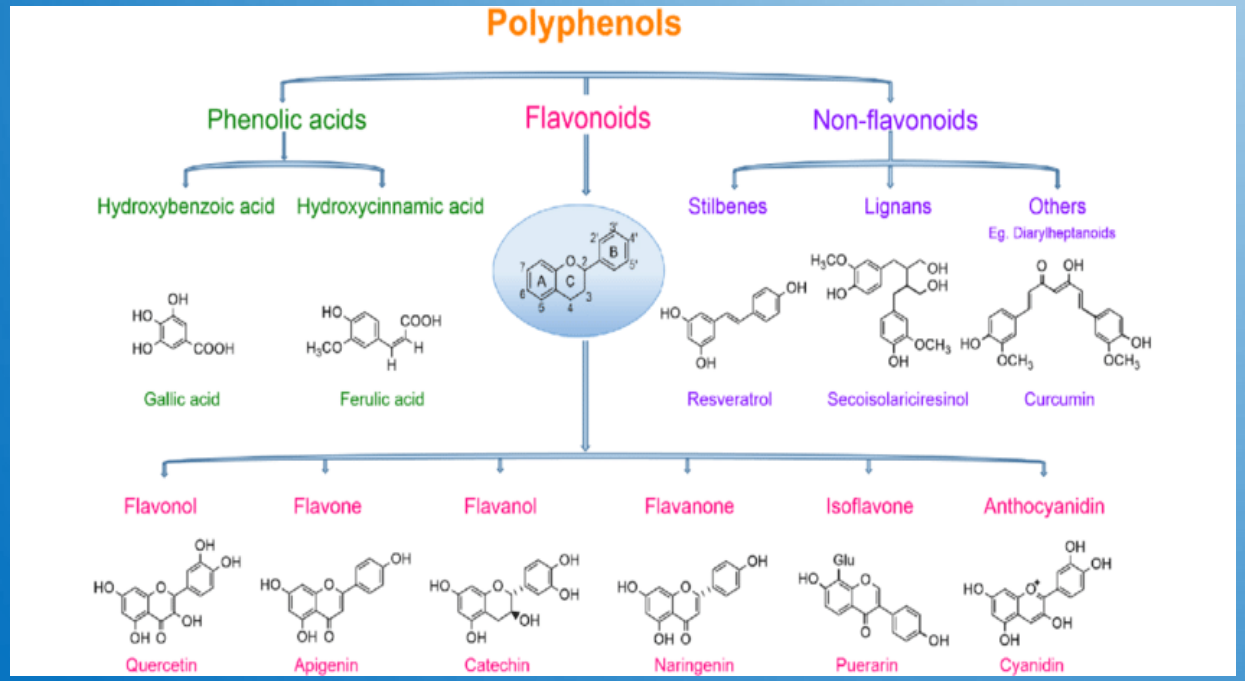
- Sulforanes from Brassica – HDAC inhibitors
- EGCG from green tea – DNA demethylation
- Genistein from soy – DNA methylation/demethylation
- Resveratrol from red grapes – affects NAD^+- dependent histone deacetylases (i.e., SIRT1) that deacetylates histones and regulatory proteins like PGC-1α
- Lunasin from soy – chromatin binding peptide and inhibitor of histone acetylation

Alfredo Galvez 10/13/2007

EFFECT OF PLANT INGREDIENTS ON ALL EPIGENETIC MECHANISMS

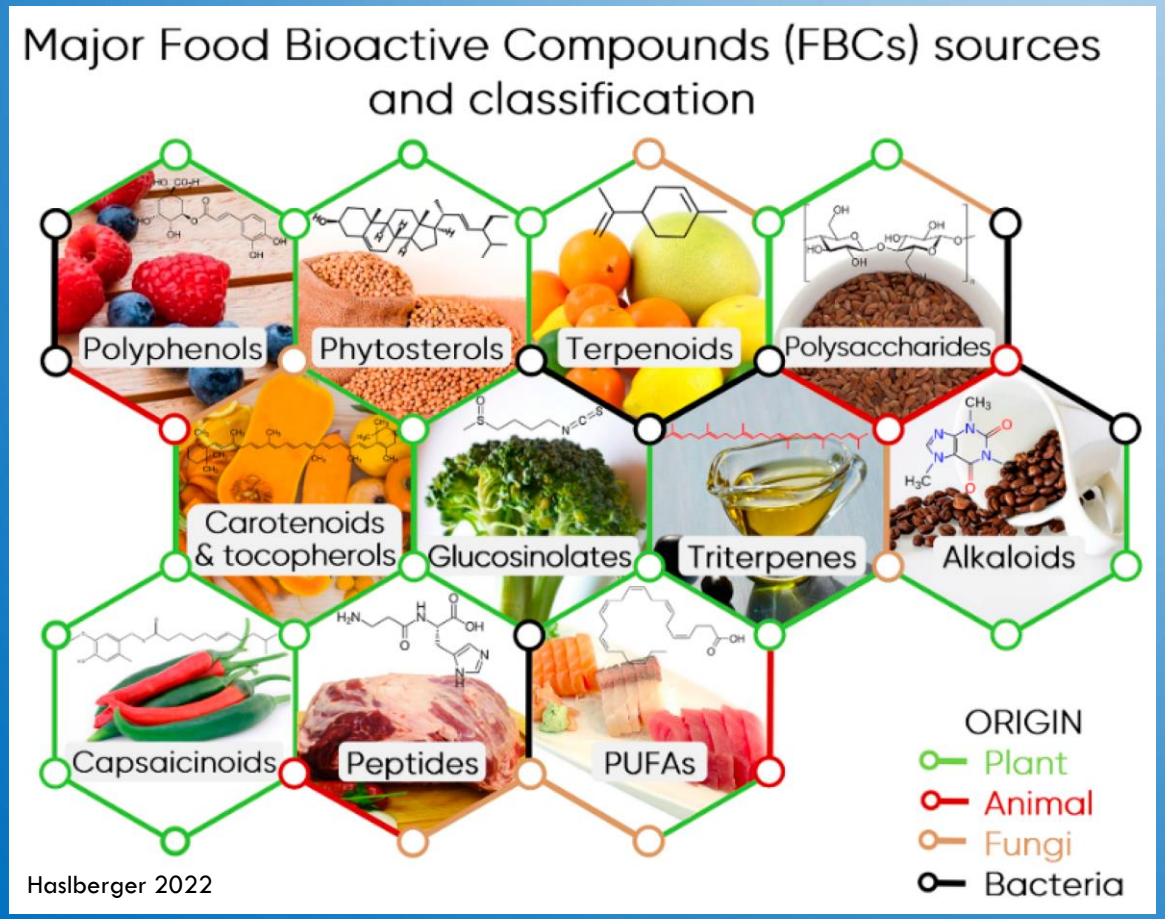


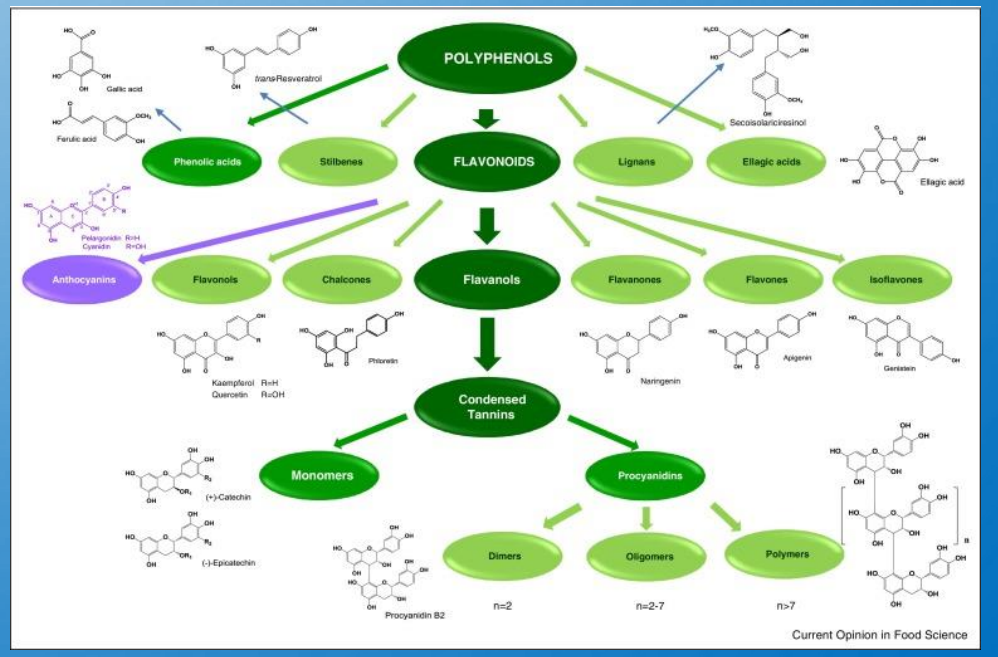
POLYPHENOLS



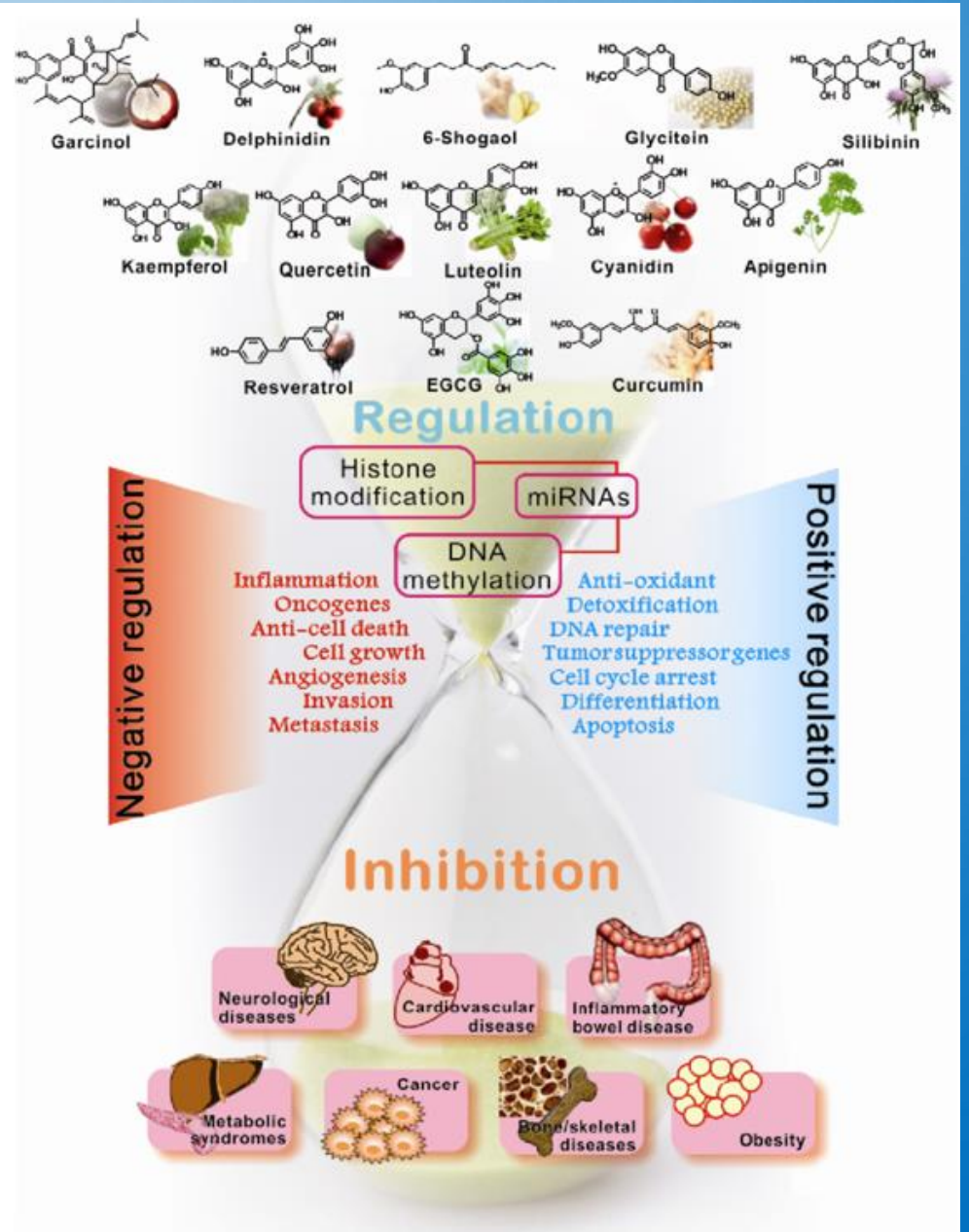
Polyphenols are molecules chemically characterized by the presence of at least one aromatic ring with one or more hydroxyl groups attached . Polyphenols are plant secondary metabolites that are thought to help plants to survive and proliferate, protecting them against microbial infections or herbivorous animals, or luring pollinators . Polyphenols are found in many medicinal and edible plants which represent important alimentary sources, including fruits, vegetables, beverages (such as tea and red wine) and extra virgin oil

TYPES AND CLASSIFICATION OF BIOACTIVE COMPOUNDS FROM FOOD

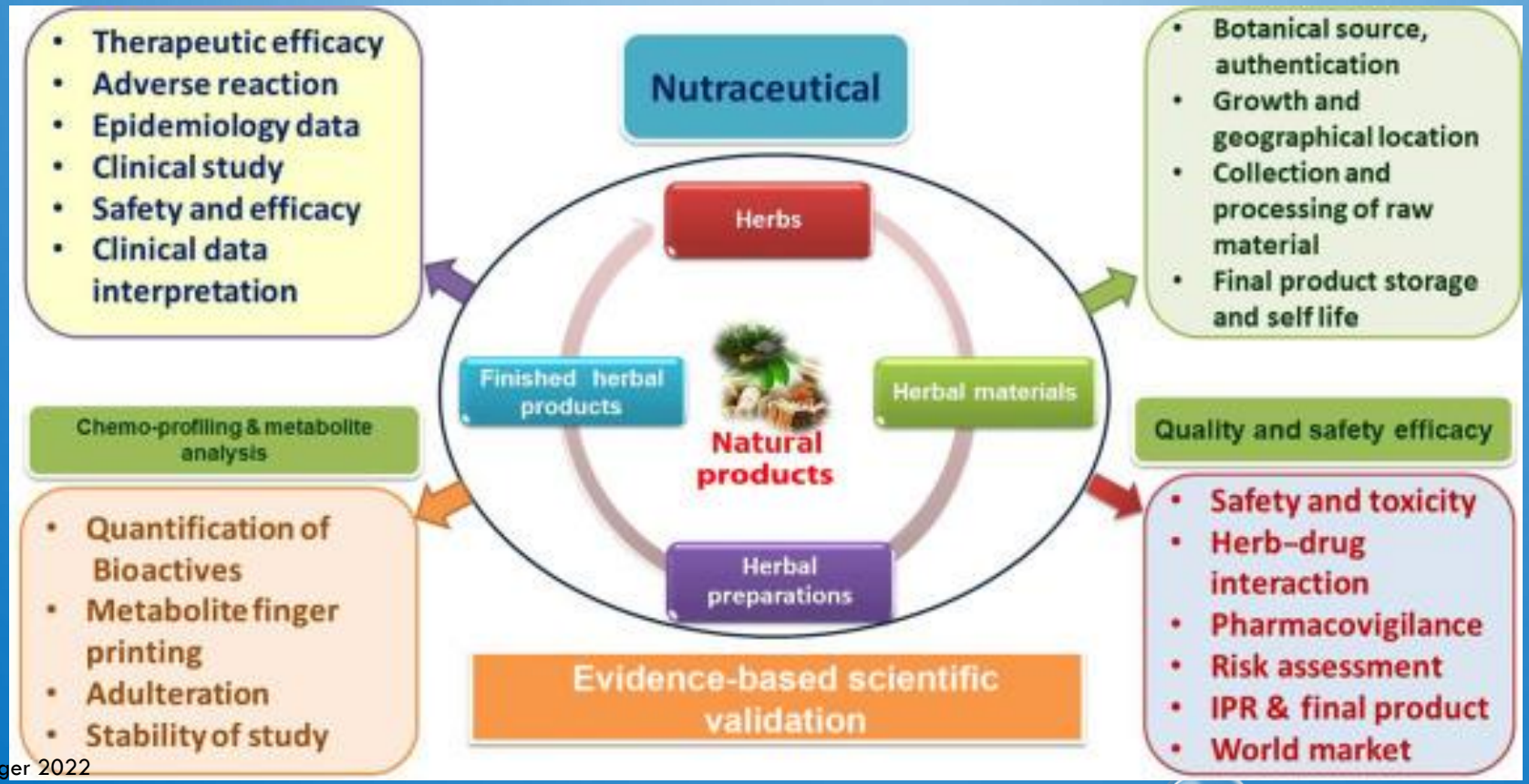




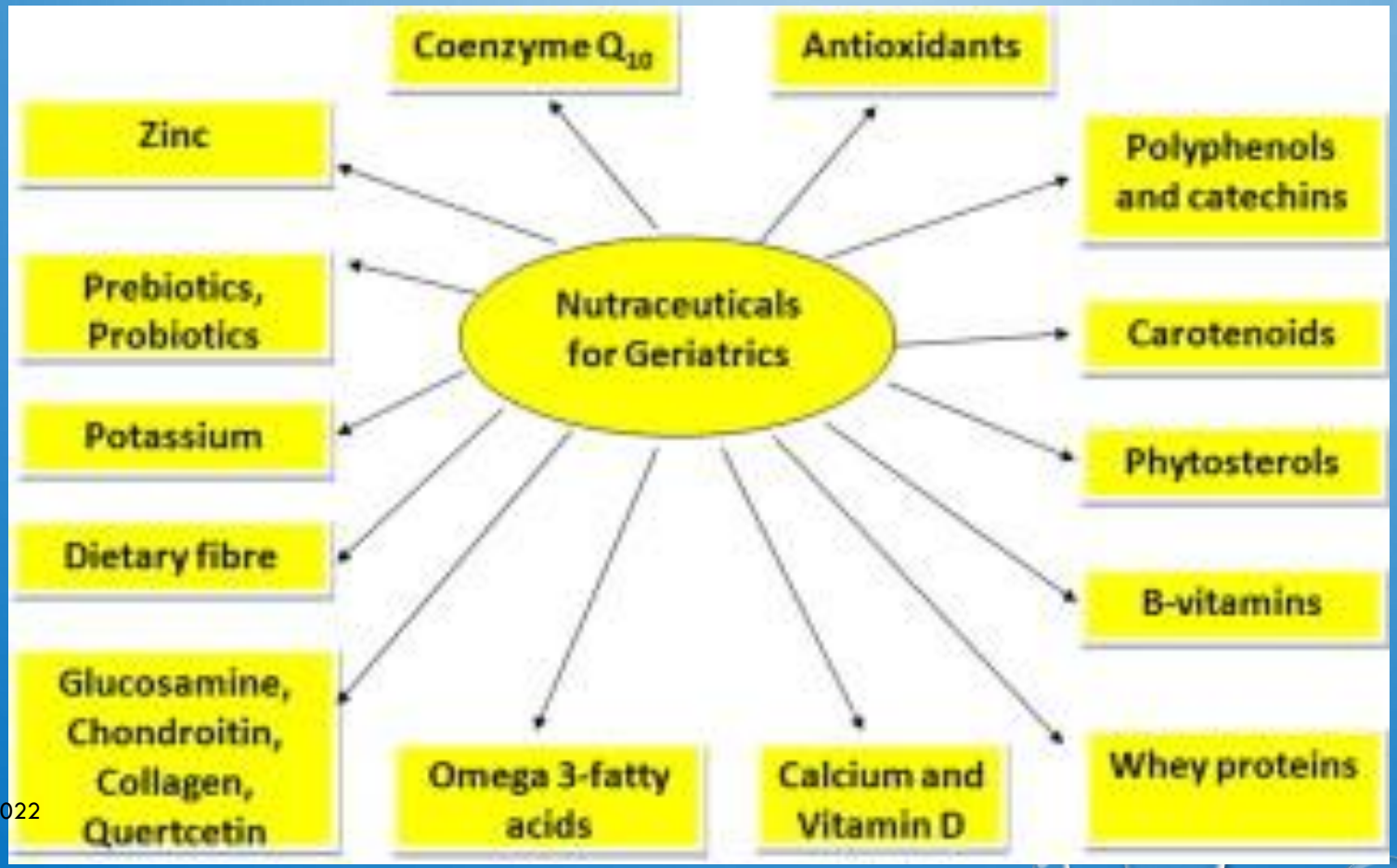
BIO-ACTIVE FOODS ANTI-OXYDATIVE, EPIGENETICALLY ACTIVE



NUTRACEUTICALS



NUTRACEUTICALS FOR AGING



DISCUSSED ACTIVITIES OF NUTRACEUTICALS ALONG THE HALLMARKS OF AGING, AGE RELATED COMPLEX DISEASES, FACTS OR HYPOTHESIS ?

Anti oxydative	Epigenetic active
inflammation	neuroinflammation
Telomers	Mitochondria
Autophagy	Apoptose
Senolytic	DNa repair
Immune senescence	Nuro infl
Anti bacterial	Anti viral
AGING	

EGCG TELOMERASE, C-MYC, H-TERT

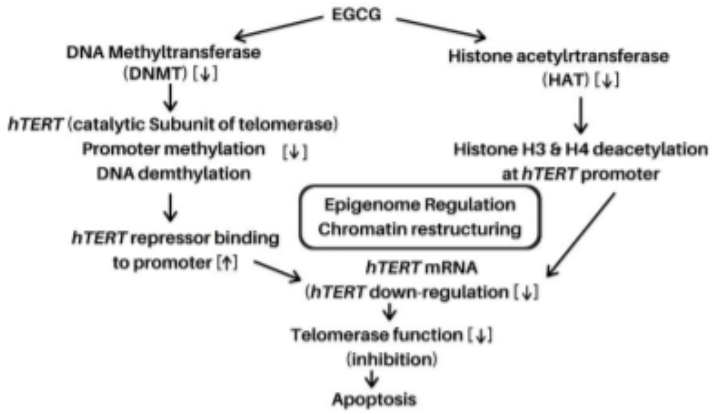
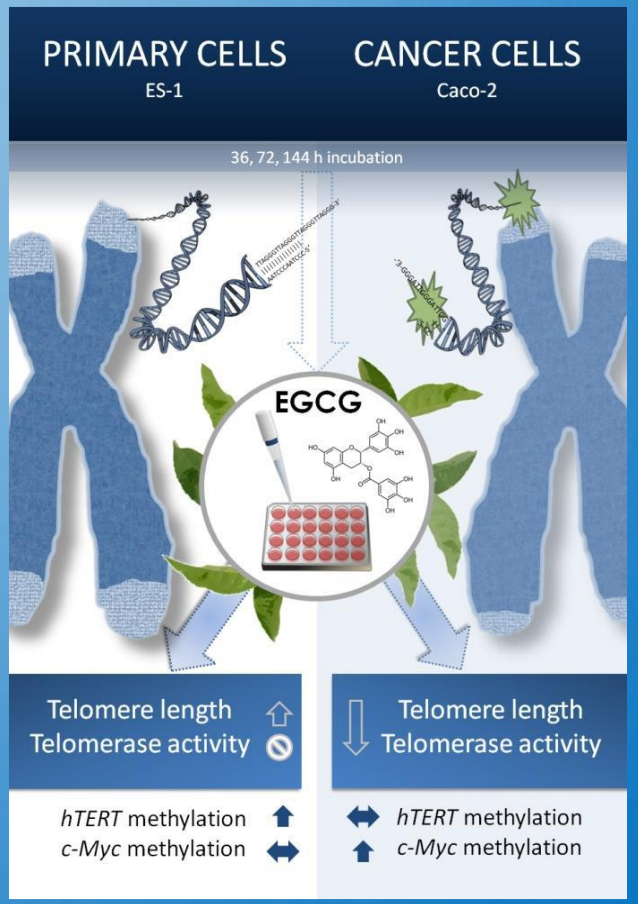


Figure 12. Mechanism of EGCG-induced apoptosis in cancer cells through epigenetic regulation of telomerase. EGCG inhibits both deoxyribonucleic acid (DNA) methyltransferase (DNMT) and histone acetyltransferase (HAT), leading to the DNA demethylation and histones H3 and H4 deacetylation of the

Page | 168

Functional Food and Healthy Aging **First Edition**

human telomerase– reverse transcriptase (hTERT) promoter, respectively. These events result in the epige-



FFHD
Functional Foods in Health and Disease

The green tea polyphenol EGCG is differentially associated with telomeric regulation in normal human fibroblasts versus cancer cells

Angelika Pointner[1], Christine Mölzer[1,2], Ulrich Magnet[1], Katja Zappe[1,3], Berit Hippe[1], Anela Tosevska[1,4], Elena Tomeva[1], Elisabeth Dum[1], Stephanie Lilja[1], Ulrike Krammer[1], Alexander

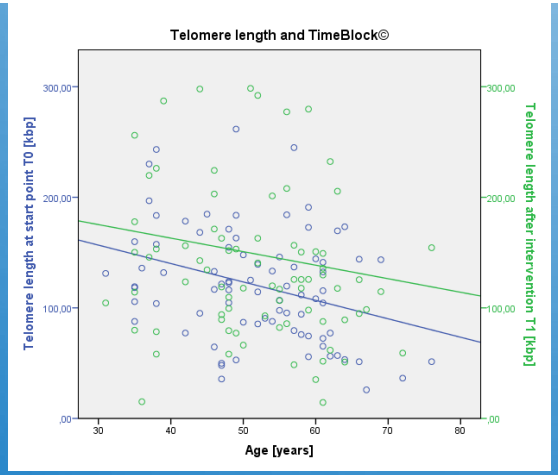
EGCG/TIMEBLOCK INCREASE TELOMERE LENGTH AND AFFECTS EPIGENETIC MARKERS

Journal of Nutrition & Food Sciences
ISSN: 2155-9600
Pointner et al., J Nutr Food Sci 2017, 7:1
DOI: 10.4172/2155-9600.1000577
Research Article
OMICS International

EGCG Containing Combined Dietary Supplement Affects Telomeres and Epigenetic Regulation

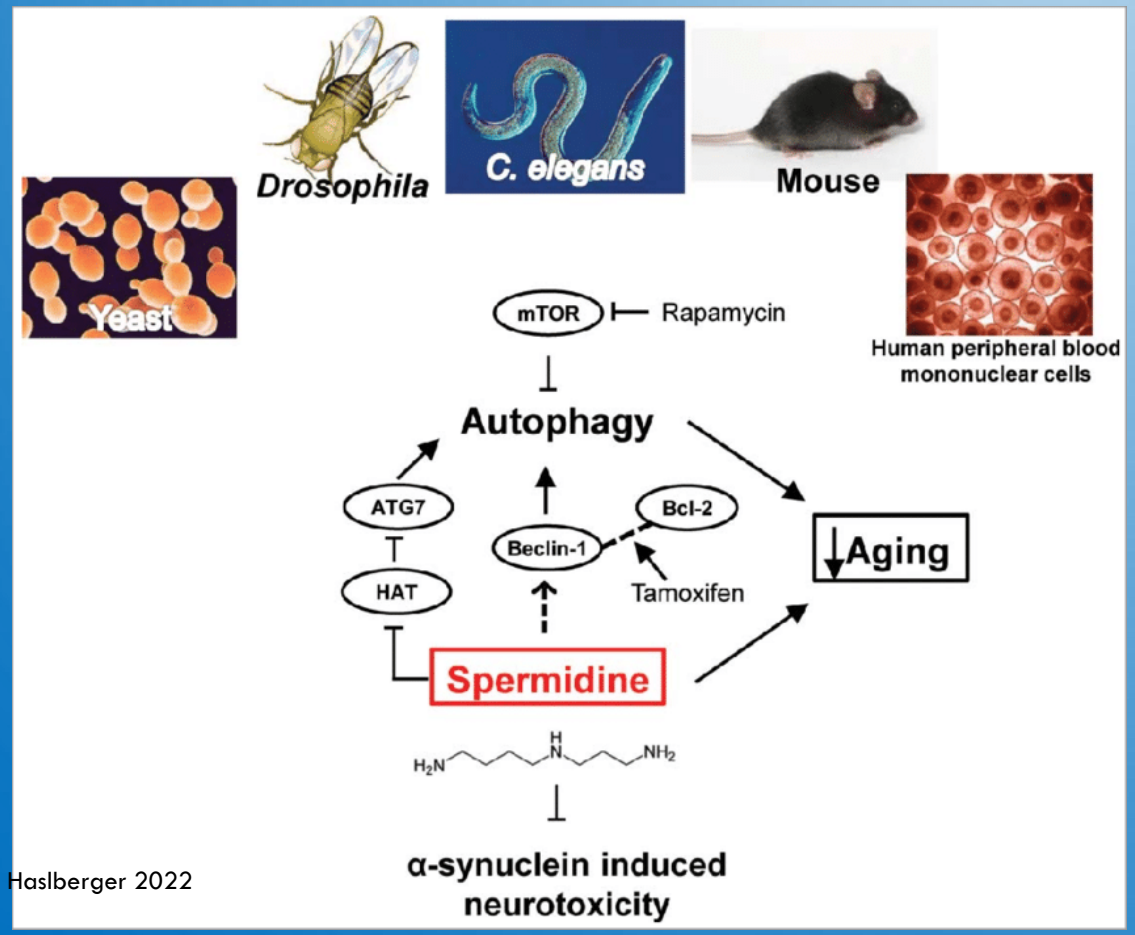
Angelika Pointner, Ulrich Magnet, Elena Tomeva, Elisabeth Dum, Christina Bruckmueller, Christine Mayer, Eva Aumueller and Alexander Haslberger*

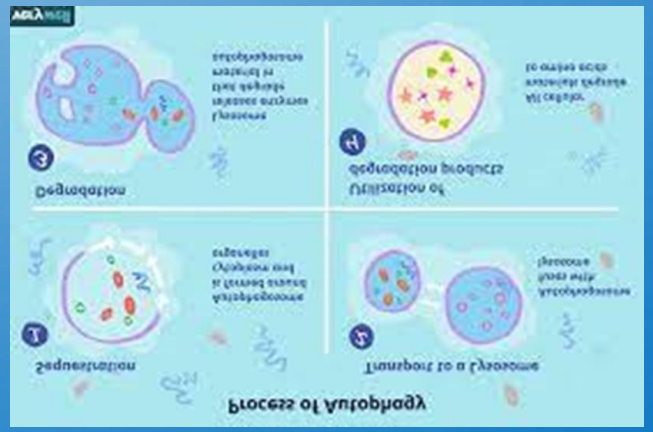
Department of Nutritional Sciences, University of Vienna, Austria



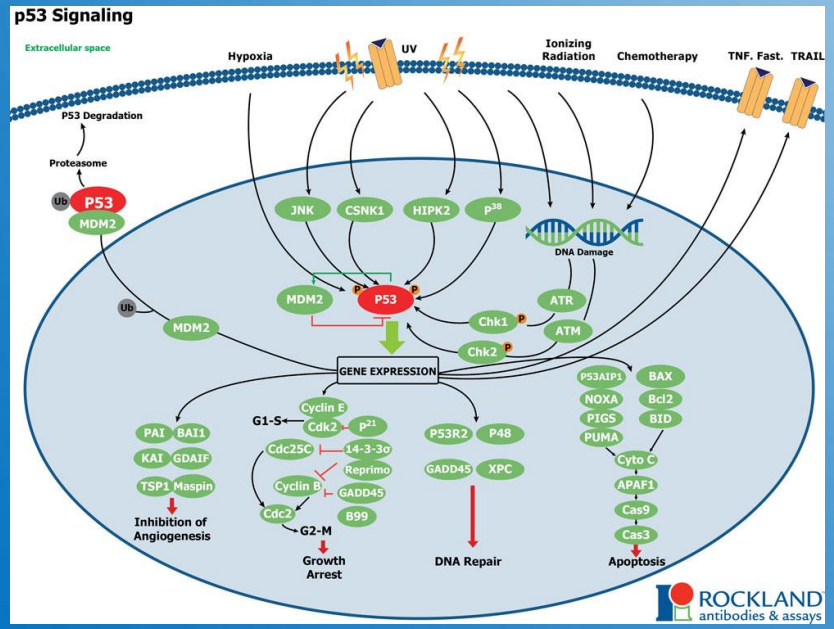
- **After 6 months of administration (TimeBlock©) there is a significant increase in telomere length of approximately 17 %, p=0,004* ANOVA**

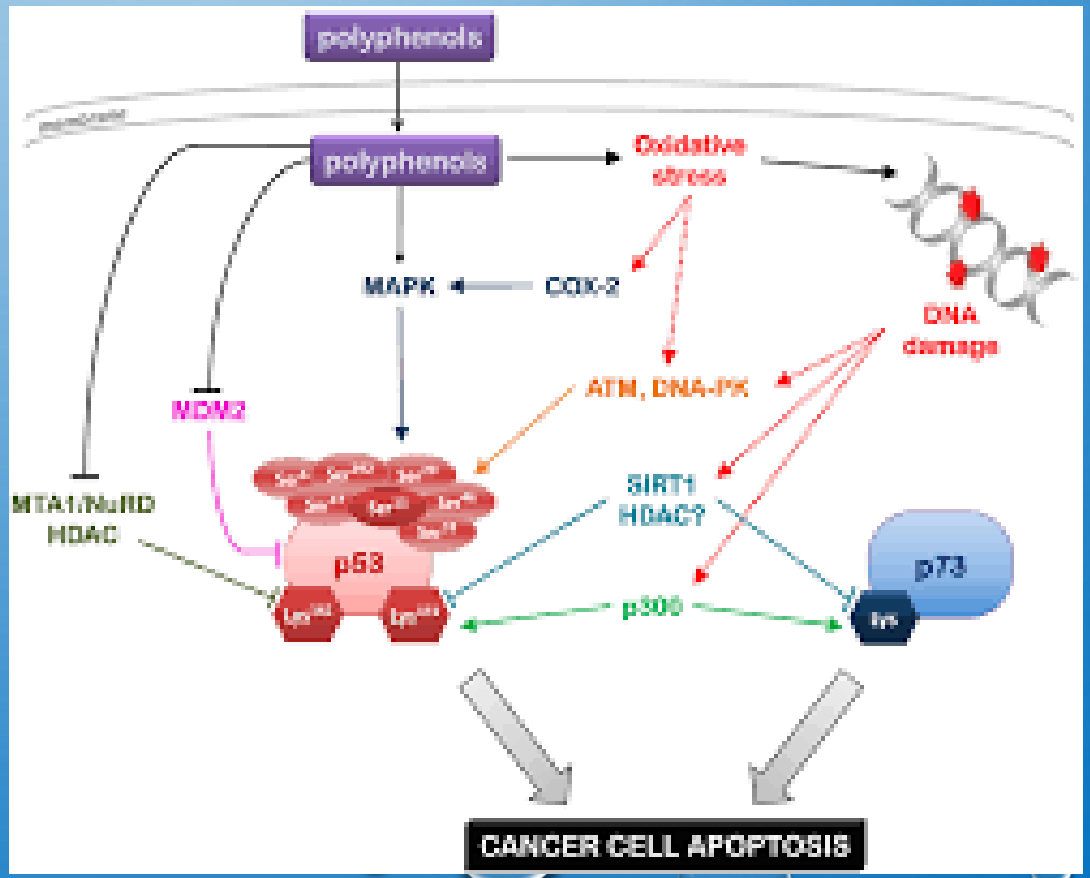
POLYPHENOLS AND AUTOPHAGY



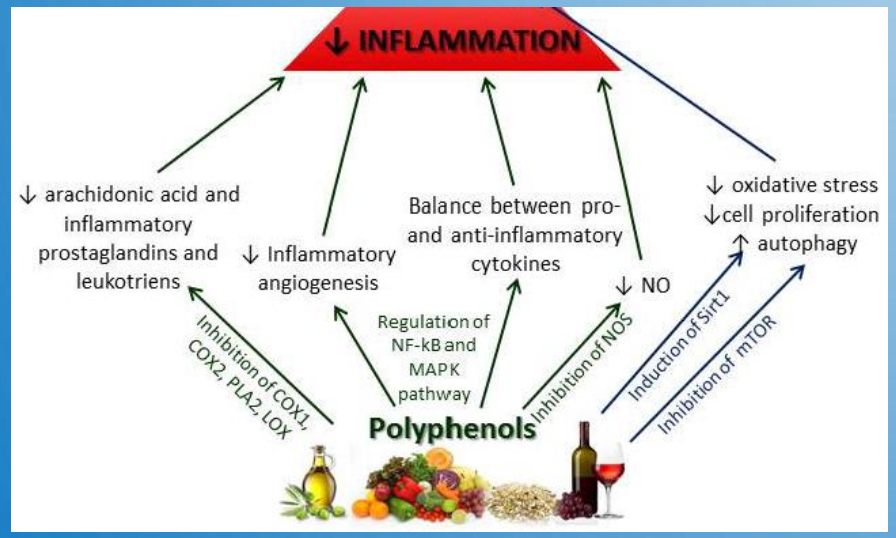


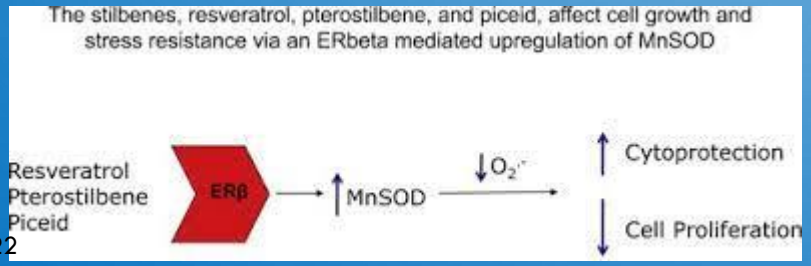
APOPTOSIS, P53 AND POLYPHENOLS

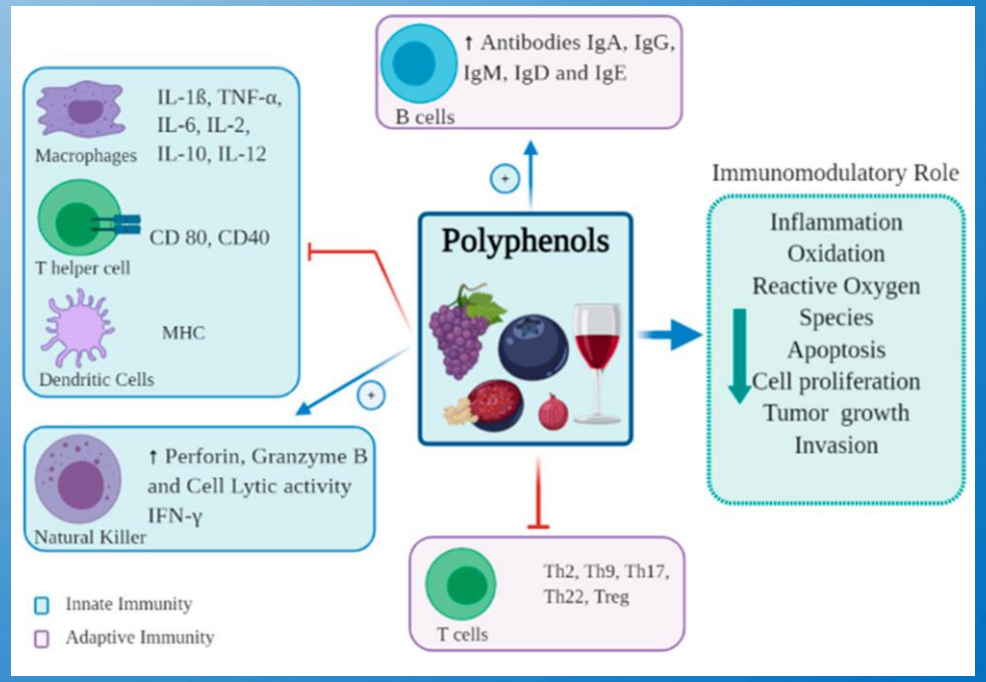




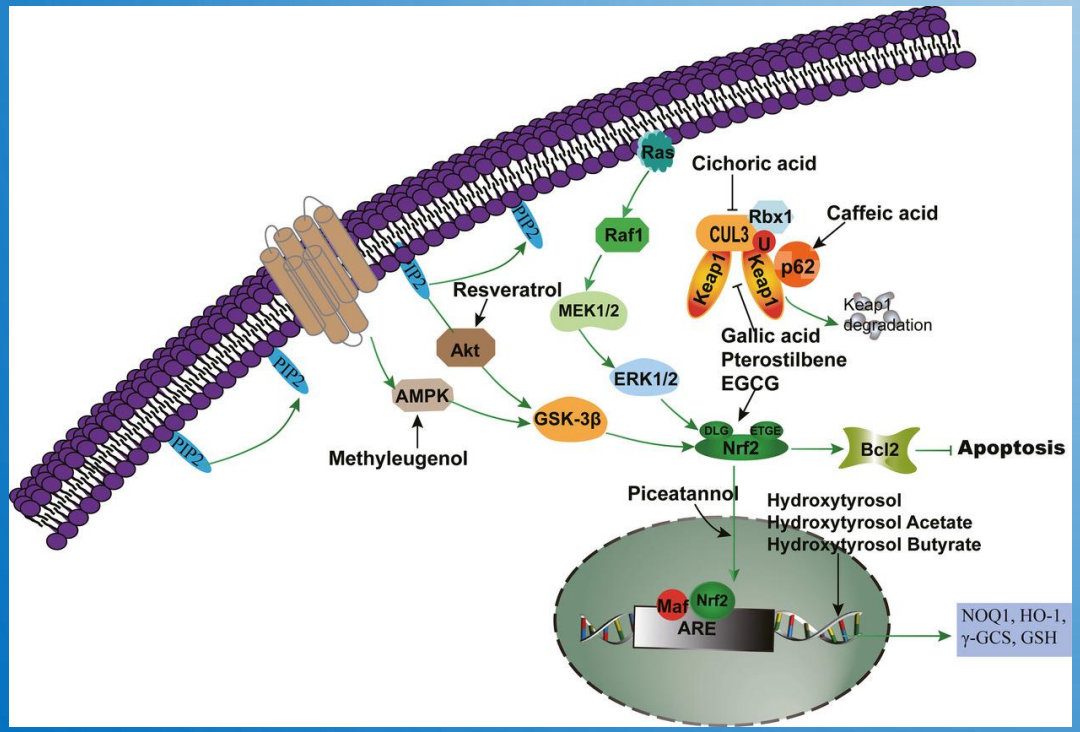
POLYPHENOLS AND INFLAMMATION:

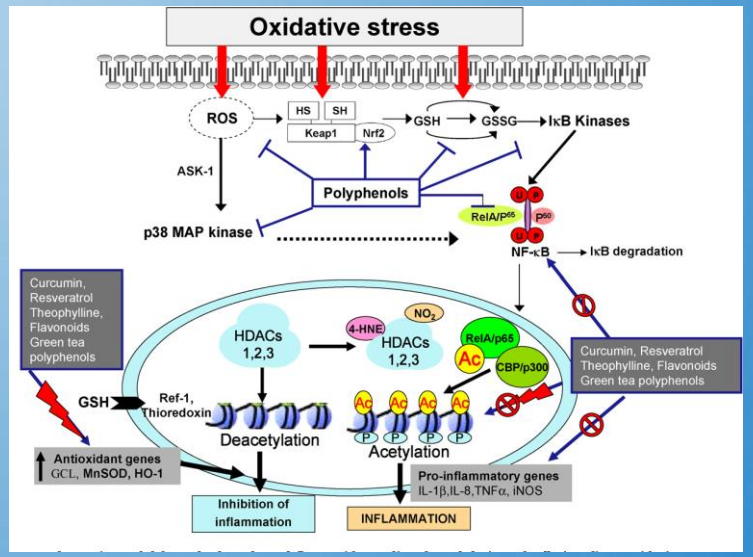






POLYPHENOLS AND NRF2



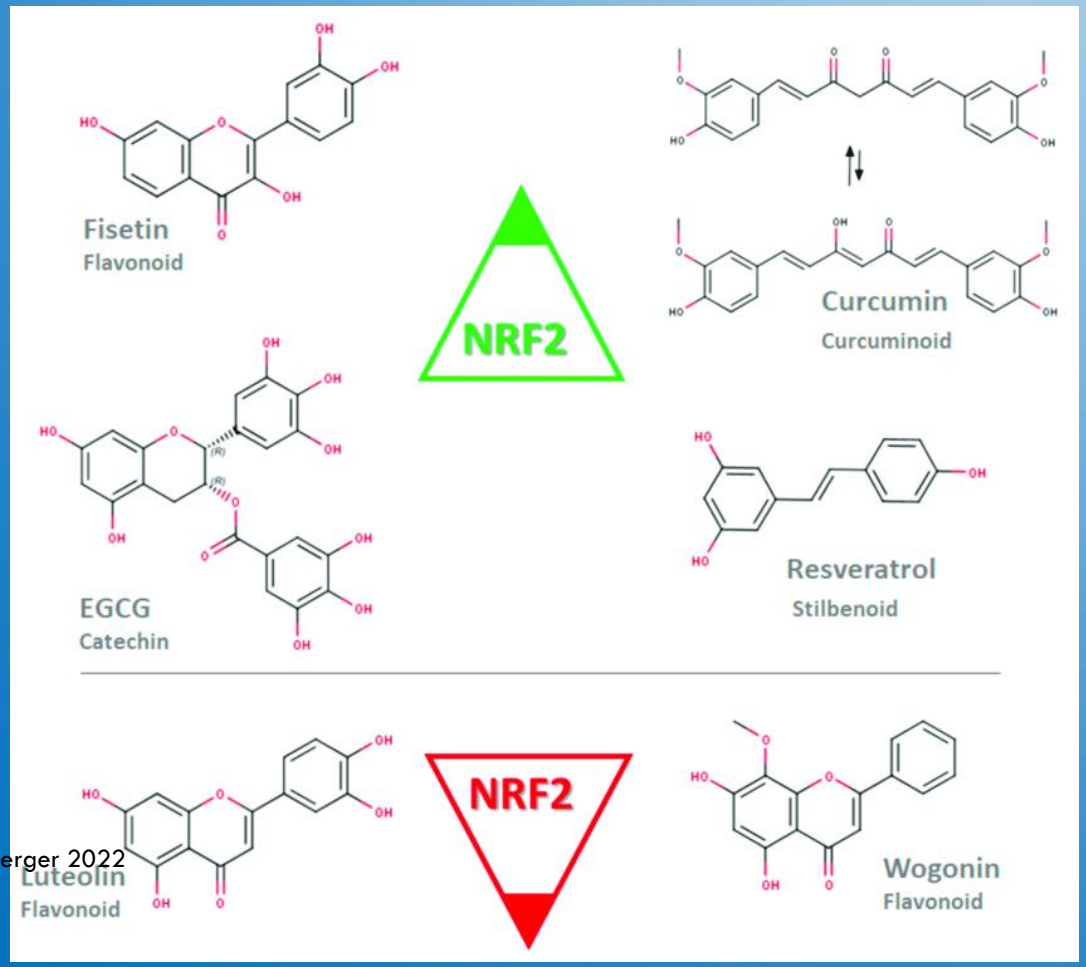


Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases

*Antonio Cuadrado[1,2], Ana I. Rojo[1], Geoffrey Wells[3], John D. Hayes[4], Sharon P. Cousin[5], William L. Rumsey[6], Otis C. Attucks[7], Stephen Franklin[8], Anna-Liisa Levonen[9], Thomas W. Kensler[10] and Albena T. Dinkova-Kostova[4,11]**

Abstract | The transcription factor NF-E2 p45-related factor 2 (NRF2; encoded by *NFE2L2*) and its principal negative regulator, the E3 ligase adaptor Kelch-like ECH-associated protein 1 (KEAP1), are critical in the maintenance of redox, metabolic and protein homeostasis, as well as the regulation of inflammation. Thus, NRF2 activation provides cytoprotection against numerous pathologies including chronic diseases of the lung and liver; autoimmune, neurodegenerative and metabolic disorders; and cancer initiation. One NRF2 activator has received clinical approval and several electrophilic modifiers of the cysteine-based sensor KEAP1 and inhibitors of its interaction with NRF2 are now in clinical development. However, challenges regarding target

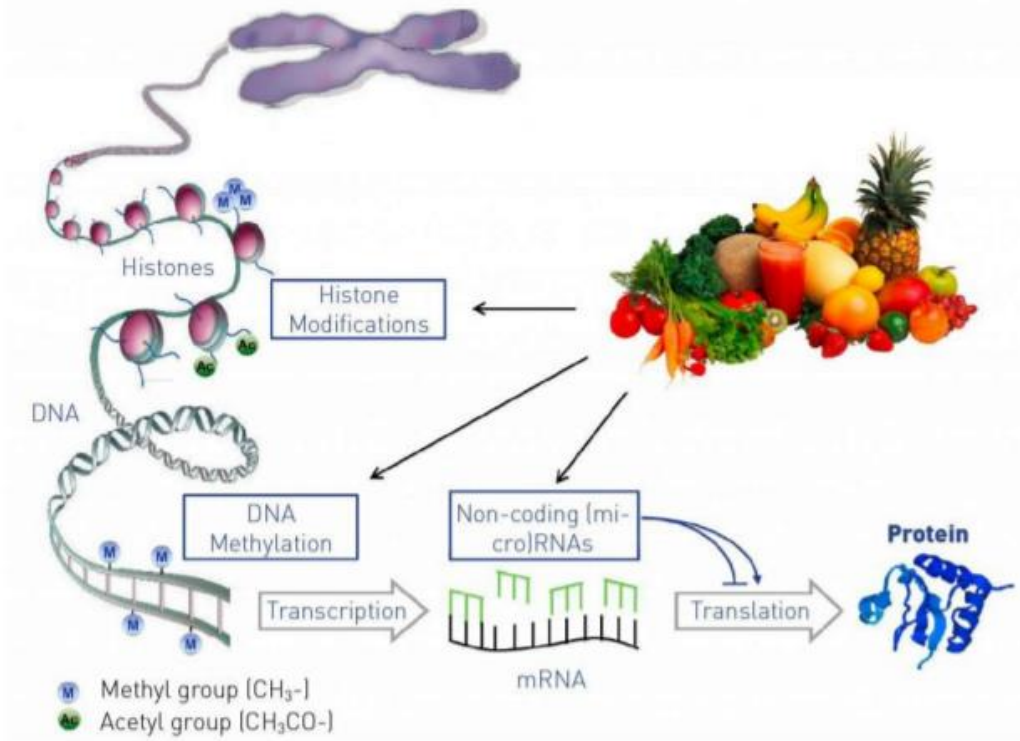
NRF2 AGONISTS, ANTIAGONISTS



NRF2 (or NFE2L2) is a protein, naturally found within the body. It's job is **to help regulate the work of antioxidant proteins that can help protect against oxidative damage**.

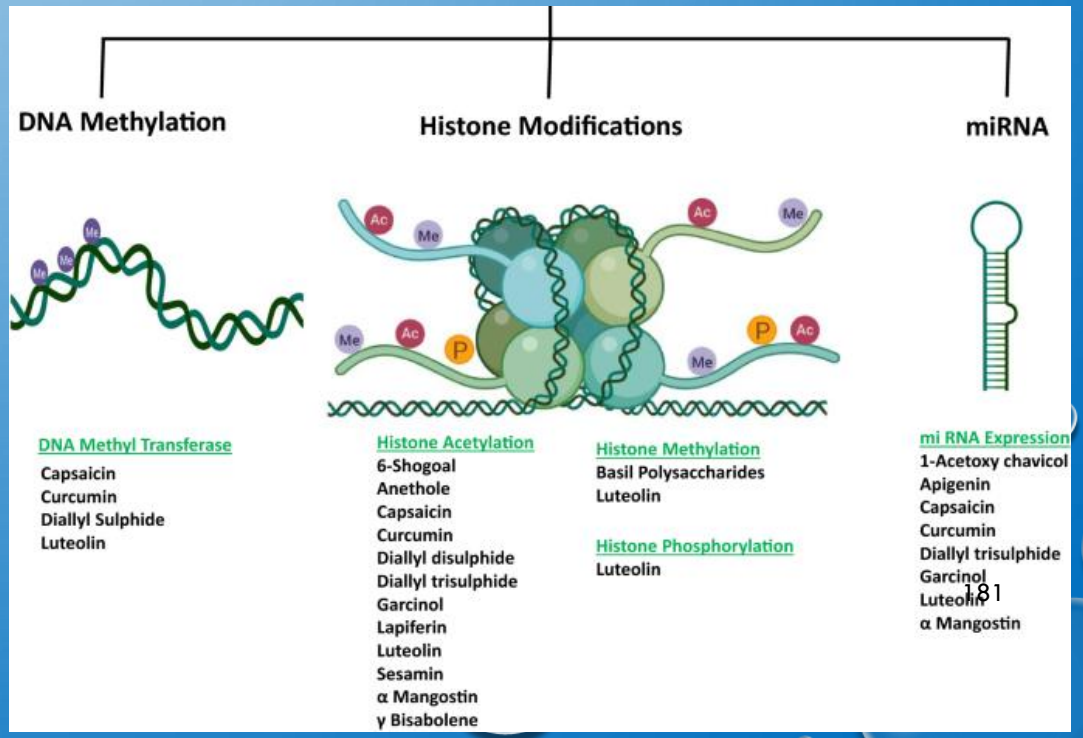
This oxidative damage can be triggered by injury and inflammation and involves the production of free radicals.

NOVEL FOODS, FUNCTIONAL FOODS AND EPIGENETICS

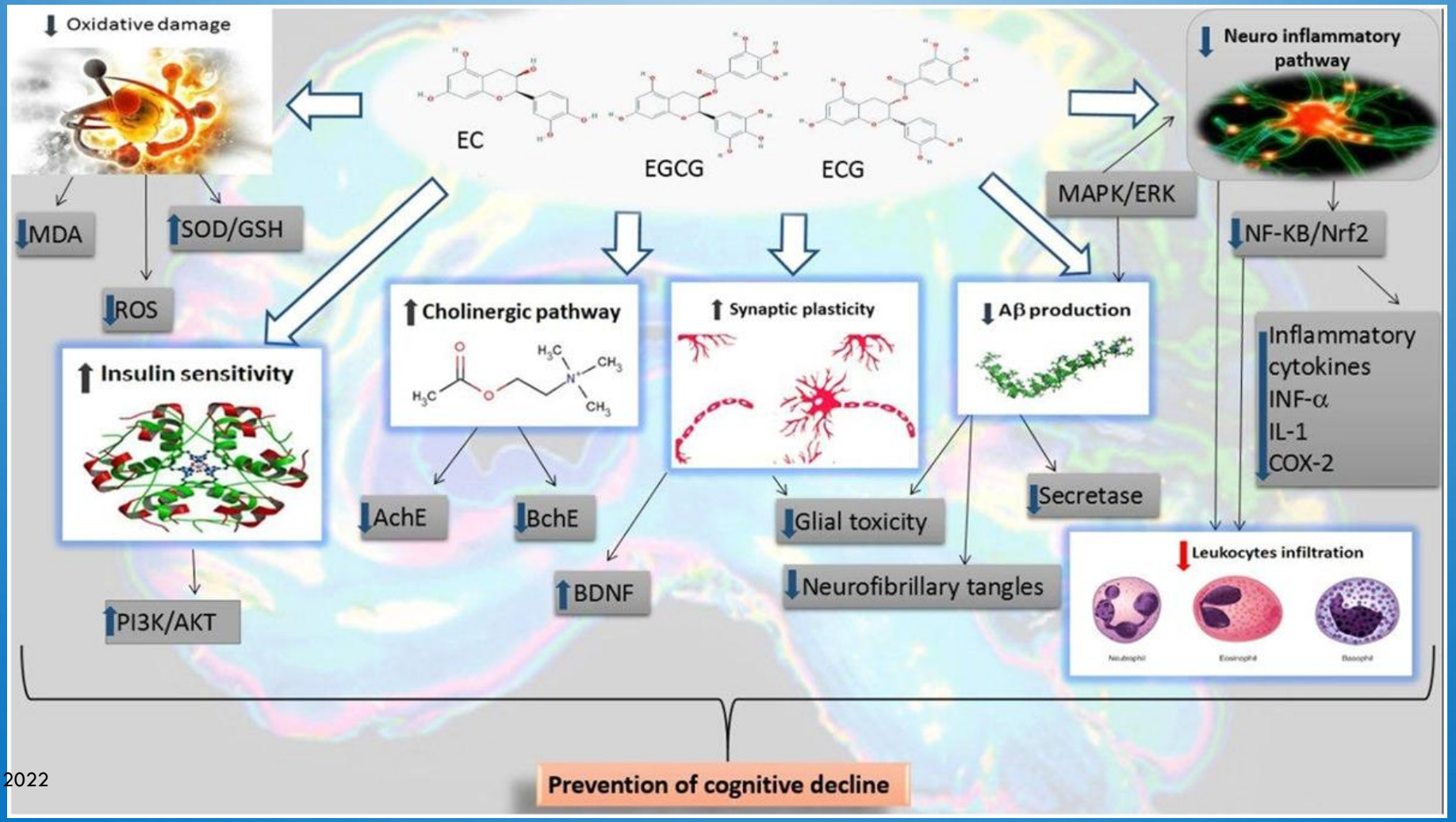


Haslberger 2022

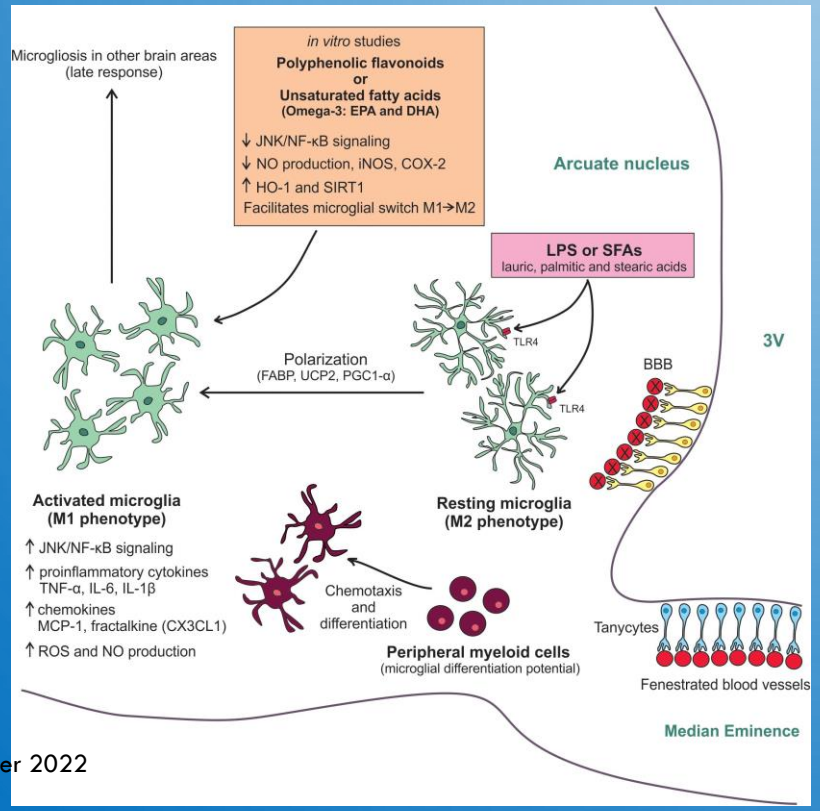
Figure 4. Polyphenols address all epigenetic mechanisms.

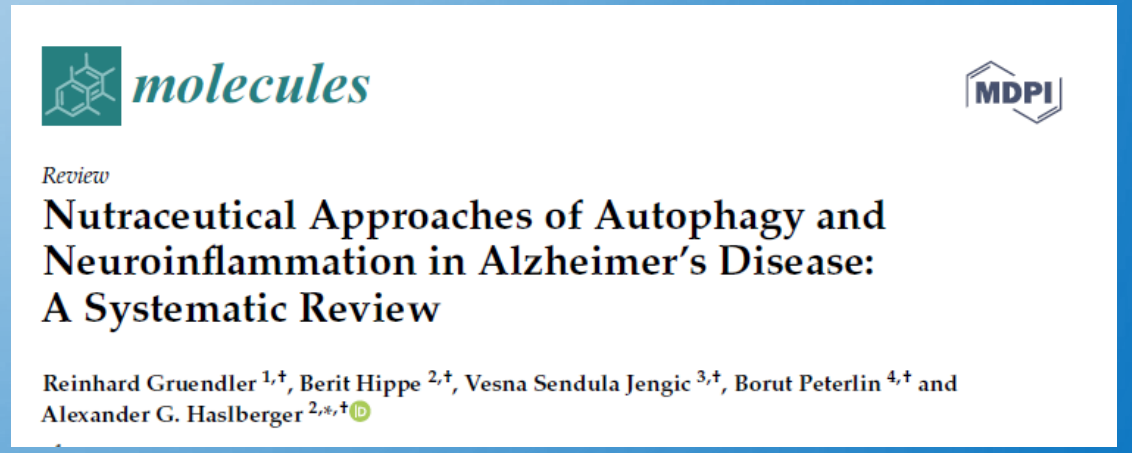


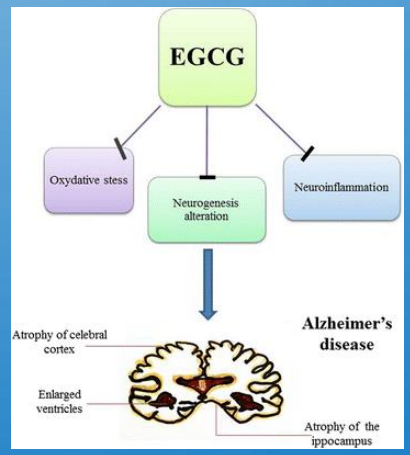
EGCG AND NEURO- INFLAMMATION, COGNITIVE DECLINE



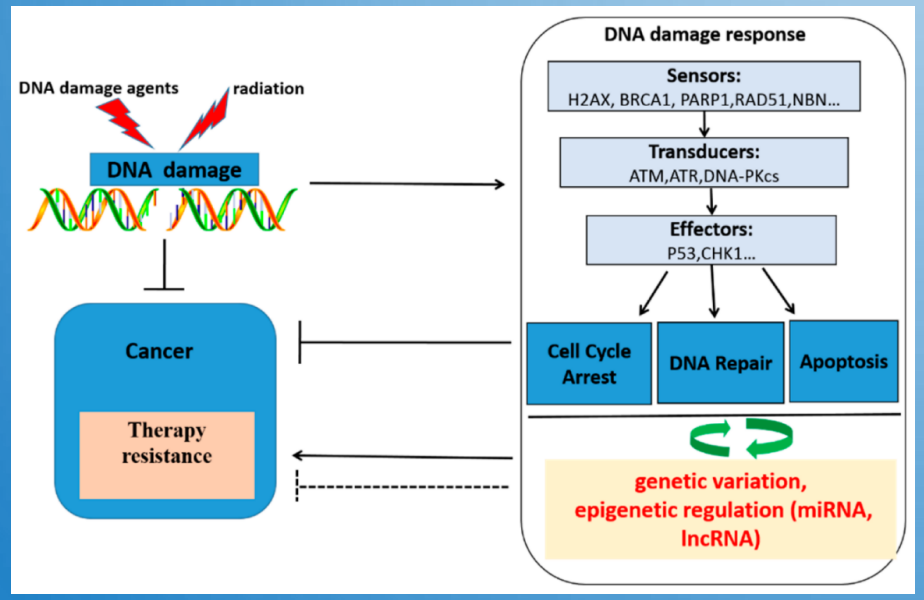
POLYPHENOLS AND MICROGLIA

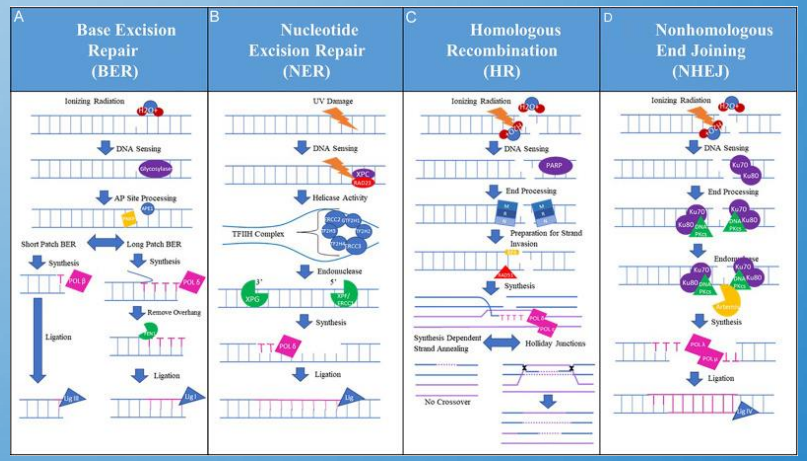


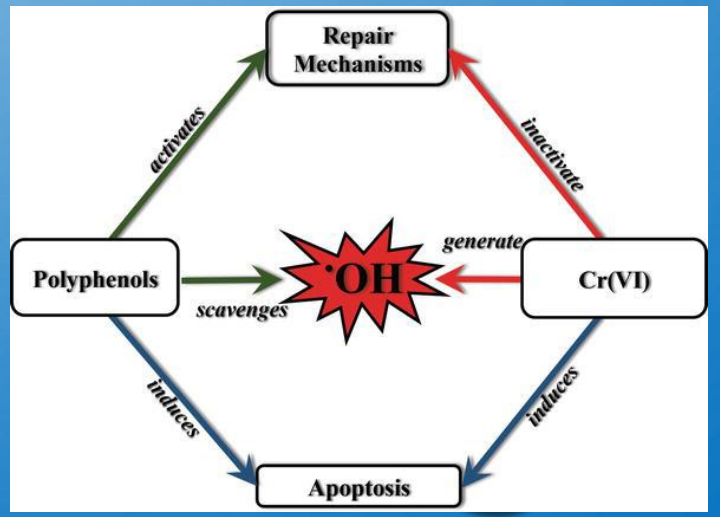




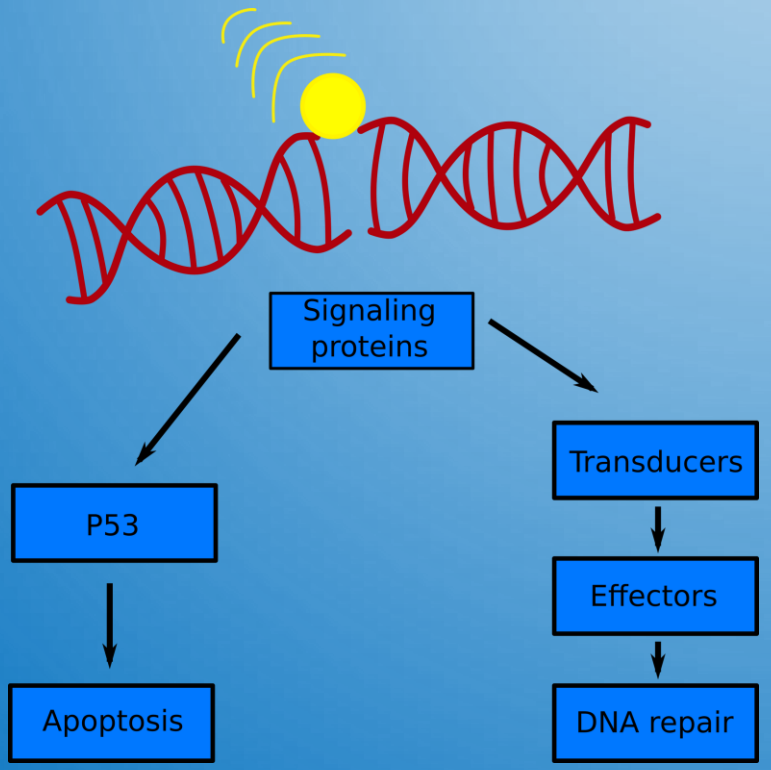
AGING DNA-DAMAGE RESPONSE, DNA-REPAIR, EPIGENETICS, POLYPHENOLS

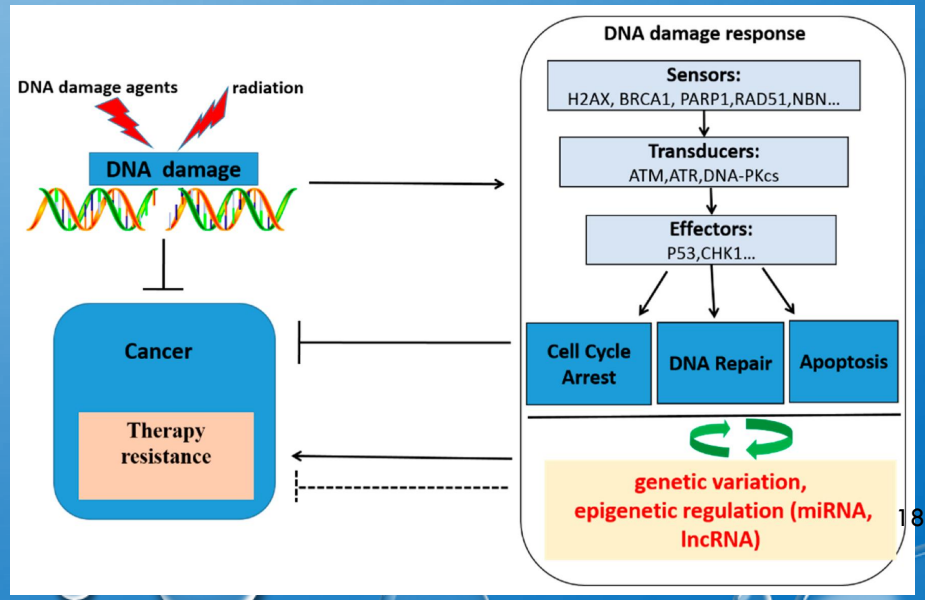




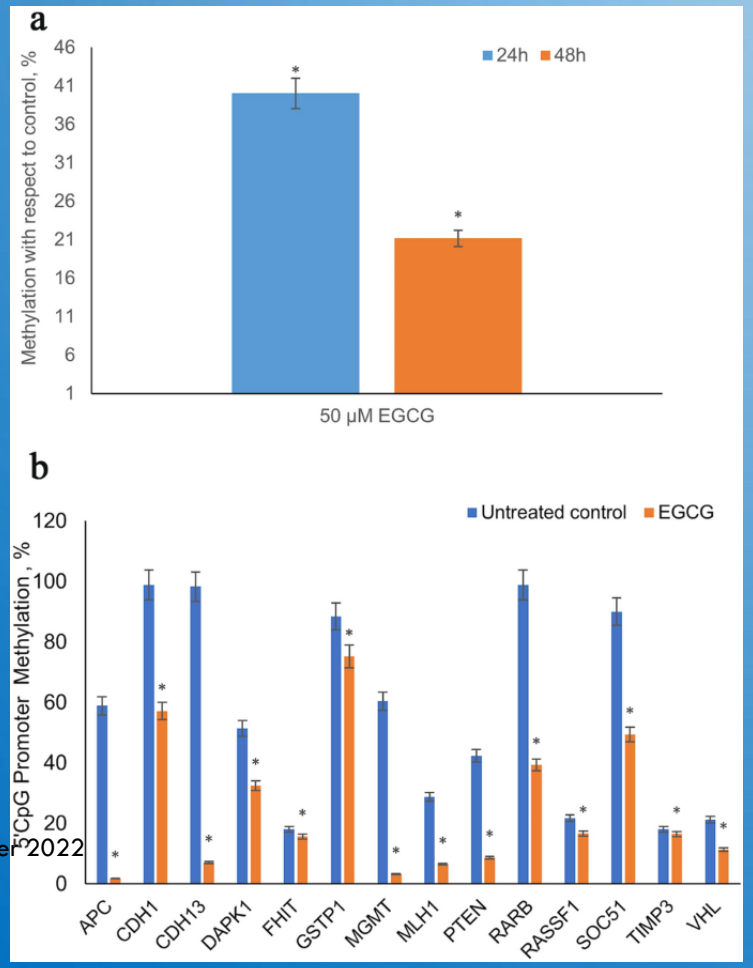


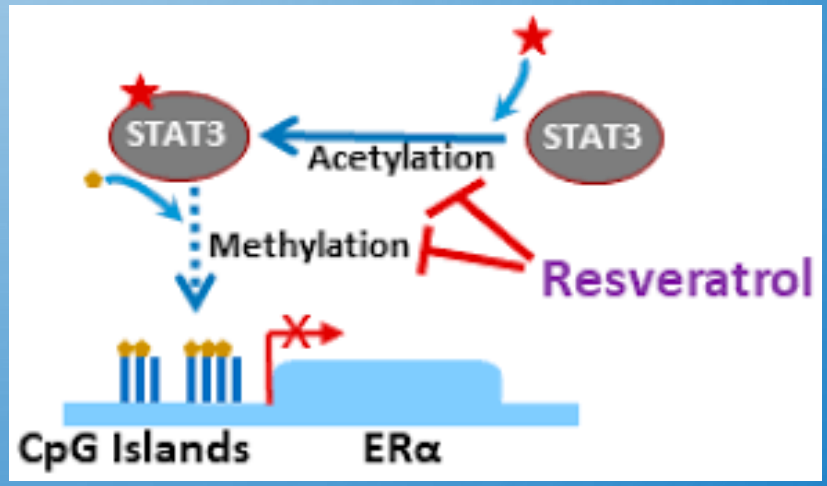
EPIGENETICS REGULATES DNA REPAIR



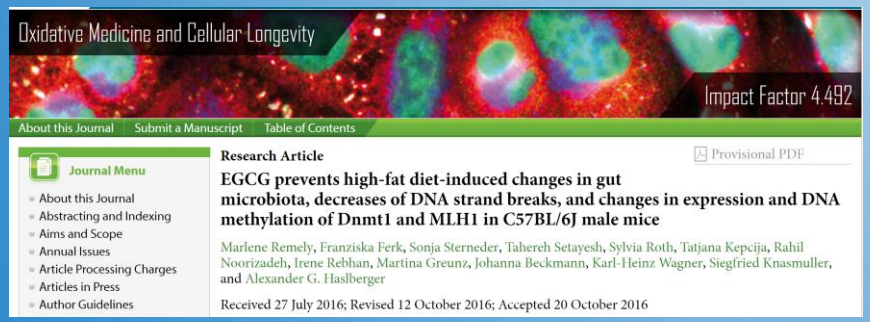


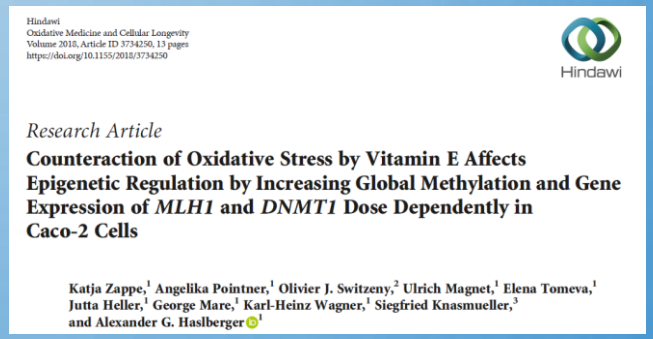
MGMT AND MLH1 DNA REPAIR ENYMES AND PROMOTOR METHYLATION, EGCG

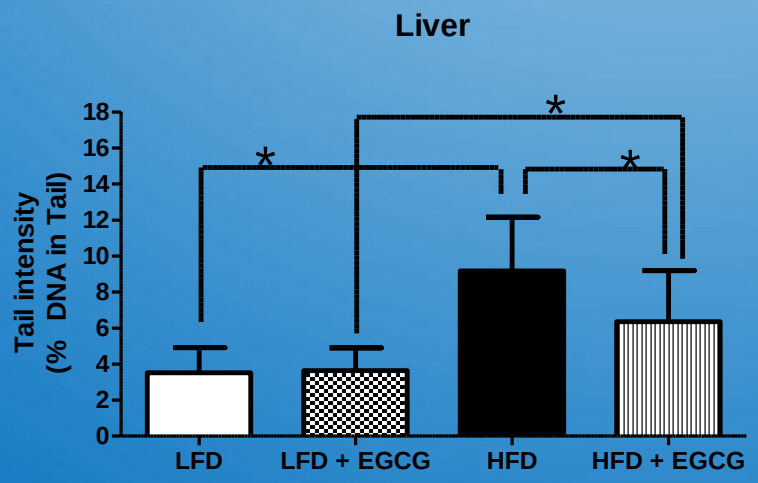


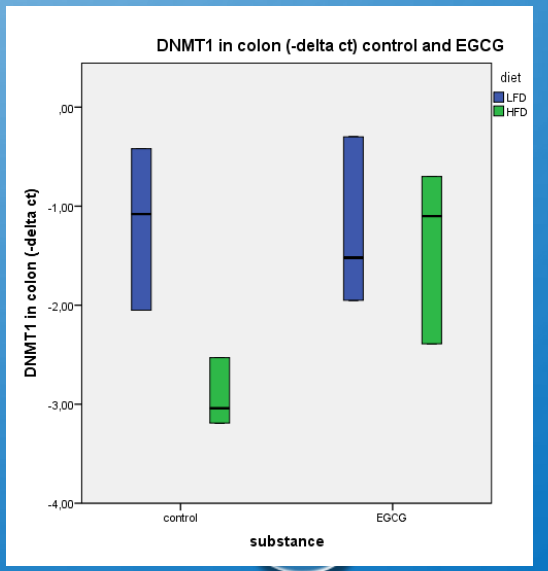


HIGH FAT MICE: EGCG REDUCES ROS INDUCED DNA BREAKS, INCREASES DNA REPAIR ENZYM MLH1 AND IMPROVED DYSBALANCED GI- MICROBIOTA

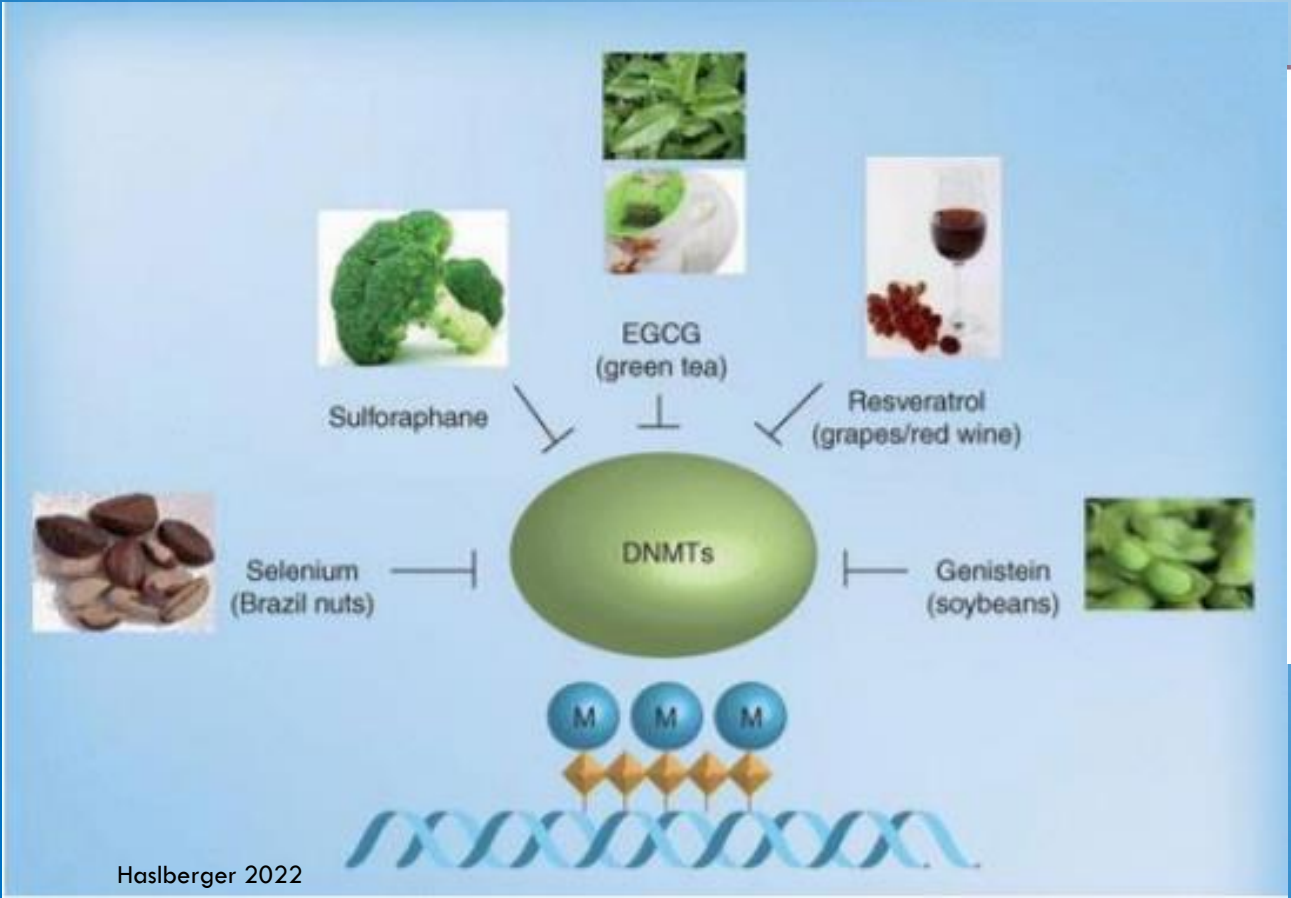


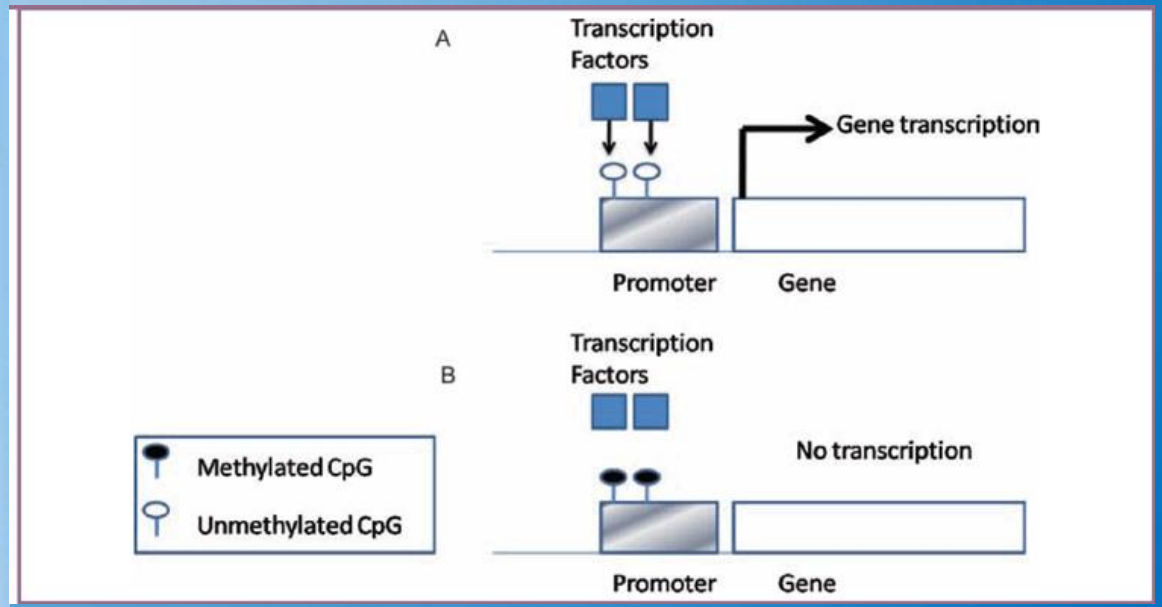






DNA, CPG METHYLATION





EFFECTS ON HISTONES, CHROMATIN

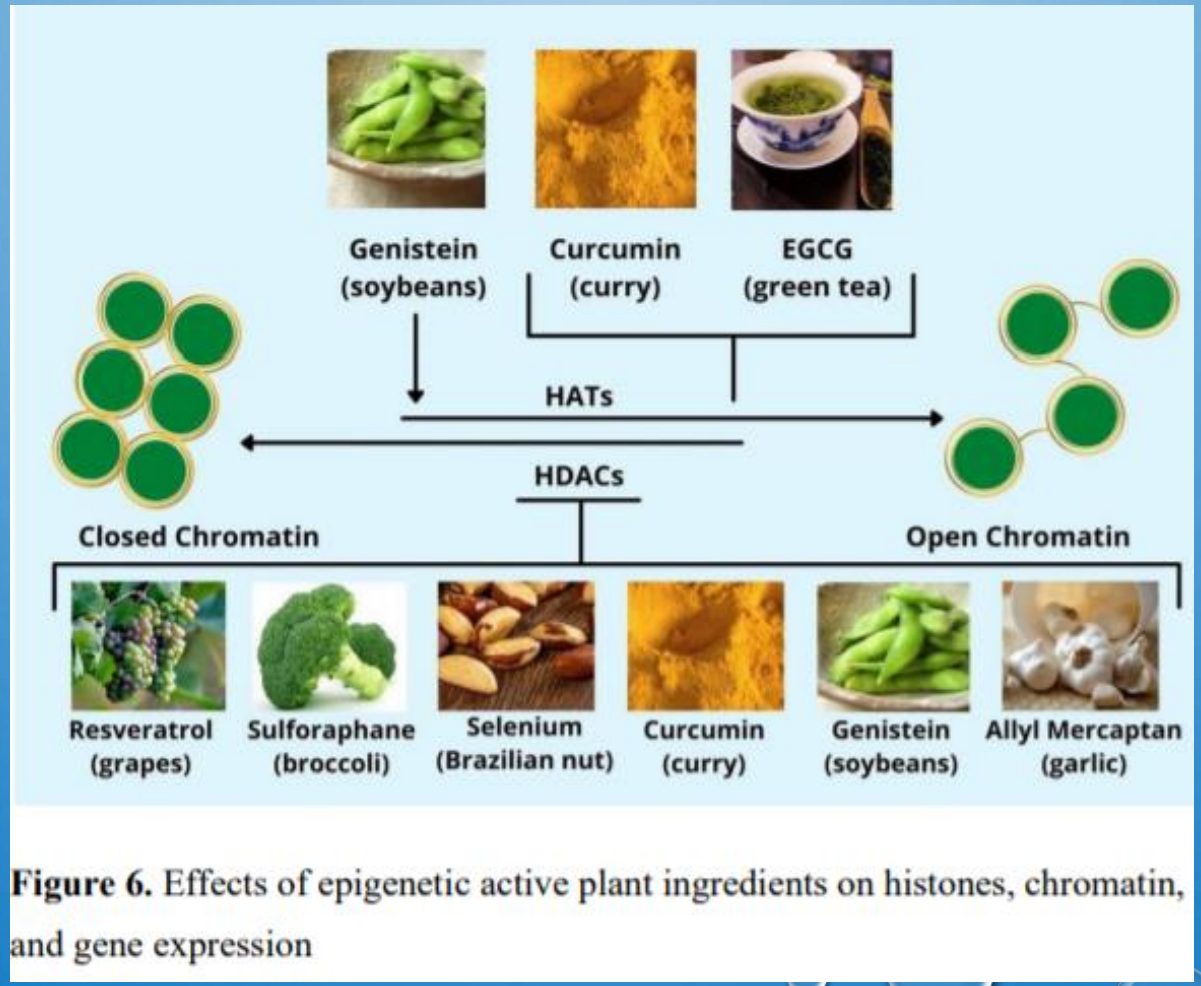
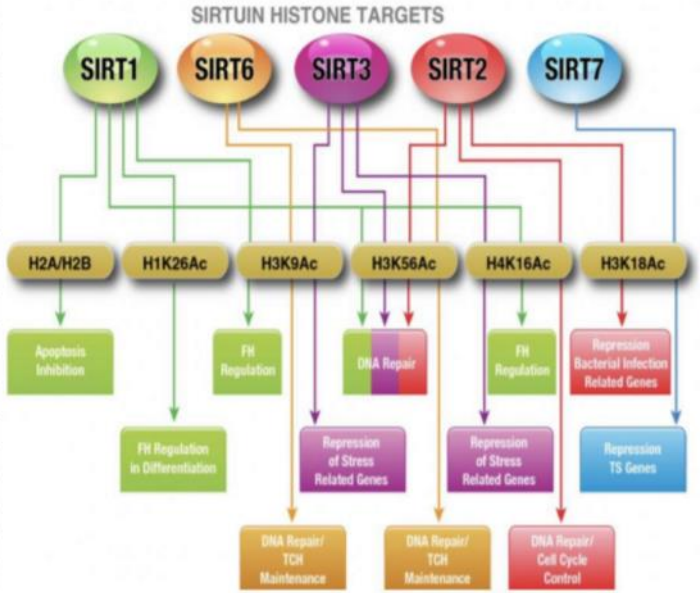
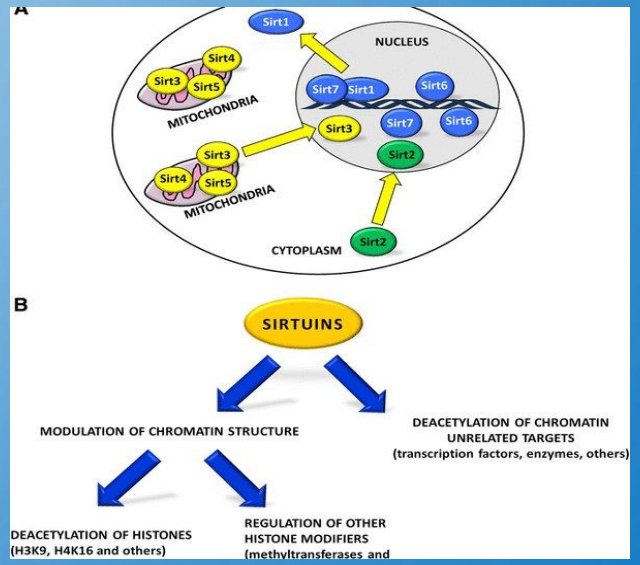


Figure 6. Effects of epigenetic active plant ingredients on histones, chromatin, and gene expression

HISTONES, ACETYLASES, DEACETYLASES, SIRTUINS, NAD

Sirtfood	Major Sirtuin-Activating Nutrients
Bird's-eye chilli	Luteolin, Myricetin
Buckwheat	Rutin
Capers	Kaempferol, Quercetin
Celery, including its leaves	Apigenin, Luteolin
Cocoa	Epicatechin
Coffee	Caffeic acid, Chlorogenic acid
Extra virgin olive oil	Oleuropein, Hydroxytyrosol
Green tea (especially matcha green tea)	Epicgallocatechin gallate (EGCG)
Kale	Kaempferol, Quercetin
Lovage	Quercetin
Medjool dates	Gallic acid, Caffeic acid
Parsley	Apigenin, Myricetin
Red chicory	Luteolin
Red onion	Quercetin
Red wine	Resveratrol, Piceatannol
Rocket	Quercetin, Kaempferol
Soy	Daidzein, Formononetin
Strawberries	Fisetin
Turmeric	Curcumin
Walnuts	Gallic acid





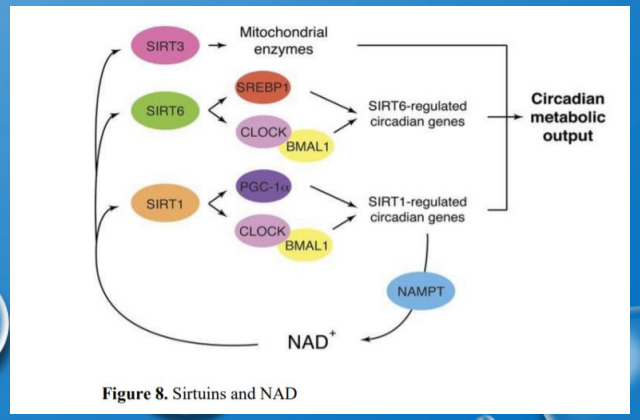
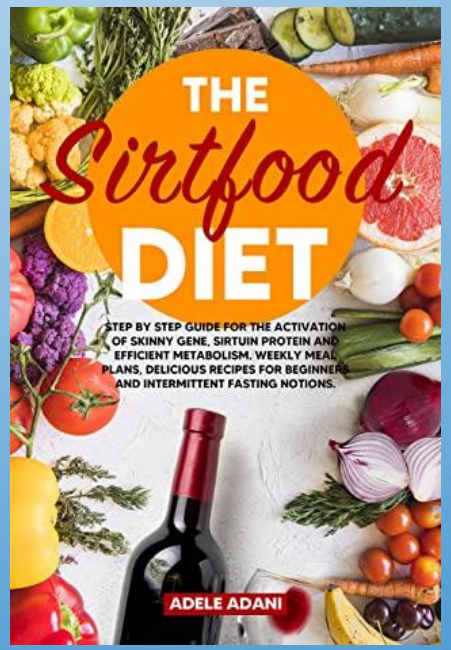


Figure 8. Sirtuins and NAD

SIRTUINS

TOP 20 SIRTFOODS

Bird's-eye chilli
Buckwheat
Capers
Celery
Cocoa
Coffee
Extra virgin olive oil
Green tea (especially matcha green tea)
Kale
Lovage
Medjool dates
Parsley
Red chicory
Red onion
Red wine
Rocket
Soy
Strawberries
Turmeric
Walnuts



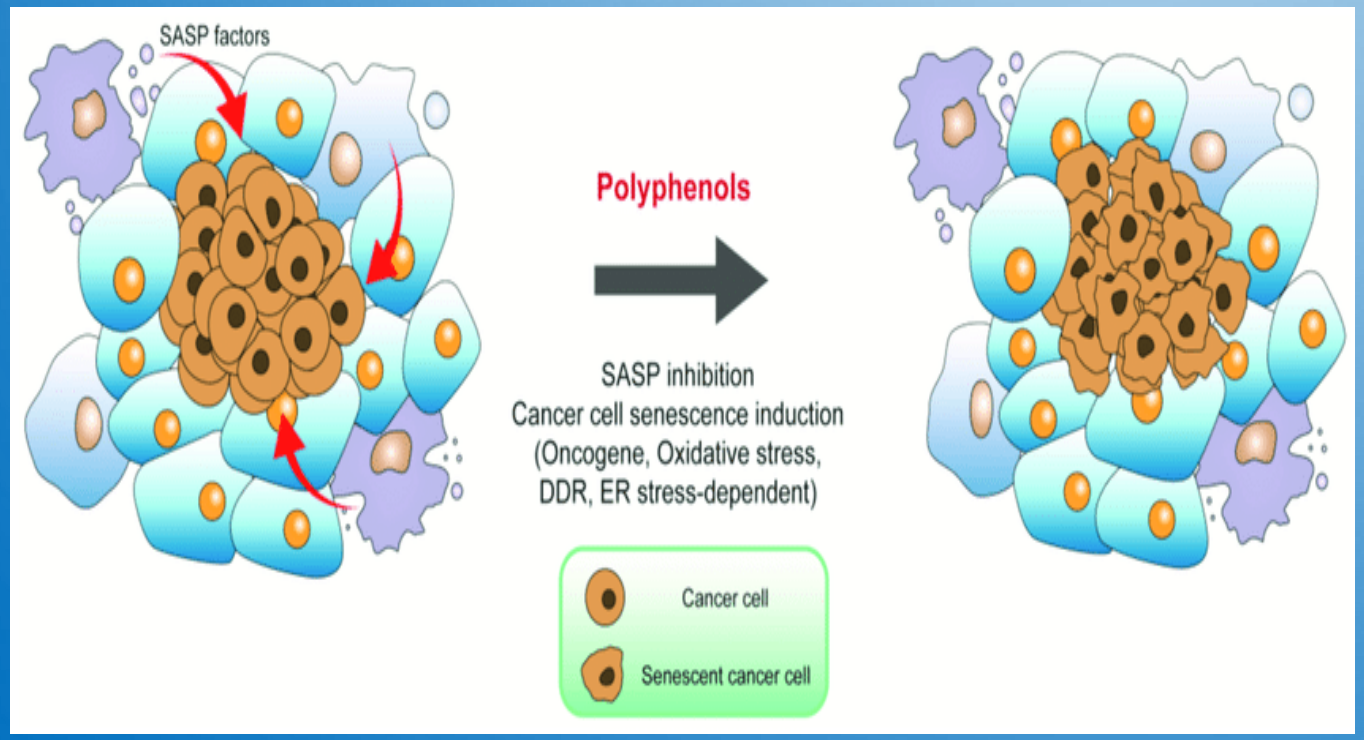
Adele hat über 40 Kilo abgenommen ...

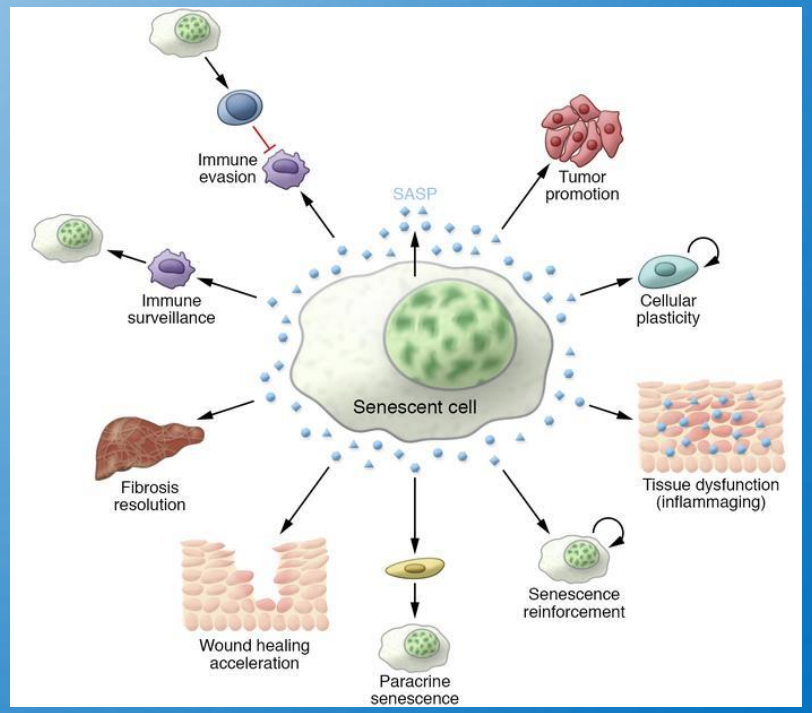
BCHD
Bioactive Compounds in Health and Disease

Increased Sirtuin expression, senescence regulating miRNAs, mtDNA, and bifidobacteria correlate with wellbeing and skin appearance after Sirtuin- activating drink

Stephanie Lilja, Hanna Bäck, Carinna Stoll, Anna Mayer, Angelika Pointner, Berit Hippe, Ulrike Krammer, Alexander G. Haslberger*

POLYPHENOLS, AGING SENESCENCE





SENESCENCE AND POLYPHENOLS

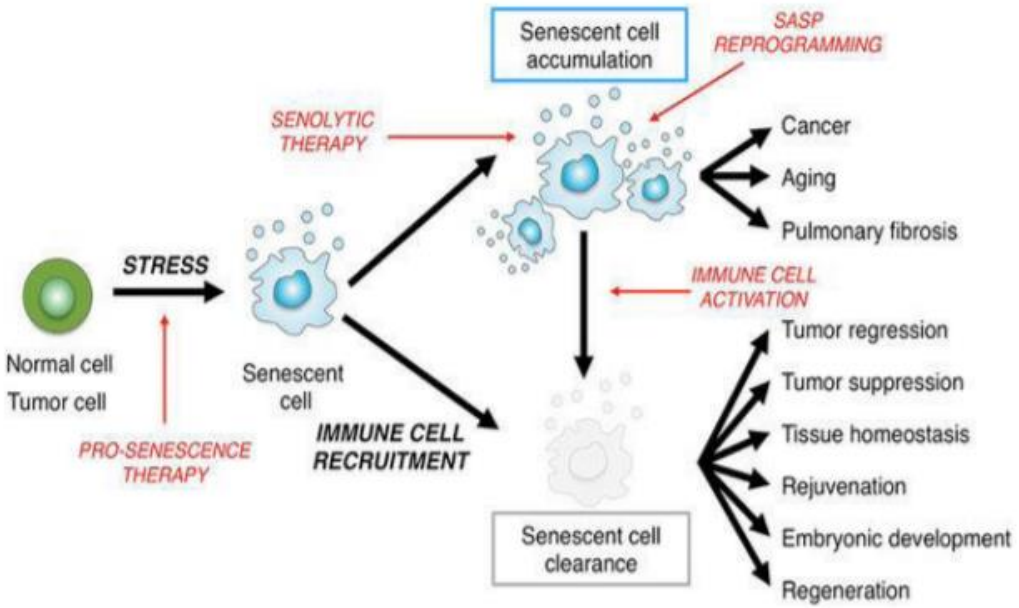
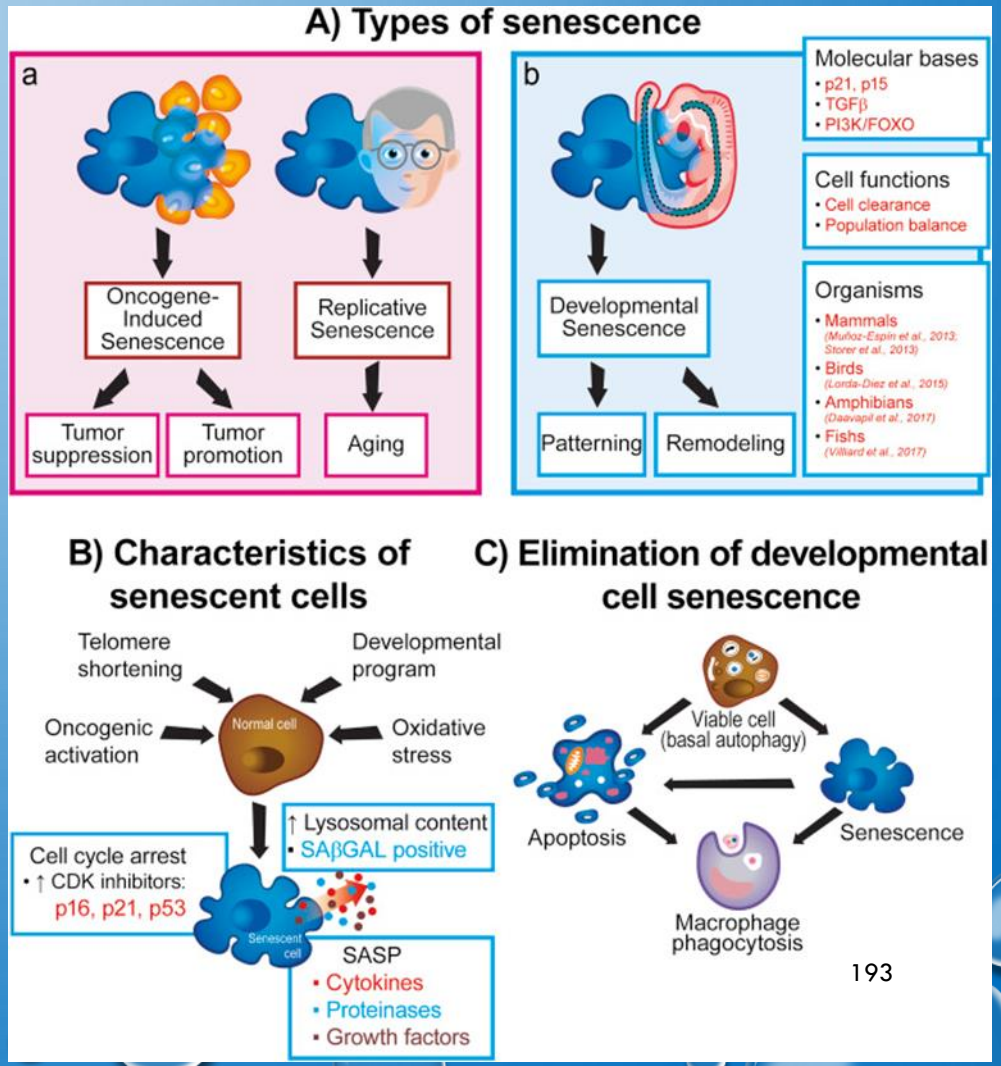


Figure 16. Clearance of senescent cells and therapeutic options. Cellular senescence is more than an anti-proliferative program. Senescent cells secrete factors that constitute the senescence-associated secretory phenotype (SASP). Cellular senescence is followed by senescent cell clearance within those processes that are considered beneficial. However, if the elimination of senescent cells does not occur, senescent cells accumulate and can lead to cancer and aging. Different therapeutic strategies (in red) could be used to exploit the beneficial aspects of cellular senescence and repress the negative ones [150].



POLYPHENOLS AND SENESCENCE

Review

Natural Polyphenols Targeting Senescence: A Novel Prevention and Therapy Strategy for Cancer

Yan Bian, Juntong Wei, Changsheng Zhao and Guorong Li *

Shandong Provincial Key Laboratory of Animal Resistant, School of Life Sciences, Shandong Normal University, Jinan 250014, Shandong, China; 2017020748@stu.sdnu.edu.cn (Y.B.); 2017020759@stu.sdnu.edu.cn (J.W.); 2017020758@stu.sdnu.edu.cn (C.Z.)

* Correspondence: grli@sdnu.edu.cn; Tel.: 86-531-86182690

Received: 3 December 2019; Accepted: 17 January 2020; Published: 20 January 2020

check for updates

Abstract: Cancer is one of the most serious diseases endangering human health. In view of the side effects caused by chemotherapy and radiotherapy, it is necessary to develop low-toxic anti-cancer compounds. Polyphenols are natural compounds with anti-cancer properties and their application is a considerable choice. Pro-senescence therapy is a recently proposed anti-cancer strategy and has been shown to effectively inhibit cancer. It is of great significance to clarify the mechanisms of polyphenols on tumor suppression by inducing senescence. In this review, we delineated the characteristics of

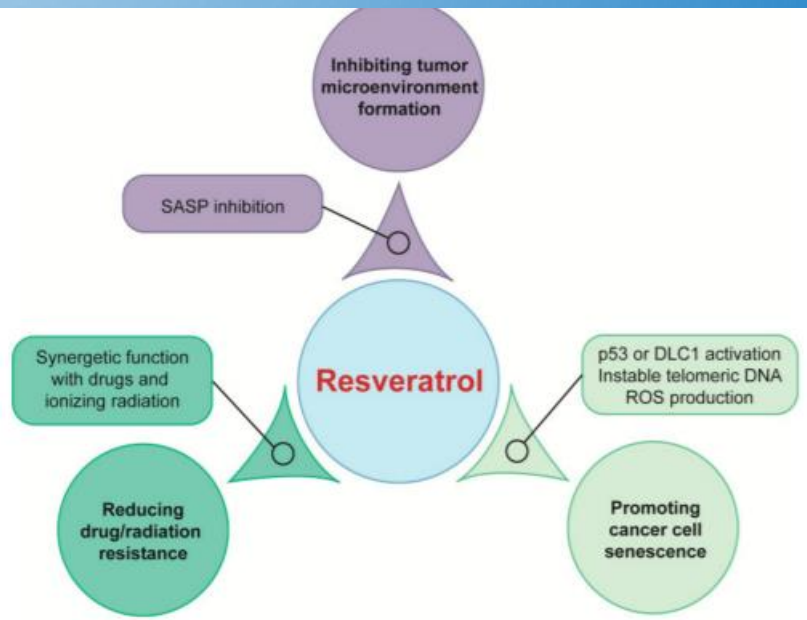
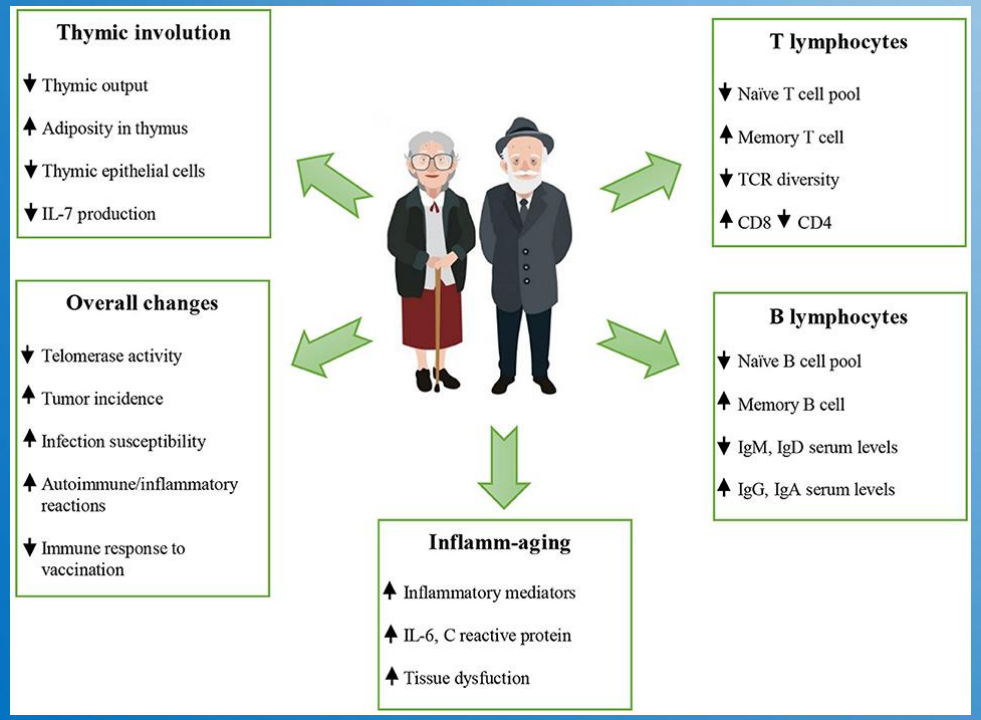


Figure 2. Potential functions of resveratrol in anti-tumor therapy. Resveratrol inhibit tumor microenvironment for cancer prevention, reduce drug/radiation resistance and induce cancer cell senescence for cancer therapy. SASP, senescence-associated secretory phenotype; DLC1, deleted in liver cancer1; ROS, reactive oxygen species.

IMMUNO SENESCENCE AND NUTRACEUTICALS



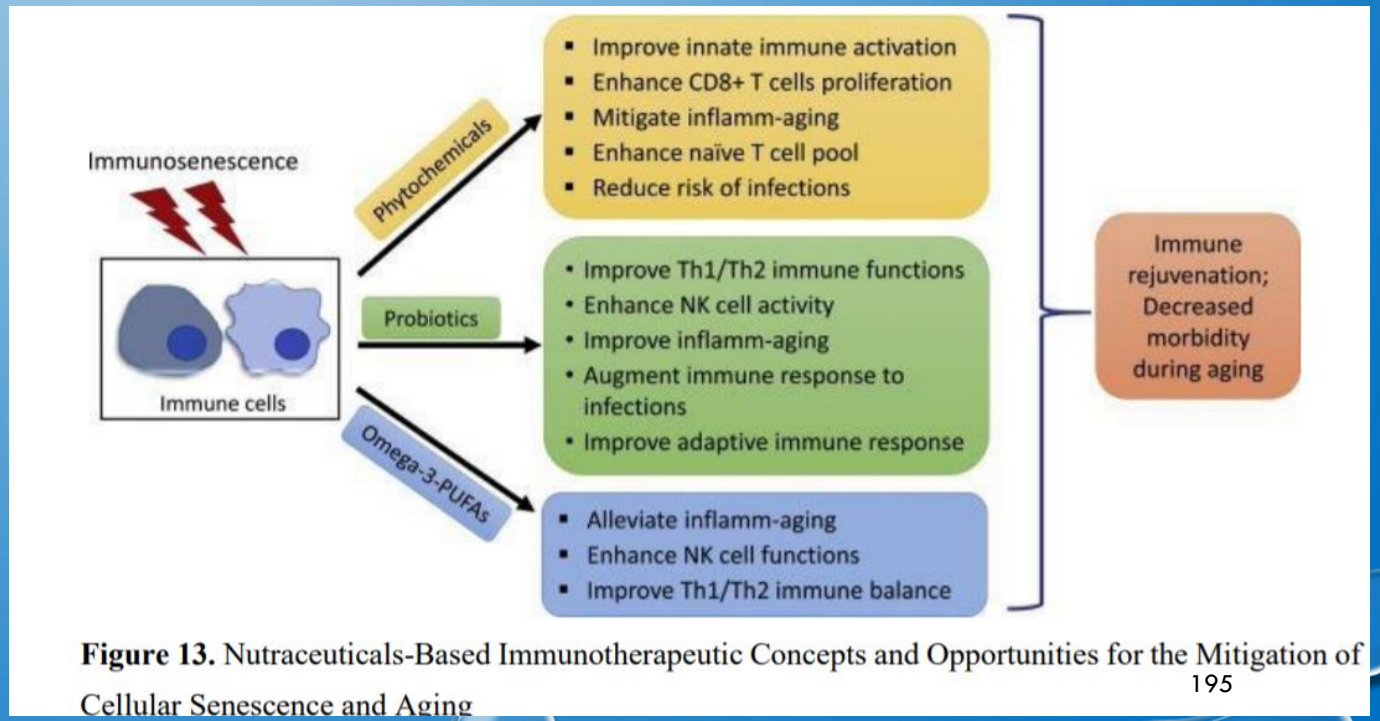


Figure 13. Nutraceuticals-Based Immunotherapeutic Concepts and Opportunities for the Mitigation of Cellular Senescence and Aging

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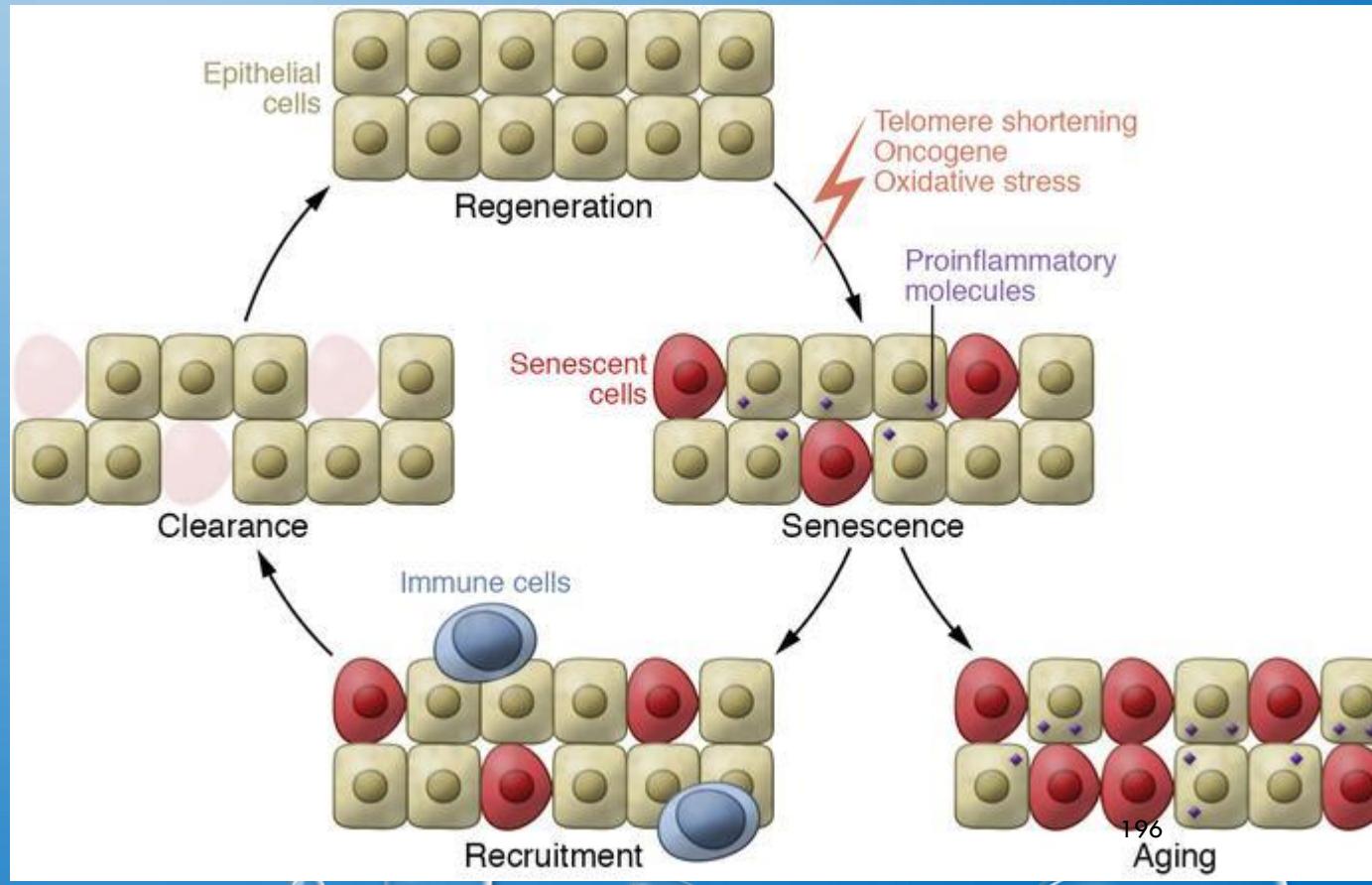
POLYPHENOLS JUVENTION OF TISSUES AND CANCER PREVENTION

Table 1. Polyphenols and polyphenol derivatives as cancer cell senescence inducers and their effect c

Classification	Compounds	Concentration	Pathways
Resveratrol and its derivatives	Resveratrol	25/50 (μM)	p53/CXCR2
		50 (μM)	BRCA1/DDR
		30 (μM)	ROS/DDR
		100 (μM)	ROS/DLC1/SASP
		6/20 (μM) 100 (μM)	Histone H2B Pokemon
		25/50 (μM)	SIRT1
		50 (μM)	Rictor/RhoA-GTPase
	Pterostilbene	2.5/5/50 (μM)	hTERT/DDR
	Pauciflorol B	10 (μM)	p16/Rb
	3,3′,4,4′-tetrahydroxy-trans-stilbene	10/50/100 (μM)	ROS DDR
Flavonoids	Quercetin	50/100/200 (μM)	RAS/MAPK/ERK PI3K/AKT
	Beta-naphthoflavone	10 (μM)	PI3K/AKT/cyclinD1/D3 MAPK/ERK
	Baicalin	10/20/40 (μM)	DEPP/RAS/Raf/MEK/ERK DEPP/p16/Rb
	IdB 1016	63.2/126.5 (μg/mL)	HER-2/neu p53
	Diosmin	5/10 (μM)	ROS DDR
	Apigenin	Above 25 (μM)	ROS/RNS p16/cyclin D1/p-Rb p21/cyclin E/p-Rb
	Coumestrol	50 (μM)	CKII/ROS/p53/p21
	Rotenone	0.4 (μM)	Ca^{2+}/ROS
	Epigallocatechin gallate	10 (μM)	DDR
	Oroxin A	5/10/15/20 (μM)	p38/ER stress
	Cristacarpin	1 (μM)	p38/ER stress/ROS/p21
	Flavokawain B	3 (μg/mL)	ATF4/DDIT3/TRIB3/AkT/mTOR



EXERCISE INHIBITS SENESCENCE

1606 Diabetes Volume 65, June 2016

Marissa J. Schafer,[1,2] Thomas A. White,[1] Glenda Evans,[1] Jason M. Tonne,[3] Grace C. Verzosa,[4] Michael B. Stout,[1,5] Daniel L. Mazula,[1] Allyson K. Palmer,[1] Darren J. Baker,[1,6] Michael D. Jensen,[7] Michael S. Torbenson,[8] Jordan D. Miller,[1,4] Yasuhiro Ikeda,[3] Tamara Tchkonia,[1] Jan M. van Deursen,[1,9] James L. Kirkland,[1,5] and Nathan K. LeBrasseur[1,2]

Exercise Prevents Diet-Induced Cellular Senescence in Adipose Tissue

Diabetes 2016;65:1606–1615 | DOI: 10.2337/db15-0291

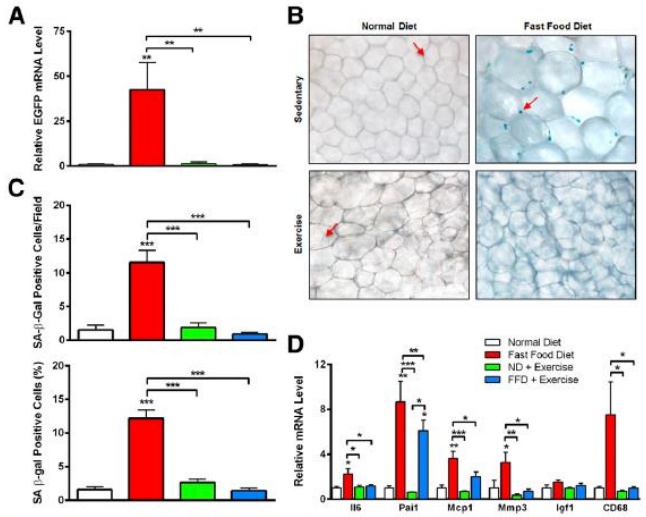


Figure 4—Exercise prevents diet-induced cellular senescence and the SASP within visceral adipose tissue. *A*: Compared with the ND, the FFD caused a marked increase in the activity of the senescence-associated $p16^{INK4a}$ promoter, as measured by EGFP expression. *B*: Representative images show the abundance of cells positive for SA-β-gal (arrow) in harvested visceral adipose tissue further validated the pro- and antisenescent effects of nutrient excess and exercise, respectively (summary data, *C*). *D*: The expression of SASP and inflammatory factors was also increased in response to FFD, and these increases were attenuated by exercise. For all analyses, $n = 6–7$ mice/group. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

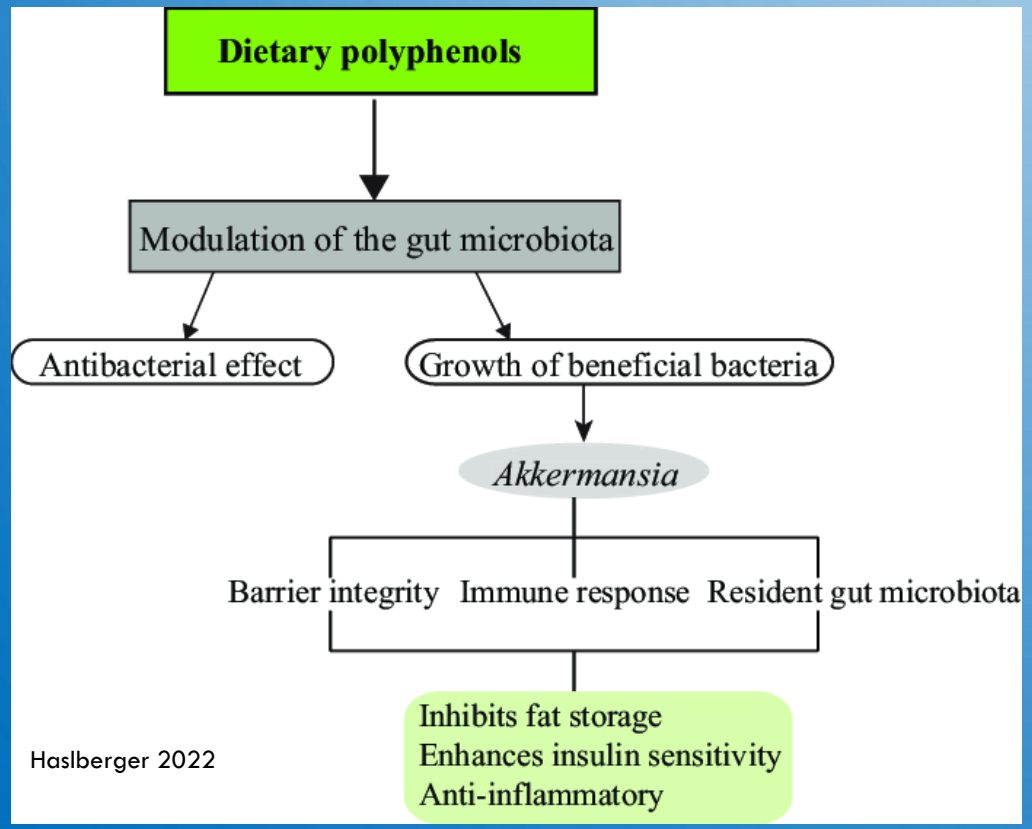
Nutrition and Healthy Aging 4 (2016) 95–99
DOI 10.3233/NHA-1614
IOS Press

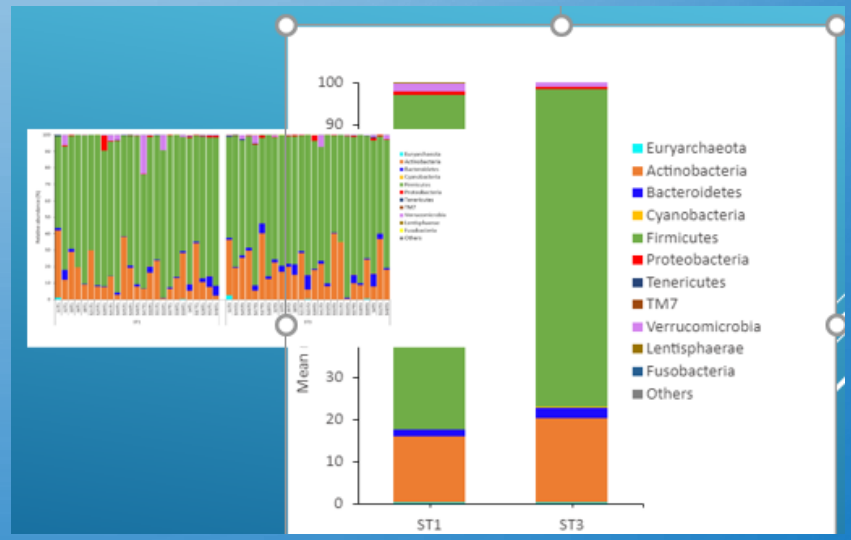
Short Communication

Diet-induced weight loss is sufficient to reduce senescent cell number in white adipose tissue of weight-cycled mice

Edward O. List[a,b,c,*], Elizabeth Jensen[a], Jesse Kowalski[a], Mathew Buchman[a], Darlene E. Berryman[a,c,d] and John J. Kopchick[a,c,d]

POLYPHENOLS AND MICROBIOTA STRUCTURE





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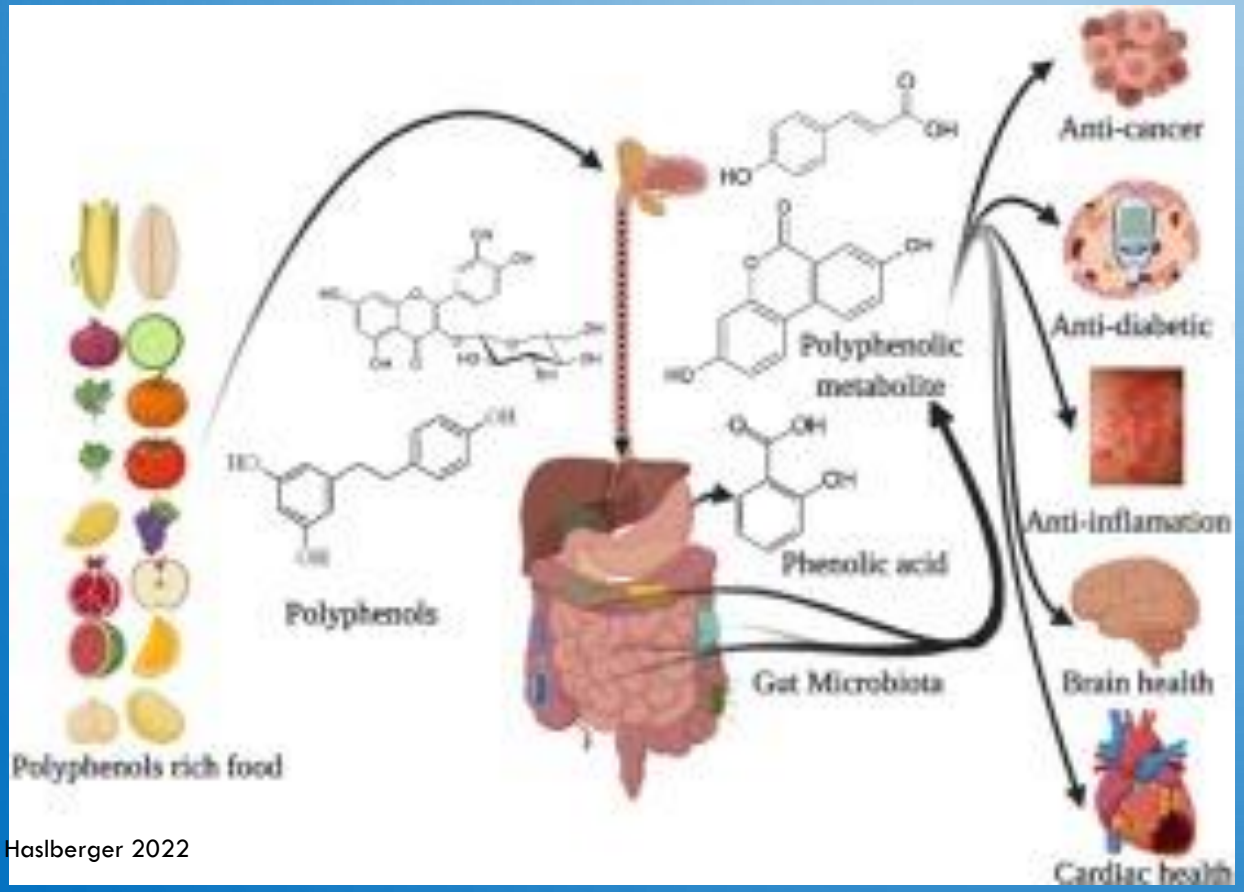
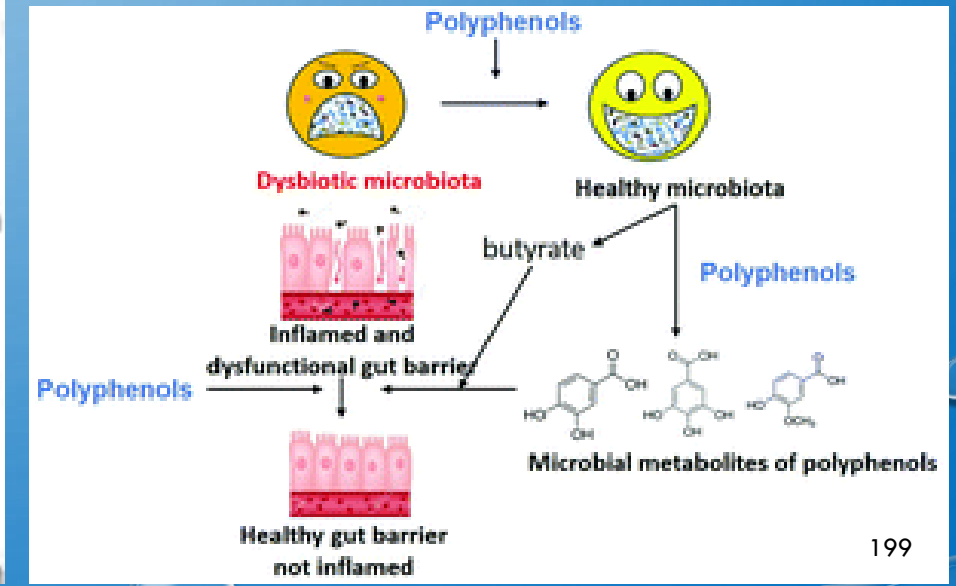
POLYPHENOLS, MICROBIOTA AND THEIR METABOLITES





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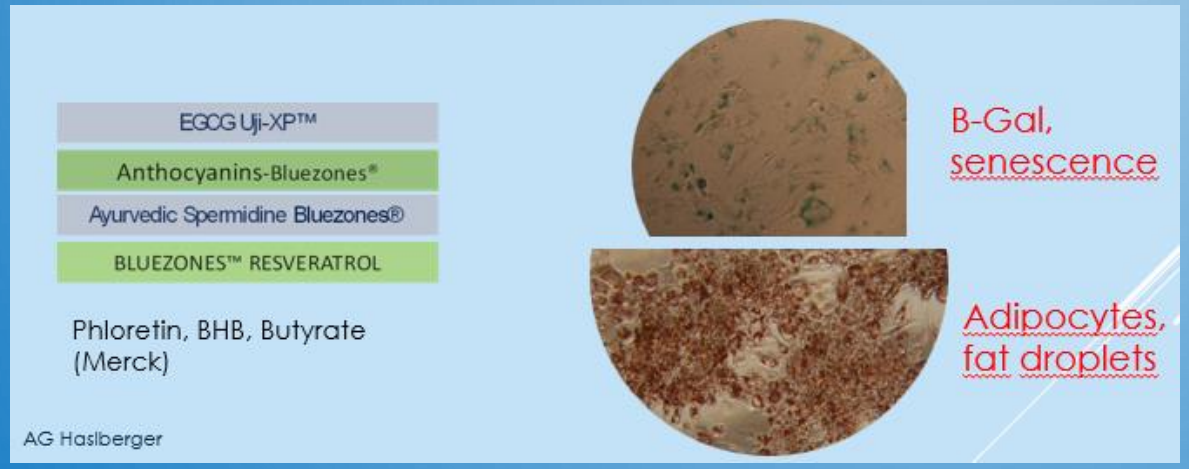
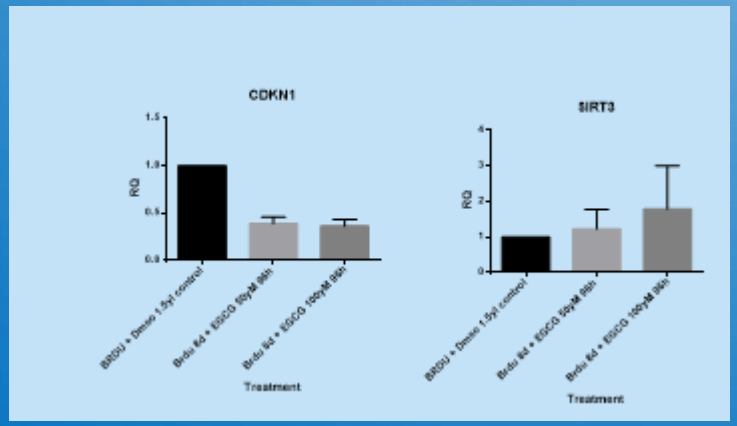




Haslberger 2022

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2020, Article ID 4793125, 13 pages
https://doi.org/10.1155/2020/4793125

Hindawi

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

Stephanie Lilja,[1] Julia Oldenburg,[1] Angelika Pointner,[1] Laura Dewald,[1] Mariam Lerch,[1] Berit Hippe,[2] Olivier Switzeny,[2] and Alexander Haslberger[1]

[1]*Department of Nutritional Sciences, University of Vienna, 1090 Vienna, Austria*
[2]*HealthBioCare GmbH Nußdorferstraße 67, 1090 Wien, Austria*

Functional Foods in Health and Disease 2020; 10(10):439-455 www.ffhdj.com Page 439 of 455

Research Article Open Access

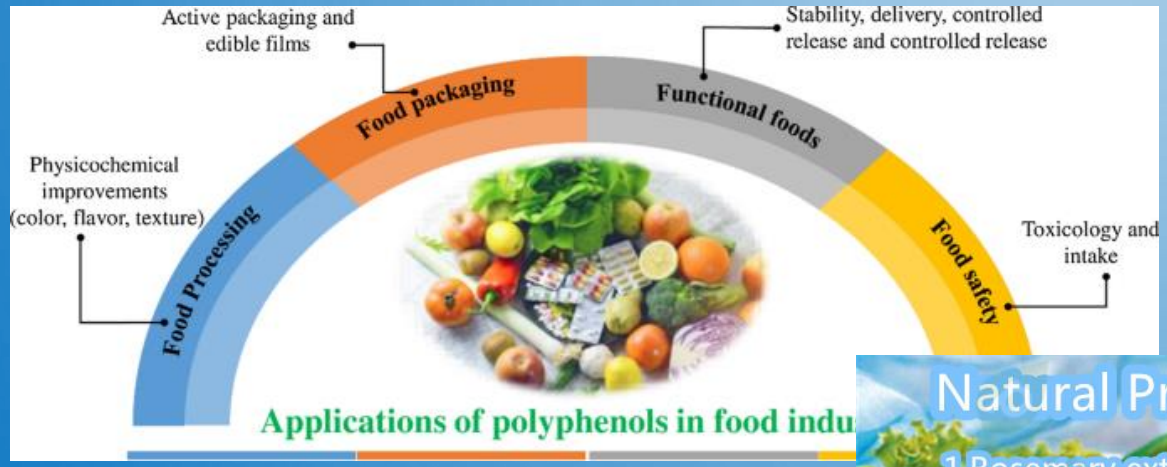
FFHD
Functional Foods in Health and Disease

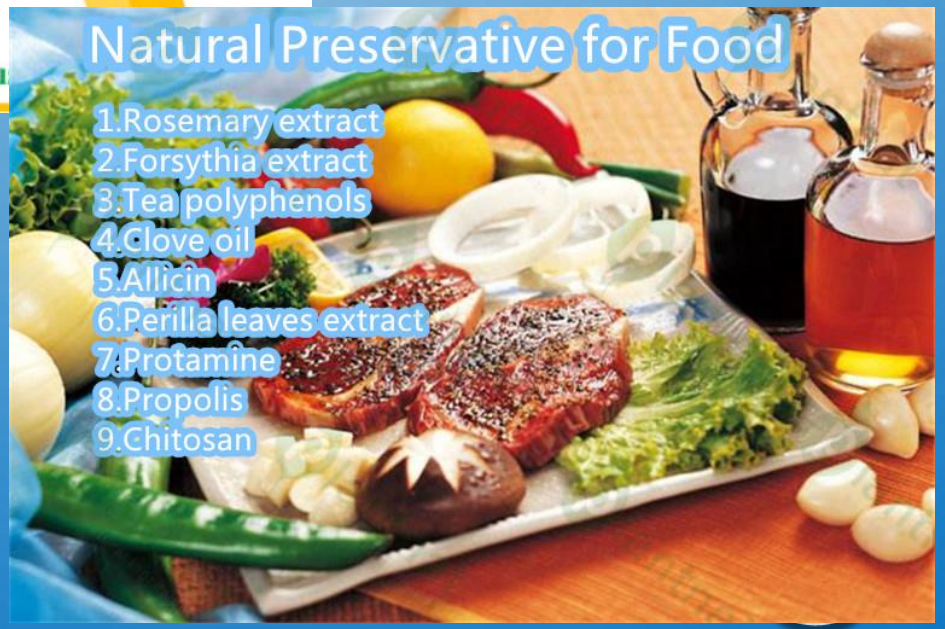
Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition

Stephanie Lilja[1], Angelika Pointner[1], Hanna Bäck[1], Kalina Duszka[1], Berit Hippe[1], Lucia Suarez[1], Ingrid Höfinger[2], Tewodros Debebe[3], Jürgen König[1], Alexander G. Haslberger[1]

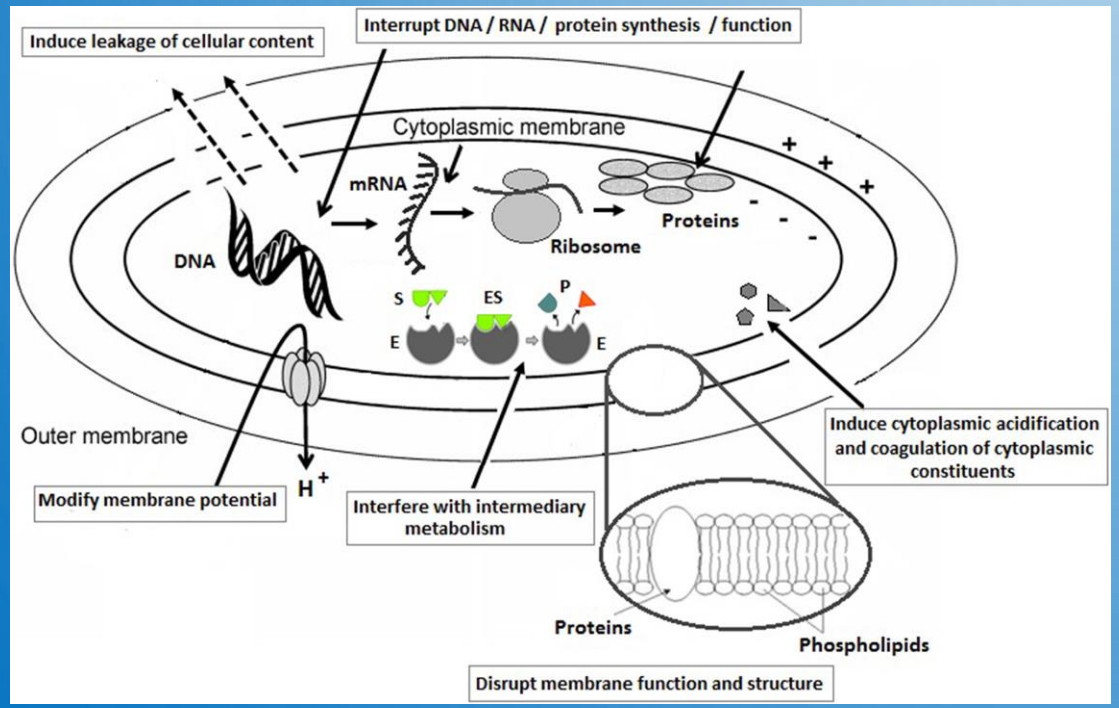
[1]Department of Nutritional Sciences, University of Vienna, 1090 Vienna, Austria, [2]Monastory, Pernegg, [3]Biomes NGS GmbH, Germany

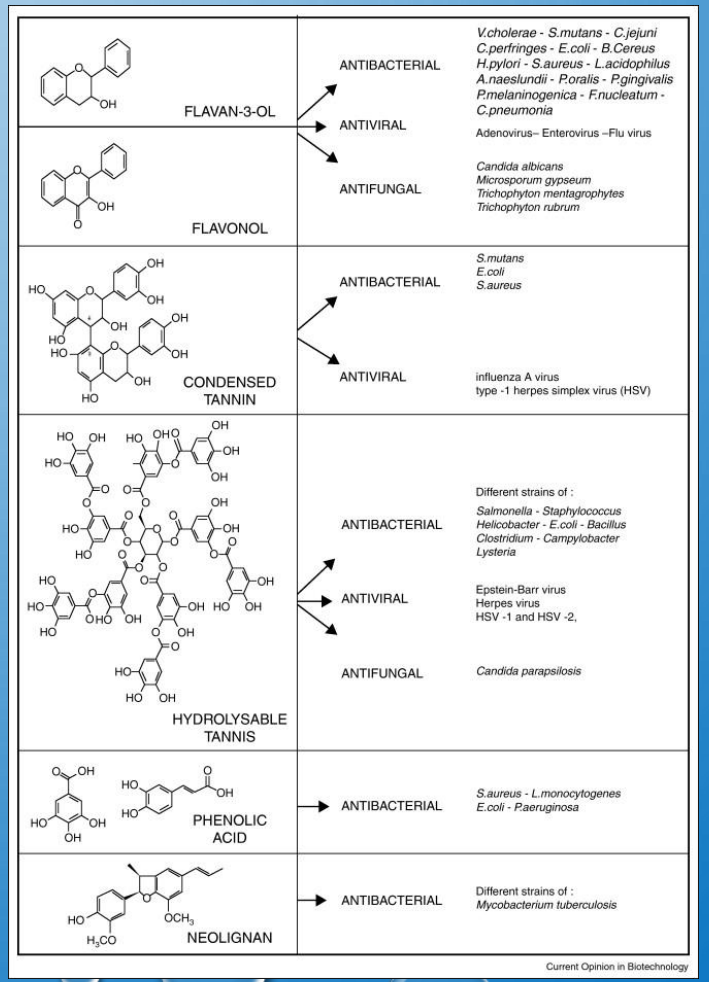
POLYPHENOLS IN FOOD PRESERVATION, PROCESSING





ANTI BACTERIAL POLYPHENOLS





ANTIVIRAL NUTRACEUTICALS

Fermented products
Probiotics enhance gut bacteria & gut–lung axis-related respiratory fitness

Herbs & roots
Prevent viral replication, enhance anti-influenza virus IgG and IgA antibodies production & T-cell function

Dairy products
Vitamin D lowers viral replication, reduce infection rate & lung pneumonia

Fish, chicken & meat
Immune defence; peptides enhance monocytes & macrophages functions & prevent infected lung injury

Antiviral Functional Foods

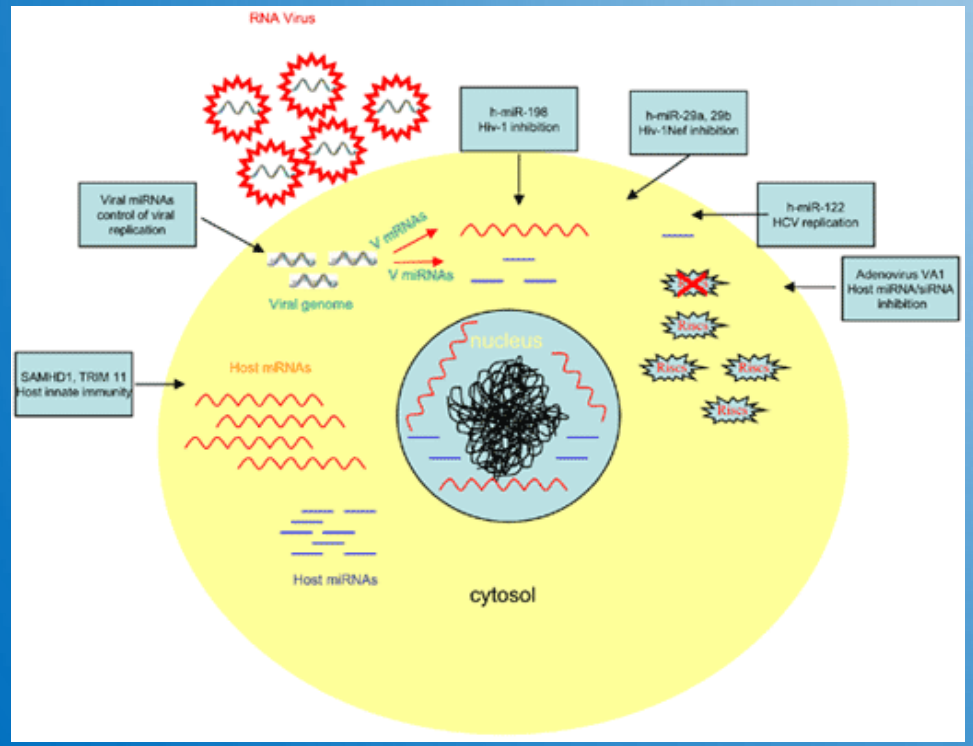
Fruit and vegetables
Vitamins & minerals antioxidant immune protection of respiratory system. Plant cyclotides prevent T-cells malfunction

Coffee
Decreases progeny virus yield, neutrophil & monocyte chemotaxis, lipopolysaccharide & prevent mucosal response to influenza pathogens

Nuts & seeds
Immuno-protective phenolic compounds for high-risk groups

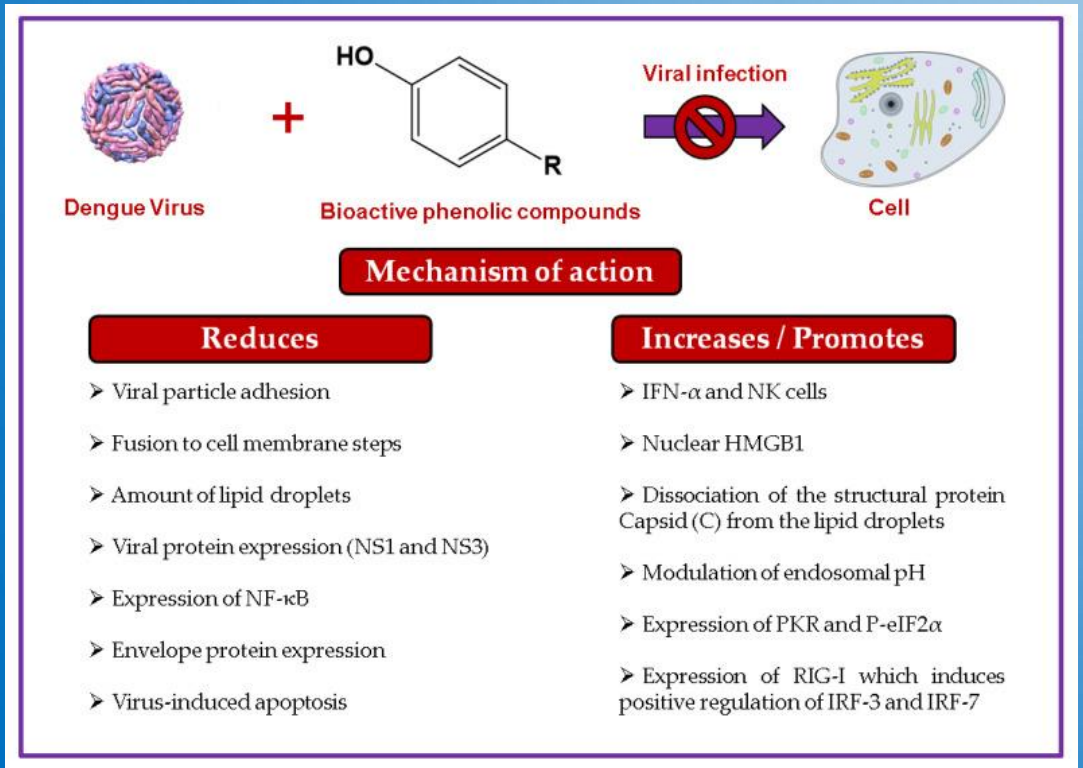
Olive Oil
Prevents respiratory syncytial virus & influenza A, B, parainfluenza 1, 2 & 3 viruses

RNA AND CORONA VIRUSES



Name	Abbrev.	Accession	Length	Base composition
SARS coronavirus Urbani	SARS	AY278741	29,727	(0.28, 0.20, 0.21, 0.31)
Avian infectious bronchitis virus	AIBV	NC_001451.1	27,608	(0.29, 0.16, 0.22, 0.33)
Bovine coronavirus	BCoV	NC_003045.1	31,028	(0.27, 0.15, 0.22, 0.36)
Human coronavirus 229E	HCoV	NC_002645.1	27,317	(0.27, 0.17, 0.22, 0.35)
Murine hepatitis virus	MHV	NC_001846	31,357	(0.26, 0.18, 0.24, 0.32)
Porcine epidemic diarrhea virus	PEDV	NC_003436.1	28,033	(0.25, 0.19, 0.23, 0.33)
Transmissible gastroenteritis virus	TGV	NC_002306.2	28,586	(0.29, 0.17, 0.21, 0.33)
Rubella virus	RUV	NC_001545.1	9,755	(0.15, 0.39, 0.31, 0.15)
Equine arteritis virus	EAV	NC_002532.2	12,704	(0.21, 0.26, 0.26, 0.27)
Rabies virus	RV	NC_001542.1	11,932	(0.29, 0.22, 0.23, 0.26)
Human immunodeficiency virus 1	HIV-1	NC_001802.1	9,181	(0.36, 0.18, 0.24, 0.22)

Influenca, Dengue,



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S. No.	Molecule	Target	Type of Study/ Techniques Used	Results	Study, Year, Reference
1	Luteolin	SARS-CoV S2 protein	• Frontal-affinity chromato-graphy-mass spectrometry • HIV-luc/SARS pseudotype virus assay • MTT assay with wild-type SARS-CoV	• Luteolin-inhibited SARS-CoV infection in a dose-depen-dent manner. • EC_{50} was 10.6 μM. CC_{50} was 0.155 mM. LD_{50} in mice was 232.2 mg/kg	Yi et al, 2004[11]
2	Quercetin	SARS-CoV S2 protein	HIV-luc/SARS pseudotype virus assay	EC_{50} of 83.4 μM and CC_{50} of 3.32 mM	Yi et al, 2004[11]
3	GCG (gallocatechin gallate)	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 91% inhibition by 200 μM. • IC_{50} of 47 μM. • Binding energy of −14 kcal/mol	Nguyen et al, 2012[14]
4	Quercetin	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 80% inhibition at 200 μM. • IC_{50} of 23.8 μM • Binding energy −10.2 kcal/mol	Nguyen et al, 2012[14]
5	EGCG	SARS-CoV 3CLPro	• Expression of recombinant 3CLPro in *Pichia pastoris* and its inhibition. • Molecular docking	• 85% inhibition at 200 μM. • IC_{50} of 73 μM • Binding energy −11.7 kcal/mol	Nguyen et al, 2012[14]
6	Resveratrol	MERS-CoV NP	• MTT assay using vero-E6 cell line • Nucleocapsid protein staining	• Found to be effective in the 125–250 μM range on viral titre as well as viral RNA amount. • Inhibits caspase 3 cleavage.	Lin et al, 2017[12]
7	Hesperetin	SARS-CoV 3CLPro	Cell free and cell-based cleavage assays	IC_{50} of 60 μM in cell free assay, IC_{50} of 8.3 μM in cell-based assay and a CC_{50} of 2718 μM	Lin et al, 2005[15]
8	Quercetin	*ACE2* and *FURIN*	• Gene silencing • Expression studies • Transgenic mouse models	• Quercetin affected *ACE2* expression. • In addition, it was found to alter the expression of 98 of 332 (30%) genes encoding human proteins that serve as target for the SARS-CoV-2.	Glinsky, 2020[16]

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Review

Polyphenols and their potential role to fight viral diseases: An overview

María Fernanda Montenegro-Landívar [a,b], Paulina Tapia-Quirós [a,b], Xanel Vecino [a,b,c], Mònica Reig [a,b], César Valderrama [a,b], Mercè Granados [d], José Luis Cortina [a,b,e,*], Javier Saurina [d]

[*] Chemical Engineering Department, Escola d'Enginyeria de Barcelona Est (EEBE), Universitat Politècnica de Catalunya (UPC)-BarcelonaTECH, C/Eduard Maristany 10–14, Campus Diagonal-Besòs, 08930 Barcelona, Spain

Table 1
Different families and type of viruses, their specific virus and the role of polyphenols as a possible alternative to treat virus.

Type of virus	Specific virus	Disease characteristics	Conventional treatment	Alternative treatment with polyphenols	Reference
Respiratory infections	Influenza virus (A, B and C)	Annually responsible for high mortality in both humans and animals worldwide	NA inhibitors and M2 protein channel blockers after infection, while vaccination is the most effective therapy	1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC_{50} of 2.36 μg/mL) purified from *Echinacea purpurea*, *Phyllanthus emblica* Linn inhibits virus replication	(Fox and Christenson, 2014; Liu et al., 2011; Moscona, 2008)
	Coronavirus (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the novel SARS-CoV-2)	Respiratory tract infections in humans with outbreaks around the world, especially in winter	Currently there are no specific treatments for the CoV infection and preventive vaccines are being developed	Polyphenol extract from *Echinacea purpurea* against SARS-CoV-2 provided 50% of inhibition Kaempferol and quercetin from *Broussonetia papyrifera* against MERS-CoV and SARS-CoV effectively inhibited with an IC_{50} of 27.9 μM and 30.2 μM, respectively	(Chiow et al., 2016; Liu et al., 2020; Park et al., 2017; Signer et al., 2020)
	Rhinovirus	The main cause of the common cold, among other respiratory diseases, also producing shortness of breath in asthmatic people, acute otitis and bronchiolitis	There are no vaccines or antiviral agents for the prevention or treatment of this virus	Resveratrol showed a therapeutic approach to reduce infection when the IC_{50} was 50 μM Gallic acid, extracted (100 μg/mL) from *Woodfordia fruticose* flowers, reported 55% virus inhibition	(Choi et al., 2010; Mastromarino et al., 2015; Ruuskanen et al., 2013)
	Syncytial virus	Causes infections in infants and the elderly, causing not only acute morbidity but also recurrent breathing problems	There is no safe and effective treatment Corticosteroids was treated children of preschool-age who had early bronchitis, but the results were not satisfactory and failed to reduce the infection or breathing problems	Resveratrol (IC_{50} 189 pg/mL) inhibits 40% virus replication and down-regulates the TIR-domain-containing adapter-inducing interferon-β (TRIF) complex, which sends signals for the activation of innate immune cells	(Beigelman et al., 2014; Tagarro et al., 2014; Xie et al., 2012)
Gastrointestinal infections	Rotavirus	Causes dehydrating gastroenteritis, especially in children under five years of age	There is a vaccine against rotavirus but annually the mortality is around 200,000 deaths worldwide. The treatment focuses on dehydration and not on the use of antiviral agents	Polyphenols (licocoumarone, glycyrin, among others) extracted from *Glycyrrhiza uralensis* root (EC_{50} 18.7–69.5 μM) can inhibit 50% virus absorption and replication after the cell's entry	(Crawford et al., 2017; Cushnie and Lamb, 2005; Kwon et al., 2010)
Hepatic infections	Hepatitis virus (A, B and C)	Cause high morbidity and mortality around the world	Anti-hepatitis virus drugs are members of nucleotides or nucleoside analogs, which inhibit the activity of polymerase or reverse transcriptase, but the prolonged use giving rise to the existence of mutant viruses	Curcumin (150 μM) inhibits hepatitis B virus	(Mouler Rechtman et al., 2010; Sukowati et al., 2016; Yugo et al., 2016)
	Epstein–Barr virus	Infects human epithelial and lymphoid cells. Infection is associated with a number of human cancers, such as Hodgkin's disease	A vaccine is not yet approved	(−)-Epigallocatechin gallate (EGCG) extracted from green tea (50 μM) blocked the EBV lytic cycle, inhibiting the transcription of immediate-early genes in a range of 40–50%	(Abba et al., 2015; Chang et al., 2003; Cohen, 2018)
	Human cytomegalovirus	Not present obvious symptoms, but infection causes morbidity and mortality in transplant recipients or patients with acquired immunodeficiency syndrome (AIDS)	Drugs such as cidofovir, valganciclovir and ganciclovir, which target viral DNA polymerase, but their side-effects include long-term toxicity, low bioavailability, plus drug resistance to the virus	Curcumin, using a low dose of 0.2 μg/mL, inhibits virus protein expression	(Ahmed, 2012; Evers et al., 2005; Lv et al., 2014)
	Herpes simplex virus (HSV-1 and HSV-2)	Responsible for orolabial and genital diseases producing, in general, benign lesions but, in some cases, putting the life of patients at risk if the infections are recurrent	There is no vaccine and existing drugs (e.g., acyclovir) do not eradicate the virus infection and cause resistance to drugs	Ent-epiafzelechin-(4α→8)-epiafzelechin extracted from *Cassia javanica* leaves (250 μM of) inhibits more than 90% of HSV-2 penetration to the host cell	(Cheng et al., 2006; Morfin and Thou, 2003; Piret and Boivin, 2011)
Exanthematous infections	Varicella-zoster virus	Causes fever and vesicular rash. Once the disease has disappeared, the virus enters into a state of latency, but it can be reactivated due to stress, causing herpes	Generally, uses drugs such as acyclovir, valacidovir, etc., which are often combined with analgesics for pain and corticosteroids for inflammation	Resveratrol (219 μM of) inhibits 100% virus replication	(Docherty et al., 2006; Johnson and Whitton, 2004)

(continued on next page)

https://www.sciencedirect.com/science/article/pii/S004896972104794X

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viruses

MDPI

Article

Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IAV) Entry

Wenjiao Wu [1], Richan Li [1], Xianglian Li [1], Jian He [1], Shibo Jiang [2,3], Shuwen Liu [1,*] and Jie Yang [1,2,*]

Received: 10 October 2015; Accepted: 30 November 2015; Published: 25 December 2015
Academic Editor: Curt Hagedorn

Abstract: Influenza A viruses (IAVs) cause seasonal pandemics and epidemics with high morbidity and mortality, which calls for effective anti-IAV agents. The glycoprotein hemagglutinin of influenza virus plays a crucial role in the initial stage of virus infection, making it a potential target for anti-influenza therapeutics development. Here we found that quercetin inhibited influenza infection with a wide spectrum of strains, including A/Puerto Rico/8/34 (H1N1), A/FM-1/47/1 (H1N1), and A/Aichi/2/68 (H3N2) with half maximal inhibitory concentration (IC_{50}) of 7.756 ± 1.097, 6.225 ± 0.467, and 2.738 ± 1.931 μg/mL, respectively. Mechanism studies identified that quercetin showed interaction with the HA2 subunit. Moreover, quercetin could inhibit the entry of the H5N1 virus using the pseudovirus-based drug screening system. This study indicates that quercetin showing inhibitory activity in the early stage of influenza infection provides a future therapeutic option to develop effective, safe and affordable natural products for the treatment and prophylaxis of IAV infections.

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Anti-influenza virus activity of EGCg

Data of Professor Kurokawa's study group at Kyushu University of Health and Welfare

Virus	EC50, ppm (Effective conc. for 50% plaque reduction)			
	①Virus+EGCg →Cells	② Virus+Solvent →Cells	③EGCg+Cells →Virus	④ Virus+Cells →EGCg
Influenza virus type A				
Bangkok/93/03(H1N1)	1.41±0.17	>30	>30	19.3±1.8
PR8/8/34(H1N1)	2.19±0.09	>30	>30	>30
Aichi/2/68(H3N2)	2.76±0.23	>30	>30	22.9±1.4
Influenza virus type B				
Singapore	0.93±0.35	>30	>30	11.1±1.6

CC50 value (cytotoxic conc. for 50% reduction of cell growth) of EGCg was 85.6 ppm.

Summary of Methods and Results

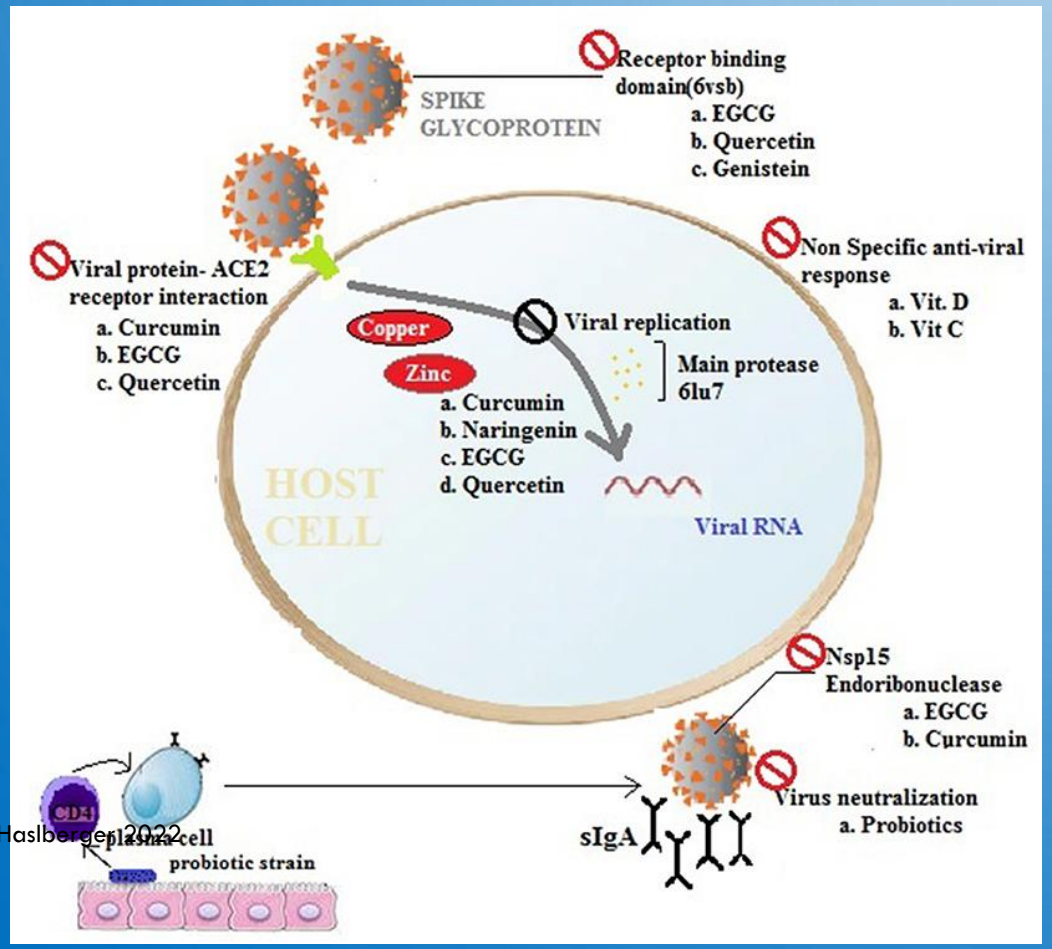
①EGCg-treated virus was adsorbed to cells.
EGCg was significantly effective in inhibiting the adsorption and/or invasion of influenza virus type A and B to cells. EC50 values of EGCg were 31 to 92-folds lower thatn the CC50 value.

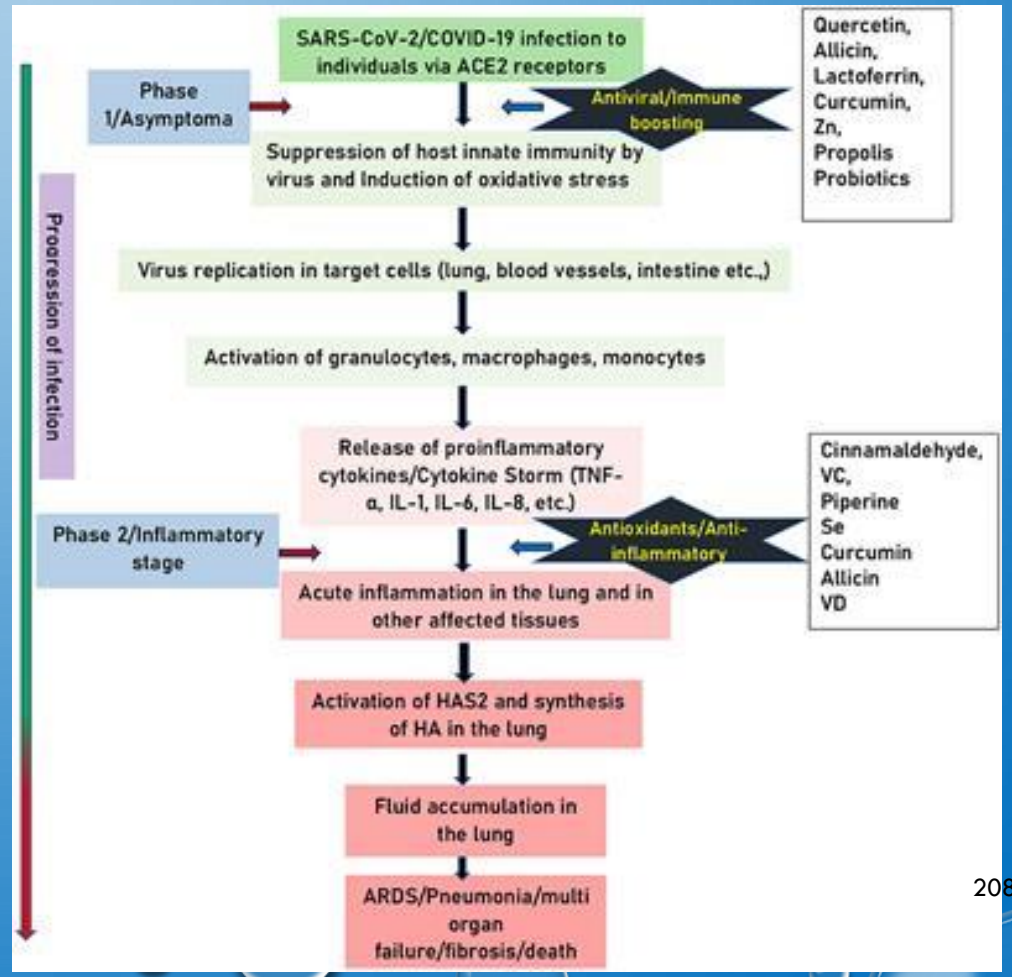
②Solvent-treated virus was adsorbed to cells. Components of solvent except EGCg did not show any anti-influenza virus activity

③Virus was adsorbed and infected to EGCg-treated cells.
EGCg was not effective in interfering with virus adsorption and/or invasion in EGCg-pretreated cells.

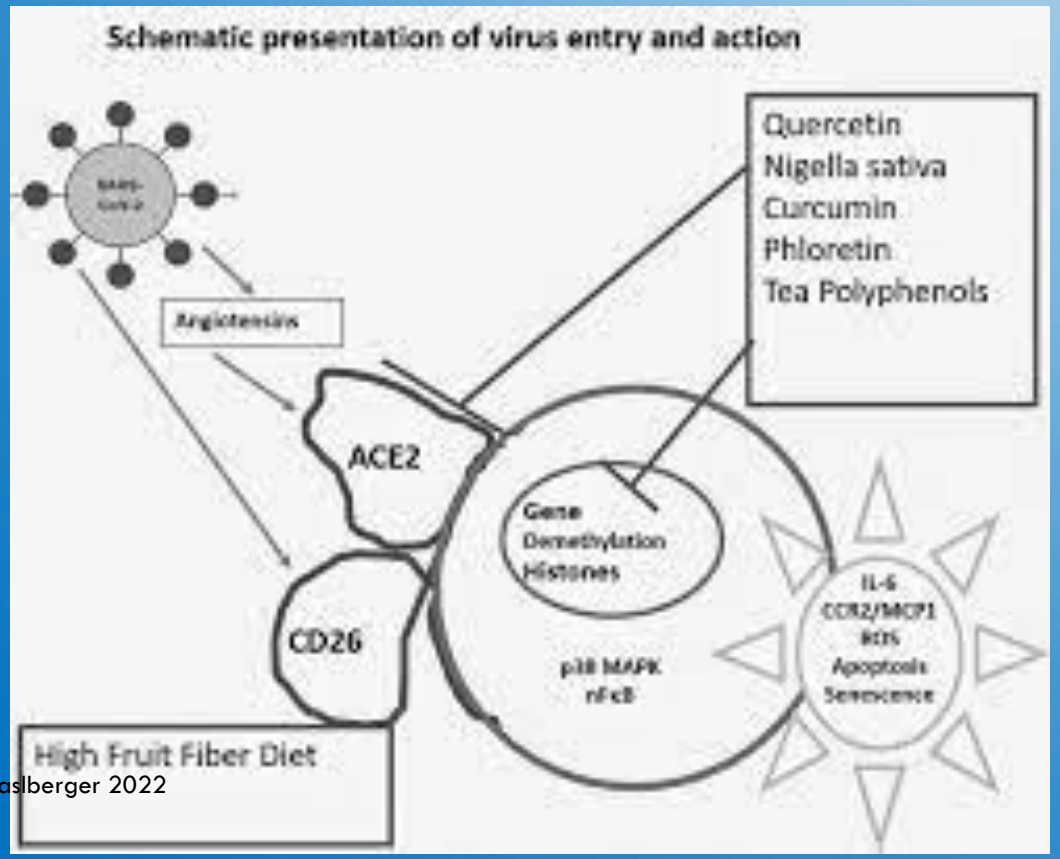
④Virus-adsorbed and infected cells were incubated in the presence of EGCg.
Progeny virus probably contacted with EGCg contained in medium and the adsorption and/or invasion into cells were interrupted.

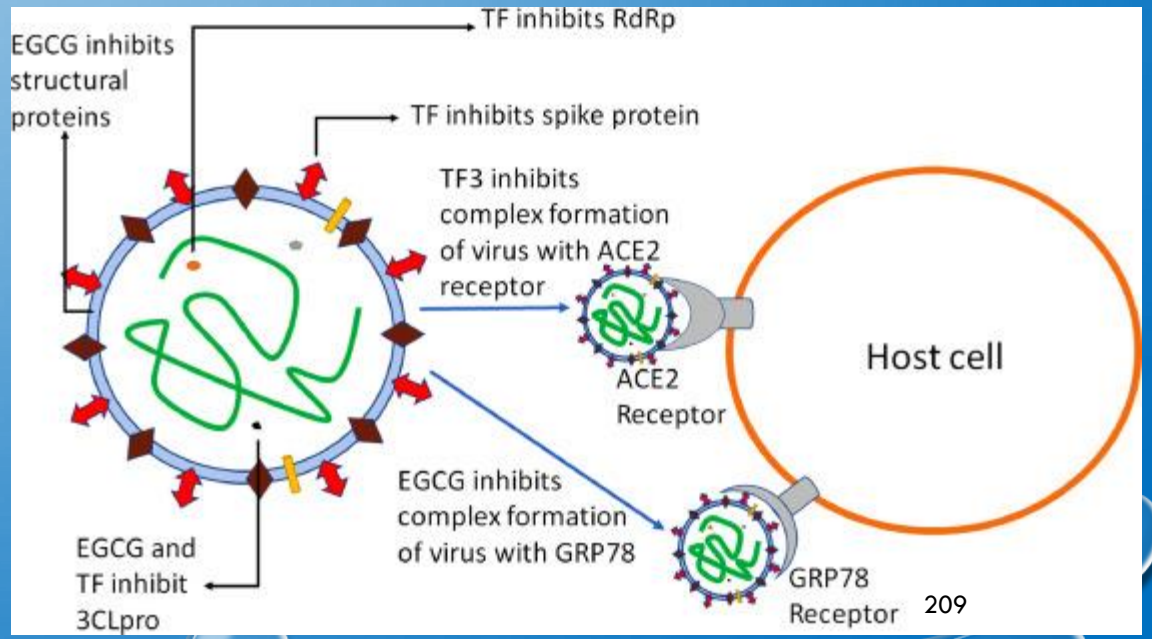
COVID , SARS-2


SPIKE GLYCOPROTEIN
Receptor binding domain(6vsb)
a. EGCG
b. Quercetin
c. Genistein
Viral protein- ACE2 receptor interaction
a. Curcumin
b. EGCG
c. Quercetin
Copper
Zinc
Viral replication
Main protease 6lu7
a. Curcumin
b. Naringenin
c. EGCG
d. Quercetin
Non Specific anti-viral response
a. Vit. D
b. Vit C
HOST CELL
Viral RNA
Nsp15 Endoribonuclease
a. EGCG
b. Curcumin
Virus neutralization
a. Probiotics
sIgA
CD4
plasma cell
probiotic strain


SARS-CoV-2/COVID-19 infection to individuals via ACE2 receptors
Phase 1/Asymptoma
Antiviral/Immune boosting
Quercetin, Allicin, Lactoferrin, Curcumin, Zn, Propolis Probiotics
Suppression of host innate immunity by virus and Induction of oxidative stress
Progression of infection
Virus replication in target cells (lung, blood vessels, intestine etc.,)
Activation of granulocytes, macrophages, monocytes
Release of proinflammatory cytokines/Cytokine Storm (TNF-α, IL-1, IL-6, IL-8, etc.)
Phase 2/Inflammatory stage
Antioxidants/Anti-inflammatory
Cinnamaldehyde, VC, Piperine Se Curcumin Allicin VD
Acute inflammation in the lung and in other affected tissues
Activation of HAS2 and synthesis of HA in the lung
Fluid accumulation in the lung
ARDS/Pneumonia/multi organ failure/fibrosis/death

NUTRACEUTICALS, EPIGENETICS AND INHIBITION OF RNA VIRUSES





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https://doi.org/10.1186/s13578-021-00680-8

Cell & Bioscience

RESEARCH Open Access

Epigallocatechin gallate from green tea effectively blocks infection of SARS-CoV-2 and new variants by inhibiting spike binding to ACE2 receptor

Jinbiao Liu[1,2], Brittany H. Bodnar[1], Fengzhen Meng[1], Adil I. Khan[1], Xu Wang[1], Sami Sa
Saroj Chandra Lohani[3], Peng Wang[1], Zhengyu Wei[1], Jinjun Luo[1], Lina Zhou[1], Jianguo
Qingsheng Li[3*], Wenhui Hu[1*] and Wenzhe Ho[1*]

Abstract

Background: As the COVID-19 pandemic rages on, the new SARS-CoV-2 variants have emerged in the different regions of the world. These newly emerged variants have mutations in their spike (S) protein that may confer resistance to vaccine-elicited immunity and existing neutralizing antibody therapeutics. Therefore, there is still an urgent need of safe, effective, and affordable agents for prevention/treatment of SARS-CoV-2 and its variant infection.

Results: We demonstrated that green tea beverage (GTB) or its major ingredient, epigallocatechin gallate (EGCG), were highly effective in inhibiting infection of live SARS-CoV-2 and human coronavirus (HCoV OC43). In addition, infection of the pseudoviruses with spikes of the new variants (UK-B.1.1.7, SA-B.1.351, and CA-B.1.429) was efficiently blocked by GTB or EGCG. Among the 4 active green tea catechins at noncytotoxic doses, EGCG was the most potent in the action against the viruses. The highest inhibitory activity was observed when the viruses or the cells were pre-incubated with EGCG prior to the infection. Mechanistic studies revealed that EGCG blocked infection at the entry step through interfering with the engagement of the receptor binding domain (RBD) of the viral spikes to angiotensin-converting enzyme 2 (ACE2) receptor of the host cells.

Conclusions: These data support further clinical evaluation and development of EGCG as a novel, safe, and cost-effective natural product for prevention/treatment of SARS-CoV-2 transmission and infection.

Keywords: Epigallocatechin gallate, Green tea, SASR-CoV-2, Variants, Receptor binding domain

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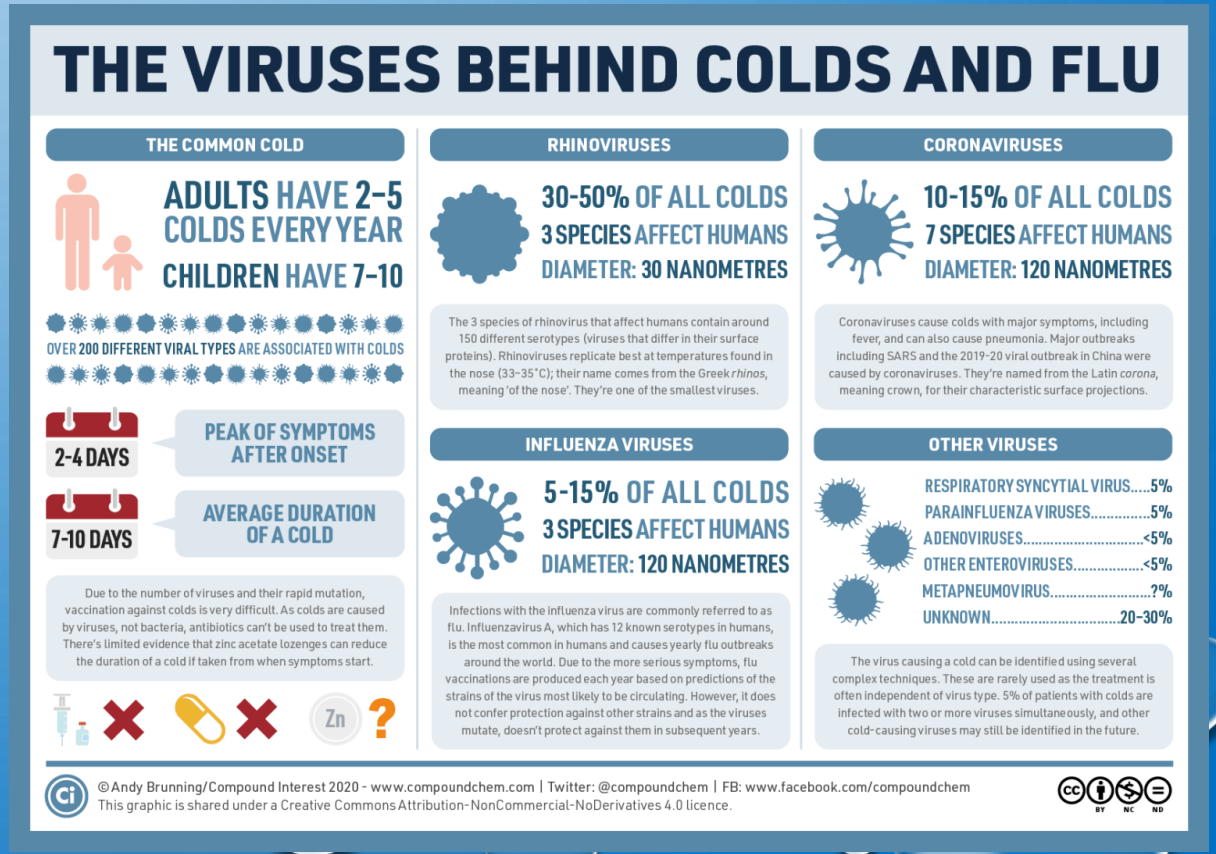
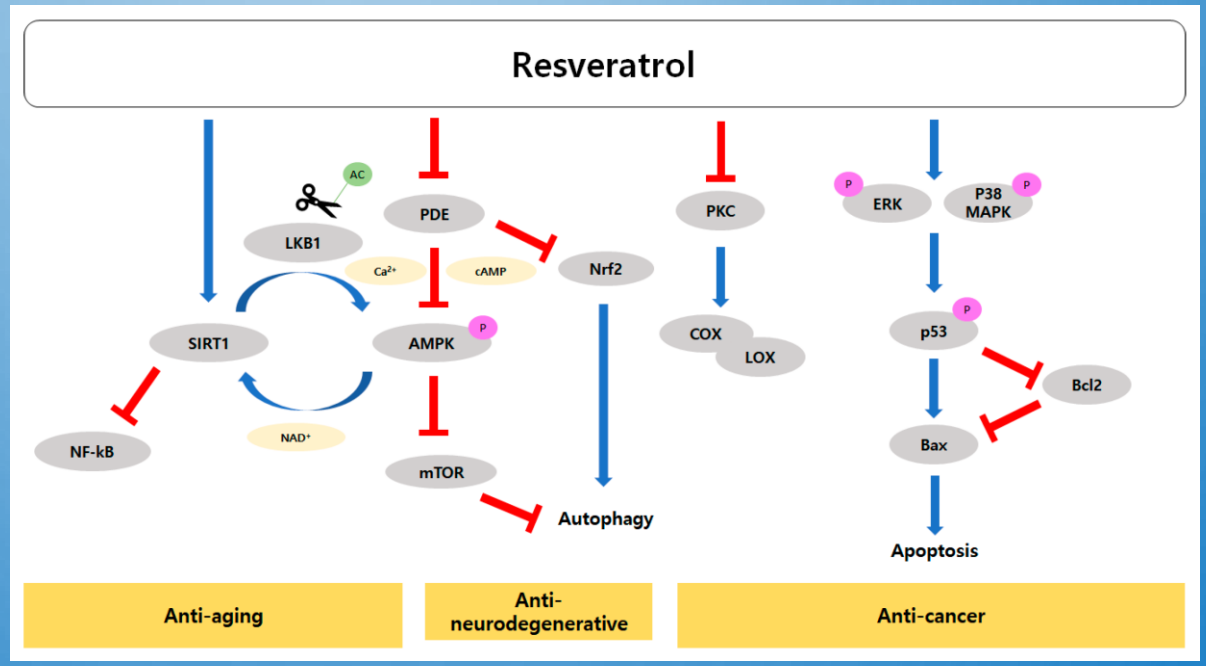
Vitamin B9 (Folate)	600 µg
Zink / *Zinc*	14 mg
Salbei Extrakt / *Sage extract* (Polyphenole)	140 mg
Grüntee Extrakt / *Green tea extrakt* (EGCG)	125 mg
Berberin / *Berberine*	4 mg
Apfel Extrakt / *Apple extract* (Phloretin)	40 mg
Zwiebel Extrakt / *Onion extract* (Quercetin)	140 mg
Holunderbeeren Extrakt / *Elderberry extract* (Anthocyanin)	110 mg
Traubenhaut-Extrakt / *Grape skin extract* (Resveratrol)	140 mg

ZUTATEN: Salbei Extrakt, Zwiebel Extrakt, Traubenhaut Extrakt, Grüntee Extrakt, Holunderbeeren Extrakt, Zinkgluconat, Apfel Extrakt, Trennmittel: Magnesiumstearat, Trennmittel: Siliciumdioxid, Vitamin D3-Cholecalciferol, Quatrefolic Vitamin B9

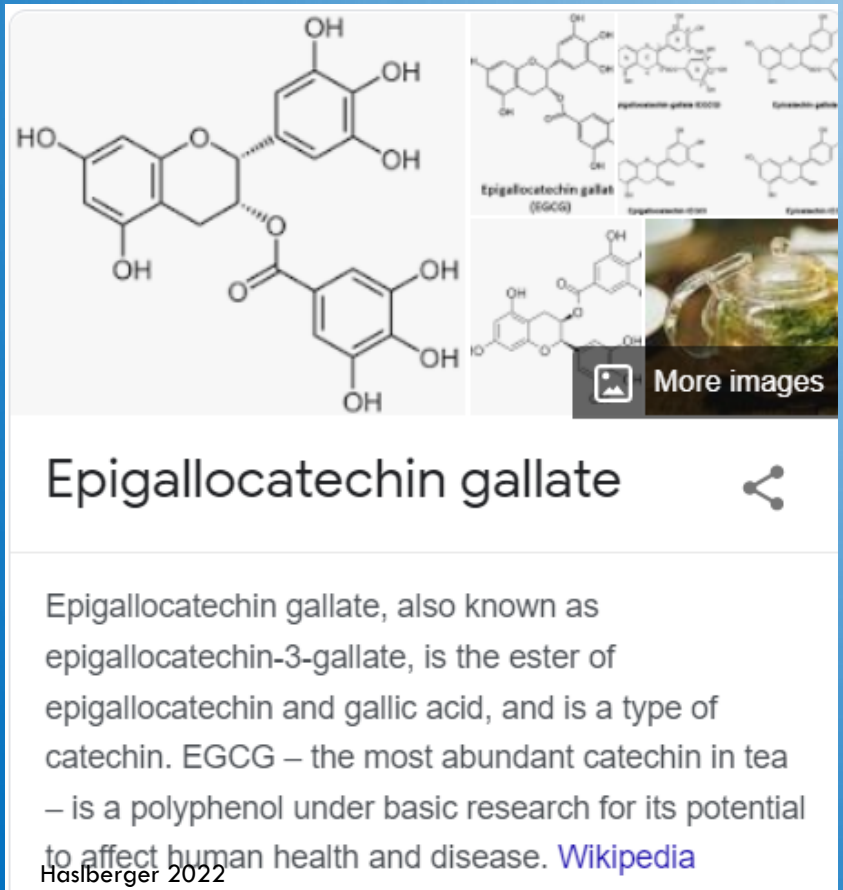


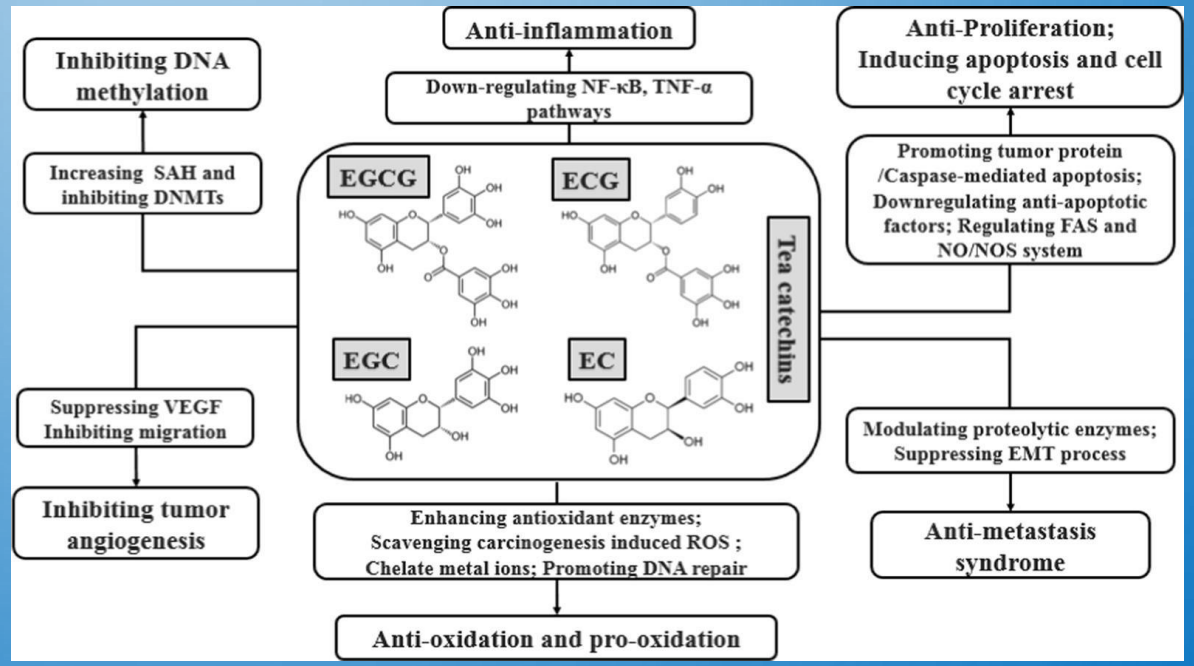
EXAMPLES, RESVERATROL



Previous studies have demonstrated that resveratrol is well-absorbed following oral administration, with ~75% of the dose absorbed. Following absorption, resveratrol undergoes rapid and extensive metabolism leading to low bioavailability

GREEN TEA EXTRACT, EGCG, CATECHINES





EGCG II

FFHD
Functional Foods in Health and Disease

The green tea polyphenol EGCG is differentially associated with telomeric regulation in normal human fibroblasts versus cancer cells

Angelika Pointner[1], Christine Mölzer[1,2], Ulrich Magnet[1], Katja Zappe[1,3], Berit Hippe[1], Anela Tosevska[1,4], Elena Tomeva[1], Elisabeth Dum[1], Stephanie Lilja[1], Ulrike Krammer[1], Alexander Haslberger[1*]

Research Article

EGCG Prevents High Fat Diet-Induced Changes in Gut Microbiota, Decreases of DNA Strand Breaks, and Changes in Expression and DNA Methylation of *Dnmt1* and *MLH1* in C57BL/6J Male Mice

Marlene Remely,[1] Franziska Ferk,[2] Sonja Sterneder,[1] Tahereh Setayesh,[2] Sylvia Roth,[1] Tatjana Kepcija,[1] Rahil Noorizadeh,[2] Irene Rebhan,[1] Martina Greunz,[1] Johanna Beckmann,[1] Karl-Heinz Wagner,[1] Siegfried Knasmüller,[2] and Alexander G. Haslberger[1]

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

Stephanie Lilja,[1] Julia Oldenburg,[1] Angelika Pointner,[1] Laura Dewald,[1] Mariam Lerch,[1] Berit Hippe,[2] Olivier Switzeny,[2] and Alexander Haslberger[1]

Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice

Joshua D Lambert [1], Jungil Hong, Dou Hwan Kim, Vladimir M Mishin, Chung S Yang

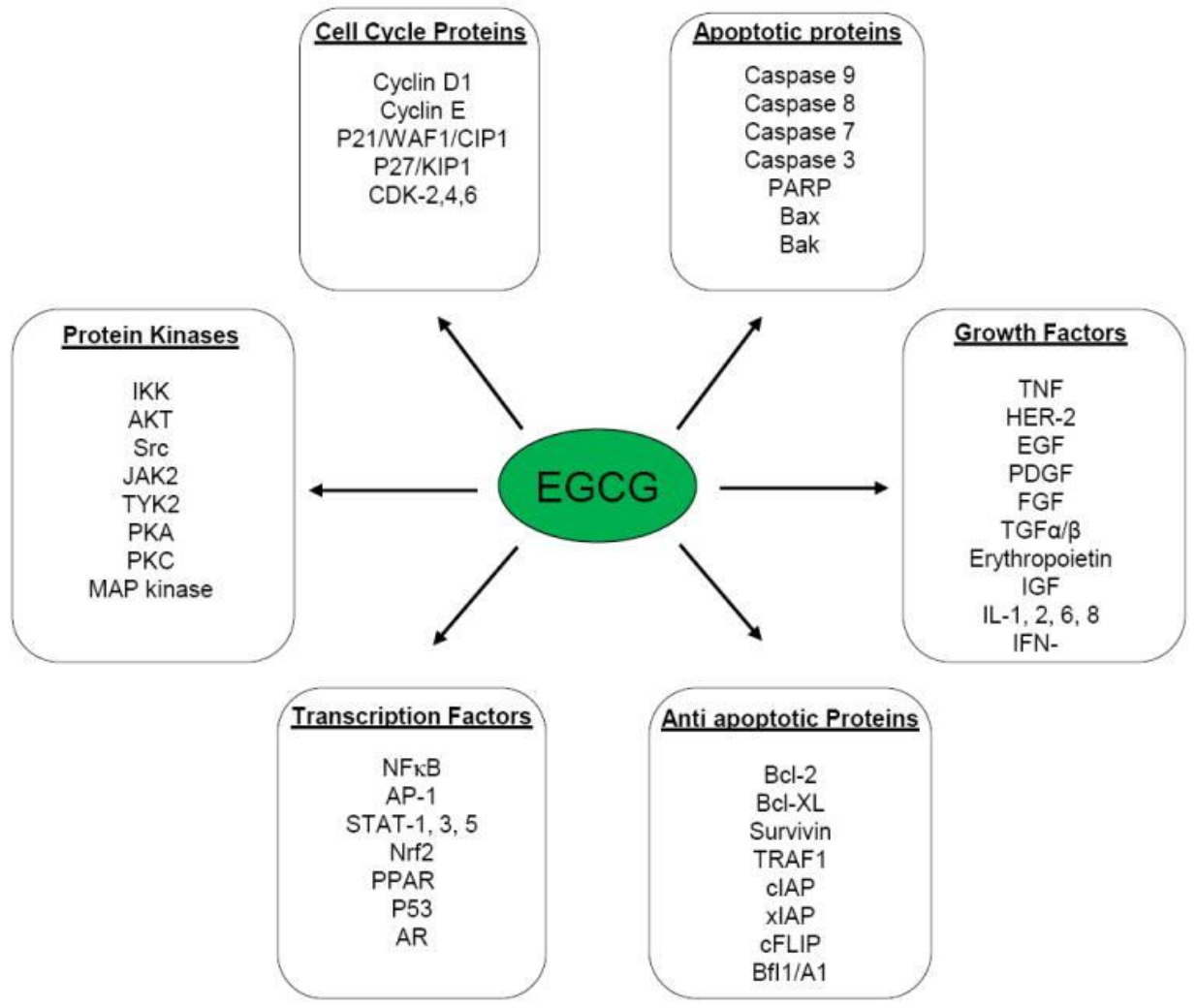
Affiliations + expand

PMID: 15284381 DOI: 10.1093/jn/134.8.1948

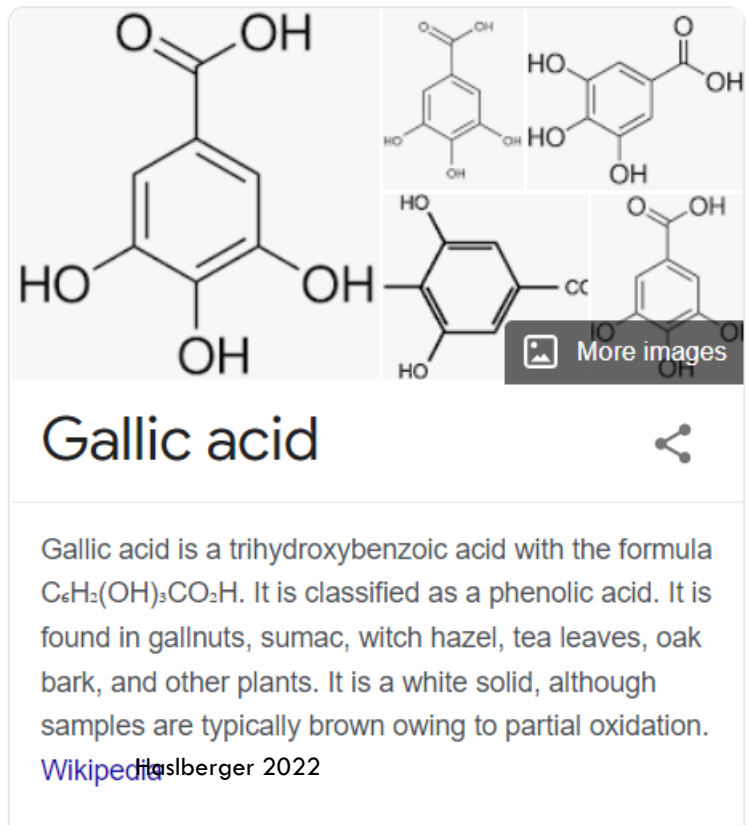
Abstract

(-)-Epigallocatechin-3-gallate (EGCG), from green tea (Camellia sinensis), has demonstrated chemopreventive activity in animal models of carcinogenesis. Previously, we reported the bioavailability of EGCG in rats (1.6%) and mice (26.5%). Here, we report that cotreatment with a second dietary component, piperine (from black pepper), enhanced the bioavailability of EGCG in mice. Intragastric coadministration of 163.8 micromol/kg EGCG and 70.2 micromol/kg piperine to male CF-1 mice increased the plasma C(max) and area under the curve (AUC) by 1.3-fold compared to mice treated with EGCG only. Piperine appeared to increase EGCG bioavailability by inhibiting glucuronidation and gastrointestinal transit. Piperine (100 micromol/L) inhibited EGCG glucuronidation in mouse small intestine (by 40%) but not in hepatic microsomes. Piperine (20

EGCG


Cell Cycle Proteins
Cyclin D1
Cyclin E
P21/WAF1/CIP1
P27/KIP1
CDK-2,4,6
Apoptotic proteins
Caspase 9
Caspase 8
Caspase 7
Caspase 3
PARP
Bax
Bak
Protein Kinases
IKK
AKT
Src
JAK2
TYK2
PKA
PKC
MAP kinase
EGCG
Growth Factors
TNF
HER-2
EGF
PDGF
FGF
TGFα/β
Erythropoietin
IGF
IL-1, 2, 6, 8
IFN-
Transcription Factors
NFκB
AP-1
STAT-1, 3, 5
Nrf2
PPAR
P53
AR
Anti apoptotic Proteins
Bcl-2
Bcl-XL
Survivin
TRAF1
cIAP
xIAP
cFLIP
Bfl1/A1

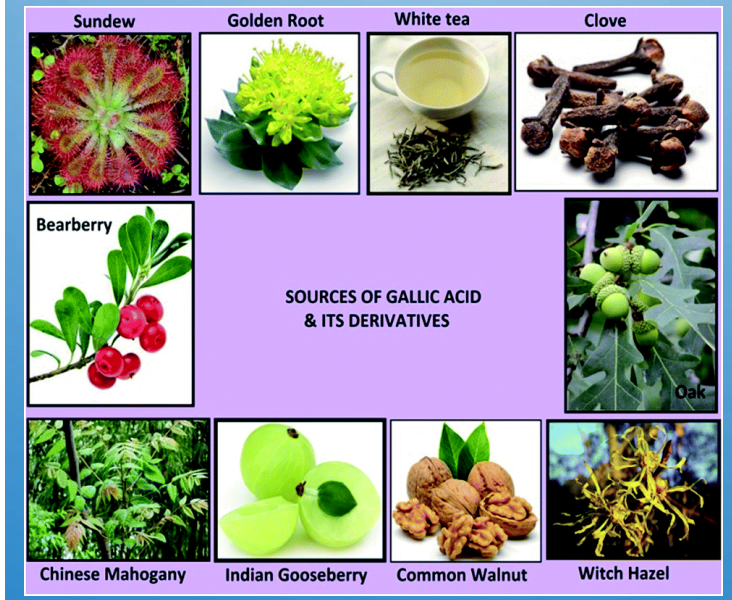
GALLIC ACID



Haslberger 2022

Gallic acid, a common dietary phenolic protects against high fat diet induced DNA damage

Tahereh Setayesh[1] · Armen Nersesyan[1] · Miroslav Mišík[1] · Rahil Noorizadeh[1,3] · Elisabeth Haslinger[1] · Tahereh Javaheri[2,3] · Elisabeth Lang[1] · Michael Grusch[1] · Wolfgang Huber[1] · Alexander Haslberger[4] · Siegfried Knasmüller[1]



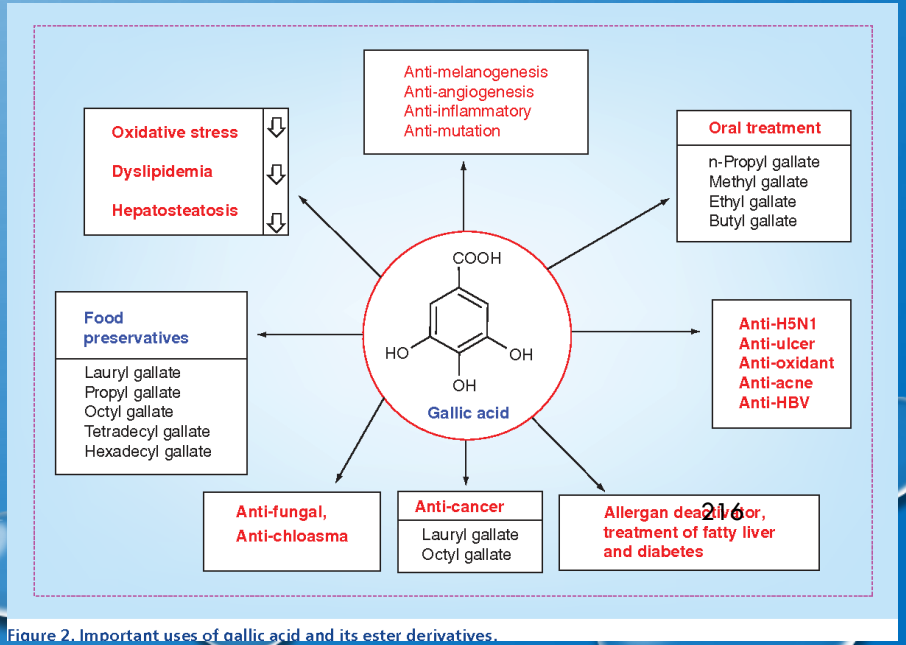


Figure 2. Important uses of gallic acid and its ester derivatives.

ASTAXANTHIN

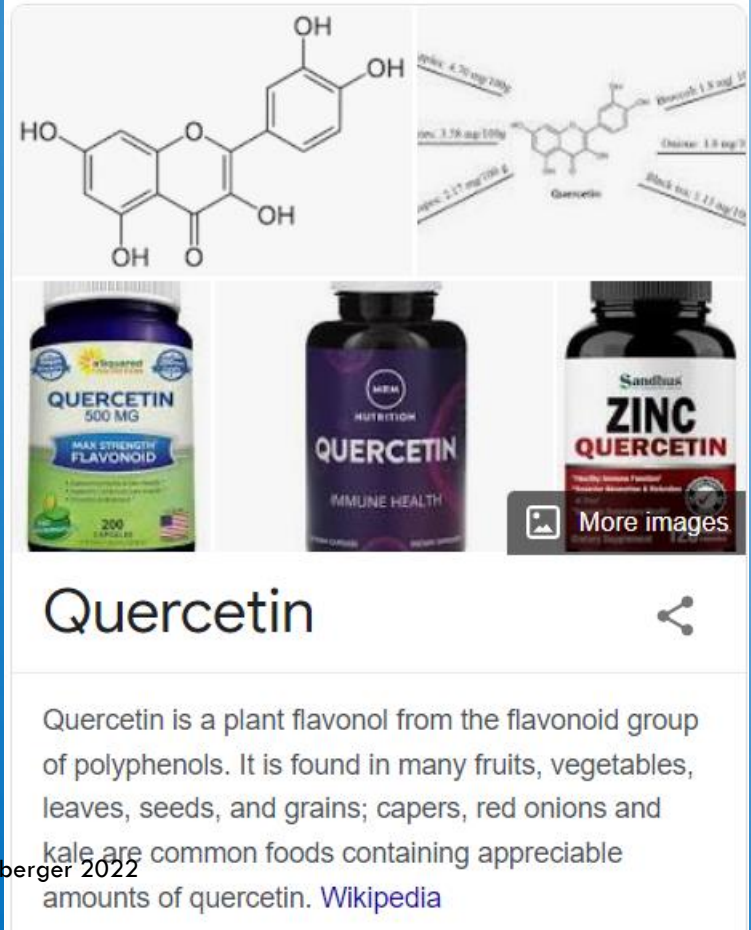
Astaxanthin

Chemical compound

Astaxanthin is a keto-carotenoid with various uses including dietary supplement and food dye. It belongs to a larger class of chemical compounds known as terpenes built from five carbon precursors, isopentenyl diphosphate, and dimethylallyl diphosphate. Wikipedia

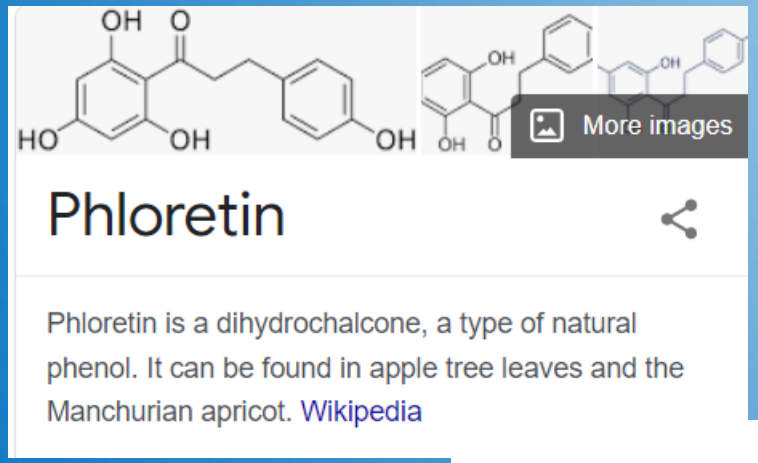
Biological Activities
Antioxidant activity
Protection from UV rays
Anti-skin cancer
Anti-inflammatory
Anti-gastric activity
Anti-hepatoprotective
Anti-diabetes
Cardiovascular prevention
Immune response
Neuroprotection

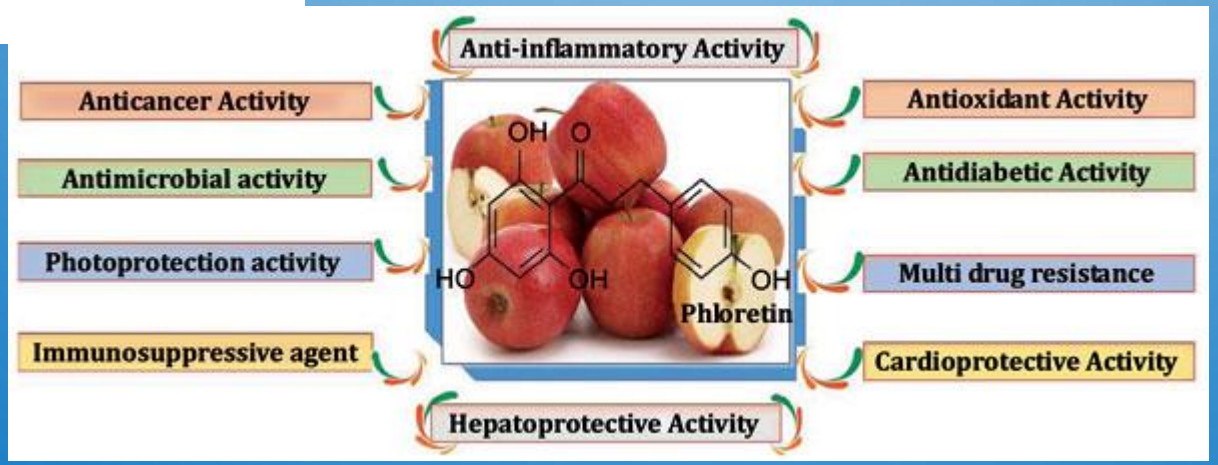
QUERCETIN



Quercetin Benefits	Additional Information
Anti-inflammatory and Immune Boosting Research has shown that quercetin displays anti-inflammatory and immune strengthening capabilities. One study even shows how quercetin was able to mitigate the inflammatory responses stimulated by the popular food additive carrageenan. Quercetin was also shown to be able to decrease the clinical indicators of arthritis.	**Recommended daily intake** • 200-250 mg/day or even lower. • Research shows that even small amounts are effective for everyday consumption.
Possible Cancer fighting properties Studies have shown that quercetin was able to restrain the growth of cancer and as such prevent the proliferation of cancer cells especially as it relates to certain types of cancers – colorectal, ovarian and breast cancer cells.	**Some foods that are high in quercetin** • Onions • Shallots • Asparagus • Green peppers • Tomatoes • Apples • Cranberries
Cardiovascular Health Research shows that quercetin was able to reduce some of the major risks factors of heart disease such as high blood pressure, oxidative stress and inflammation.	
Anti-viral properties Studies have shown that quercetin was effective in the prevention of viral or respiratory conditions as well as well as fight against viruses such as herpes and parainfluenza type 3. **Asthma** Research shows that quercetin is able to reduce inflammatory cells of the immune system as well as decrease the histamine levels which then helps to smooth the muscles of the airways and helps with breathing.	**Possible side effects** • Headaches • Stomach discomfort • Kidney damage (high doses). 
Almondsandolivez.com	

PHLORETIN


More images
Phloretin
Phloretin is a dihydrochalcone, a type of natural phenol. It can be found in apple tree leaves and the Manchurian apricot. Wikipedia

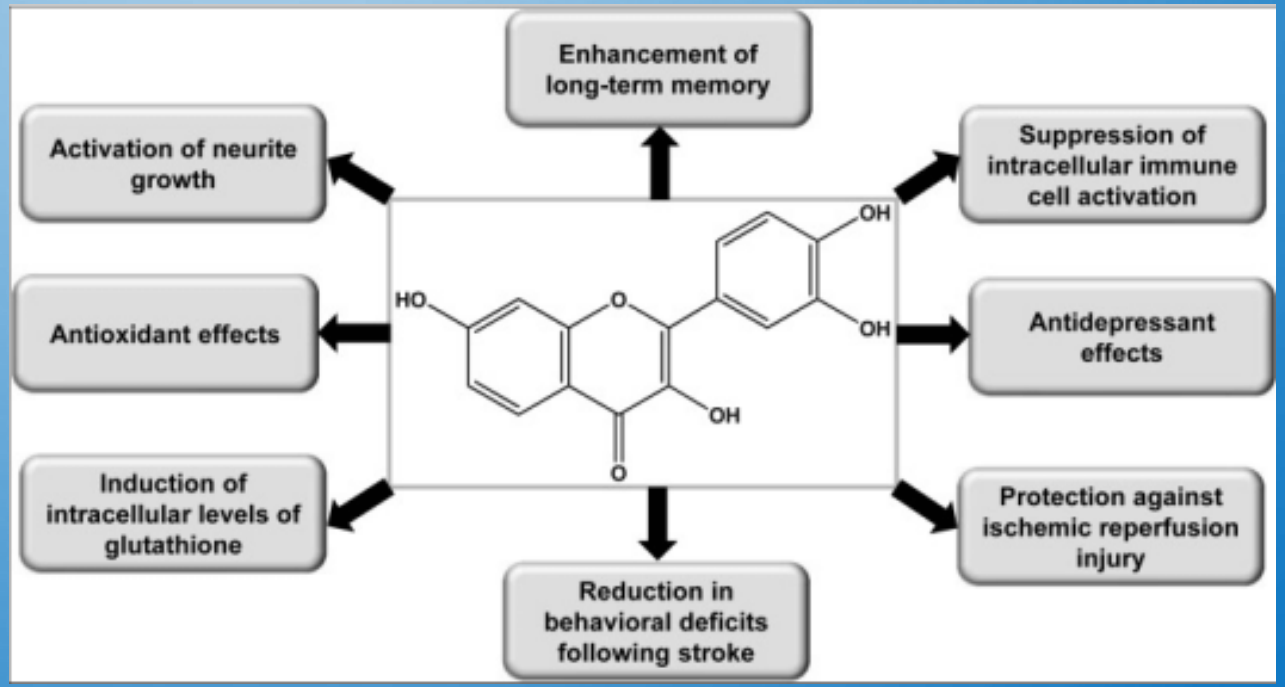

Anti-inflammatory Activity
Anticancer Activity
Antimicrobial activity
Photoprotection activity
Immunosuppressive agent
Antioxidant Activity
Antidiabetic Activity
Multi drug resistance
Cardioprotective Activity
Hepatoprotective Activity
Phloretin

FISETIN

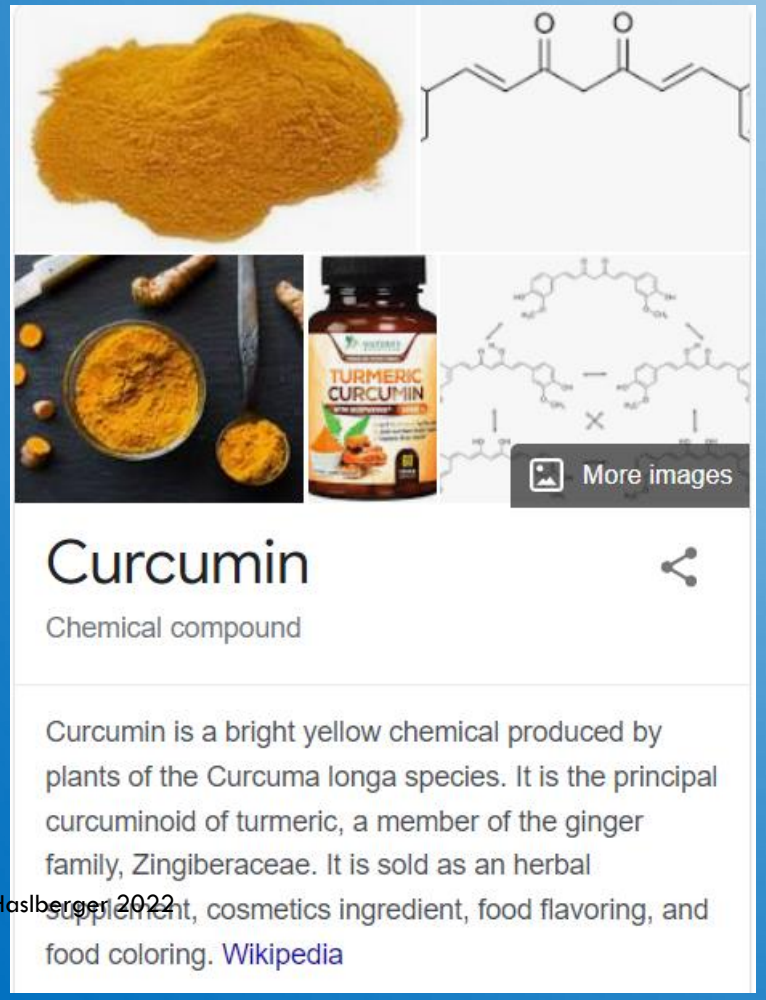
Fisetin

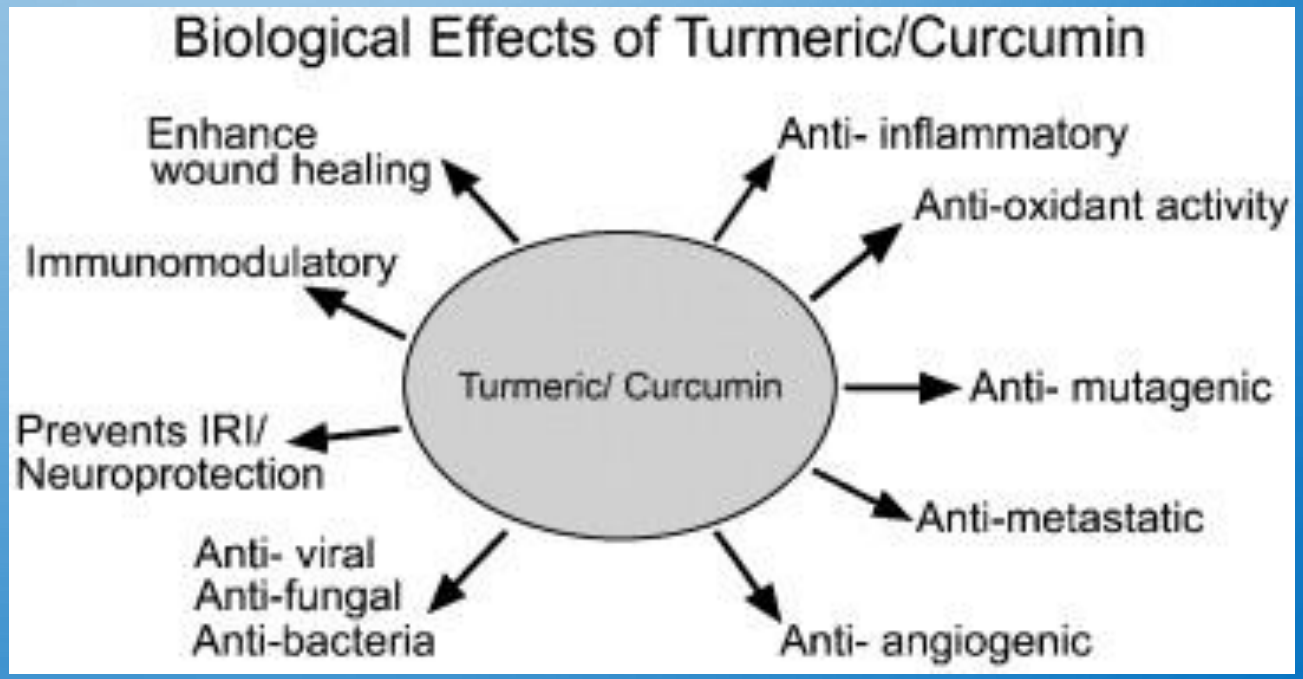
Chemical compound

Fisetin is a plant flavonol from the flavonoid group of polyphenols. It can be found in many plants, where it serves as a yellow/ochre colouring agent. It is also found in many fruits and vegetables, such as strawberries, apples, persimmons, onions and cucumbers. Wikipedia

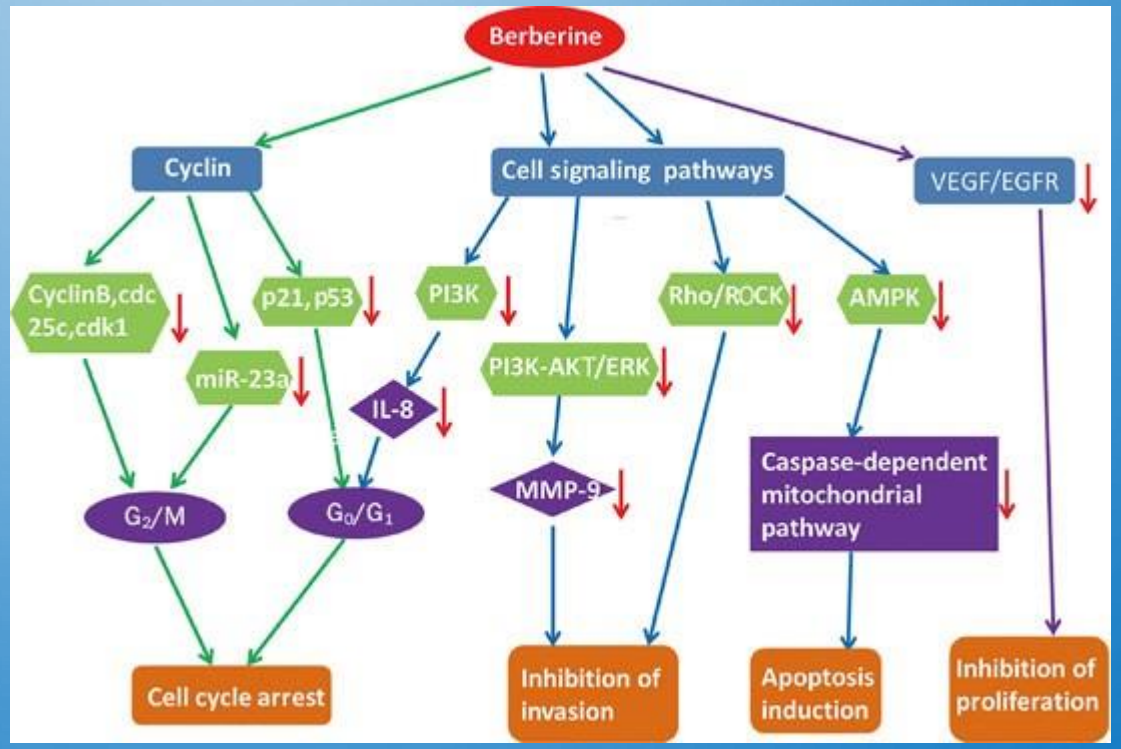


CURCUMIN


TURMERIC
CURCUMIN
More images
Curcumin
Chemical compound
Curcumin is a bright yellow chemical produced by plants of the Curcuma longa species. It is the principal curcuminoid of turmeric, a member of the ginger family, Zingiberaceae. It is sold as an herbal supplement, cosmetics ingredient, food flavoring, and food coloring. Wikipedia

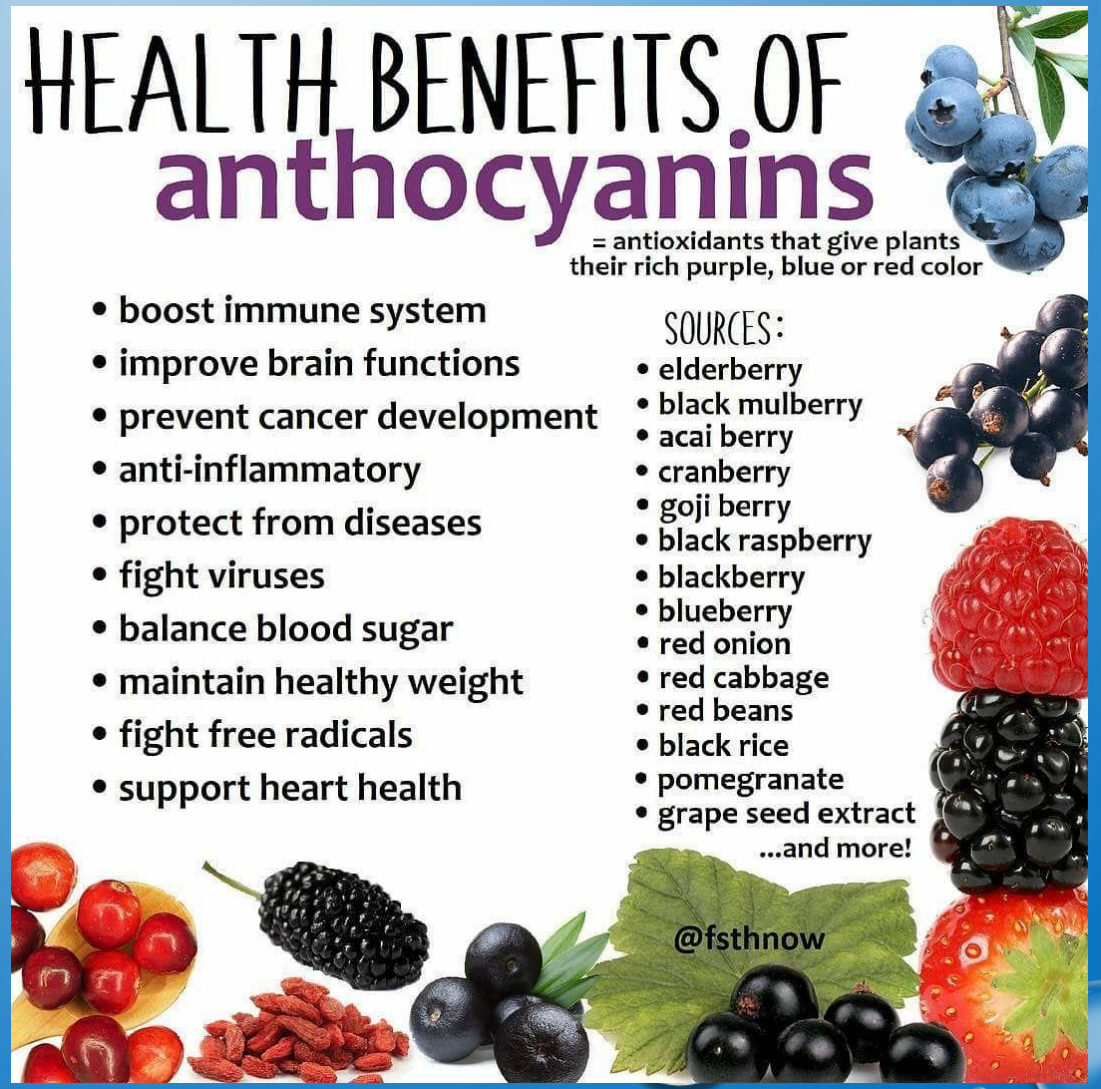

Biological Effects of Turmeric/Curcumin
Enhance wound healing
Anti- inflammatory
Anti-oxidant activity
Immunomodulatory
Turmeric/ Curcumin
Anti- mutagenic
Prevents IRI/ Neuroprotection
Anti-metastatic
Anti- viral
Anti-fungal
Anti-bacteria
Anti- angiogenic

BERBERIN, BERBERITZE

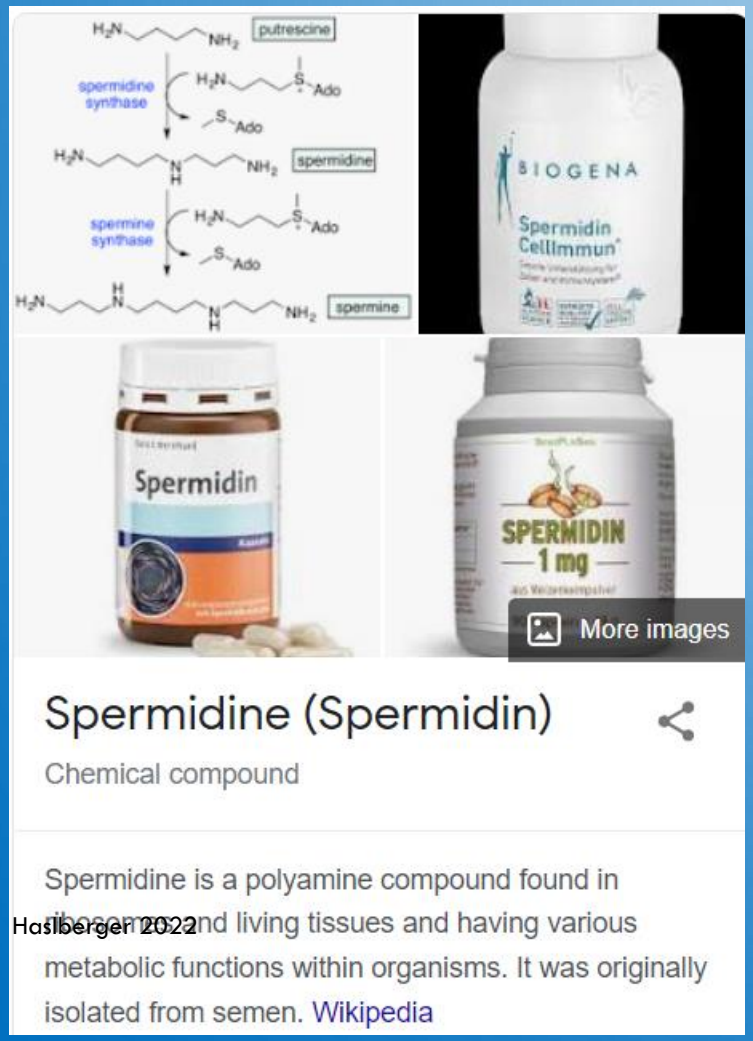


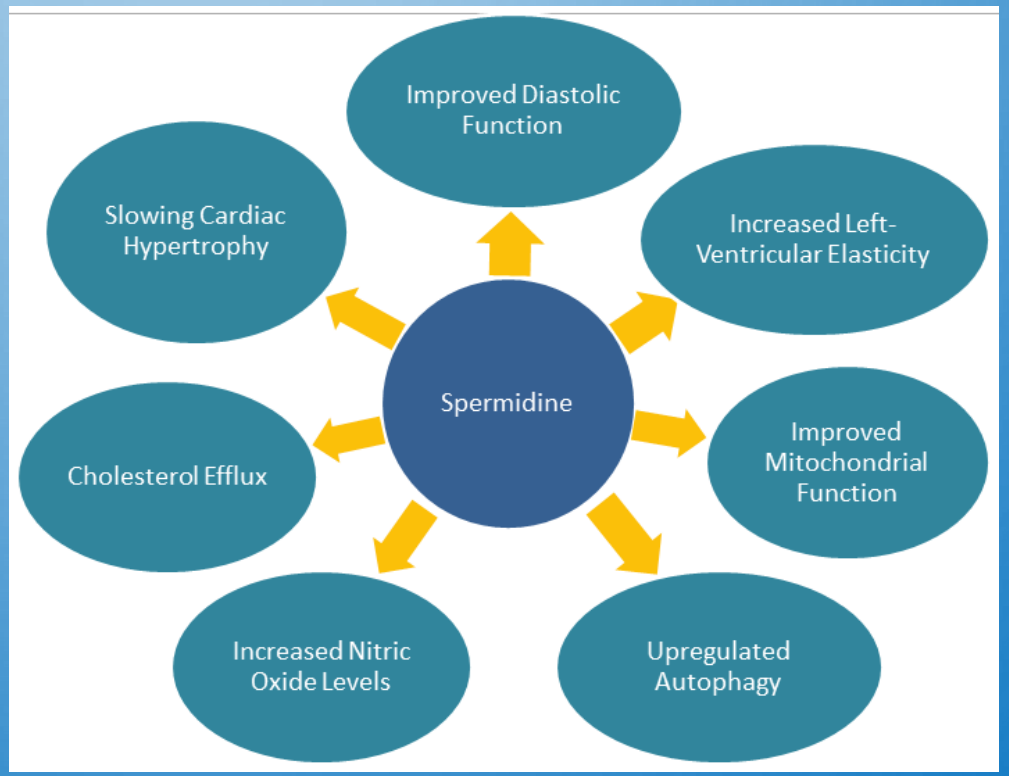
ANTHOCYANS


More images
Anthocyanin
Chemical compound
Anthocyanins are water-soluble vacuolar pigments that, depending on their pH, may appear red, purple, blue, or black. In 1835, the German pharmacist Ludwig Clamor Marquart gave the name Anthokyan to a chemical compound that gives flowers a blue color for the first time in his treatise "Die Farben der Blüthen". Wikipedia

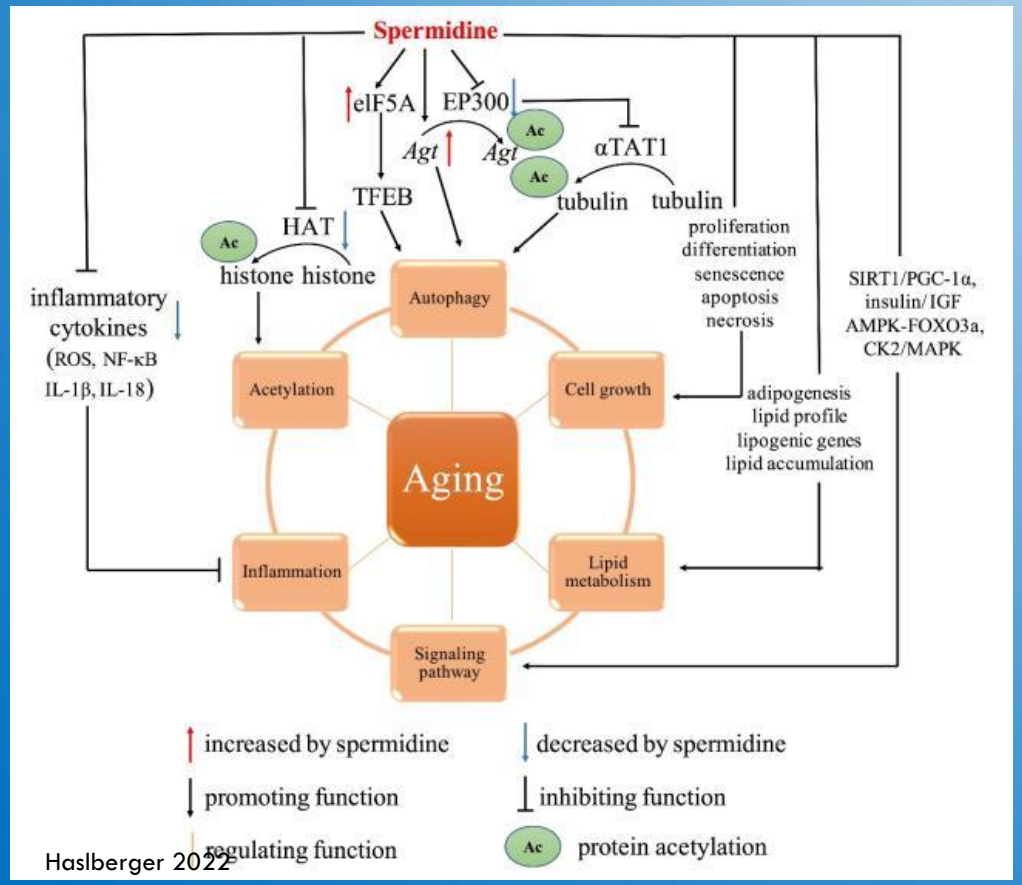

HEALTH BENEFITS OF
anthocyanins
= antioxidants that give plants their rich purple, blue or red color
• boost immune system
• improve brain functions
• prevent cancer development
• anti-inflammatory
• protect from diseases
• fight viruses
• balance blood sugar
• maintain healthy weight
• fight free radicals
• support heart health
SOURCES:
• elderberry
• black mulberry
• acai berry
• cranberry
• goji berry
• black raspberry
• blackberry
• blueberry
• red onion
• red cabbage
• red beans
• black rice
• pomegranate
• grape seed extract
...and more!
@fsthnow

SPERMIDIN


putrescine
spermidine synthase
Ado
spermidine
spermine synthase
spermine
BIOGENA
Spermidin CellImmun
Spermidin
SPERMIDIN
1 mg
More images
Spermidine (Spermidin)
Chemical compound
Spermidine is a polyamine compound found in
and living tissues and having various
metabolic functions within organisms. It was originally
isolated from semen. Wikipedia


Improved Diastolic Function
Slowing Cardiac Hypertrophy
Increased Left-Ventricular Elasticity
Spermidine
Cholesterol Efflux
Improved Mitochondrial Function
Increased Nitric Oxide Levels
Upregulated Autophagy

SPERMIDINE MECHANISMS



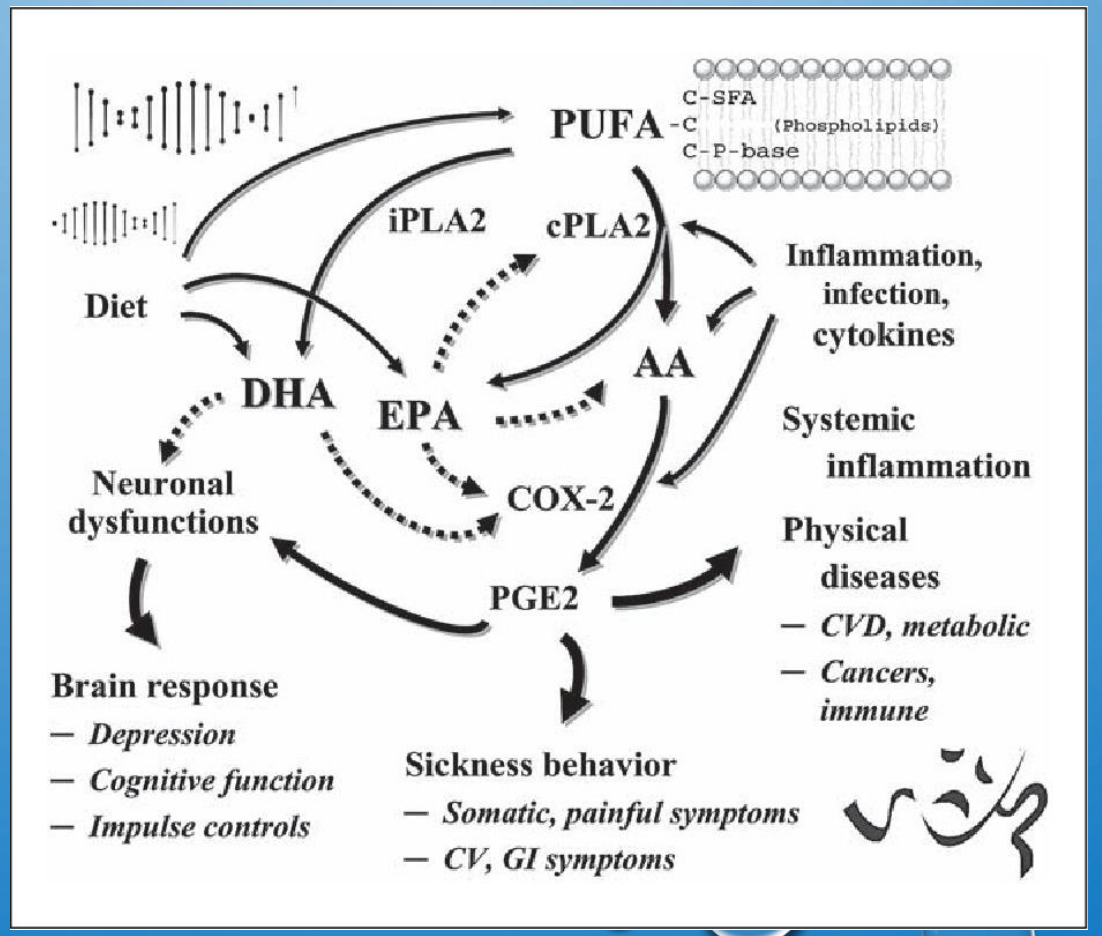
Molecular and cellular mechanisms of spermidine in age-related disease s. Spermidine is an inducer of autophagy, which is the main mechanism of anti-aging. First, spermidine **triggers autophagy by modulating the exp ressions of *Atg* genes**. Second, it regulates **transcription factor eIF5A t o promote the synthesis of transcription factor TFEB.** Third, spermidine **inhibits EP300, which directly promotes the acetylation of Atg genes** and **indirectly stimulates deacetylation of tubulin due to inhibition of αTAT1**. Besides, spermidine exerts potent anti-inflammatory roles by **sup pressing of multiple inflammatory cytokines, such as ROS, NF-κB, IL-1β and IL-18**. Moreover, it is involved in regulation **of cell proliferation, differentiation, senescence, apoptosis and necrosis**, ultimately promoti ng cell growth and inhibiting cell death.

As an anti-aging agent, spermidine suppresses histone acetylation. More over, spermidine regulates lipid metabolism. On the one hand, it promote s the differentiation of preadipocytes into mature adipocytes. On the oth er hand, it alters lipid profile, modulates lipogenic gene expressions, and represses lipid accumulation. Furthermore, spermidine can delay aging th rough specific signaling pathways, such as SIRT1/PGC-1α, insulin/IGF, A MPK-FOXO3a, and CK2/MAPK signaling pathways.

FISHOIL, EPA, DHA

Fish oil

Fish oil is oil derived from the tissues of oily fish. Fish oils contain the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, precursors of certain eicosanoids that are known to reduce inflammation in the body and improve hypertriglyceridemia. Wikipedia

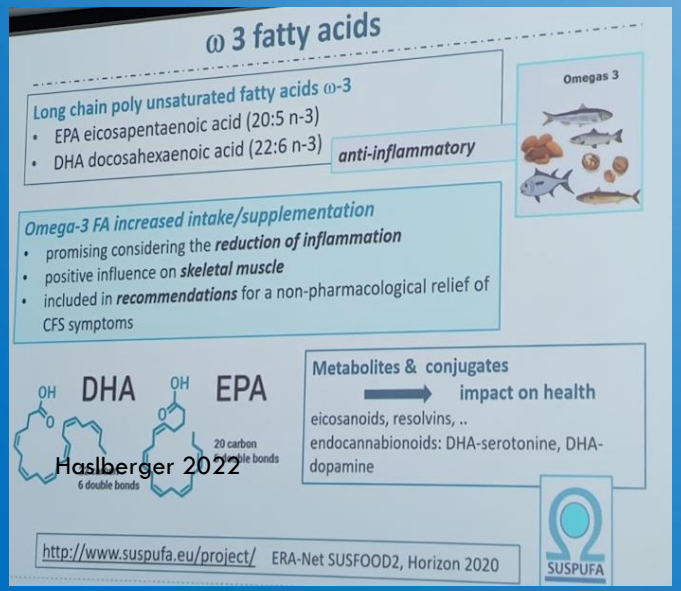


Conclusion

- Quite less ambiguity persists about a true place for marine ω3 to prevent IR
- In healthy humans, 1.8 g/d modestly increase insulin sensitivity
- But 850 mg/d aggravate dexamethasone-induced IR
- The most recent and complete meta-analysis conclude to their preventive effect towards IR
- 4 Meta-analysis conclude to a protective effect in Asian but potentially deleterious in Western populations towards the risk of T2D, probably due to the heterogeneity of western studies and a high n-6/n-3 ratio in western populations

Marine ω3 are certainly useful useful if given early and throughout life cycle, probably at least > 1g/d in adults AND in combination with exercise and maintenance of normal weight.

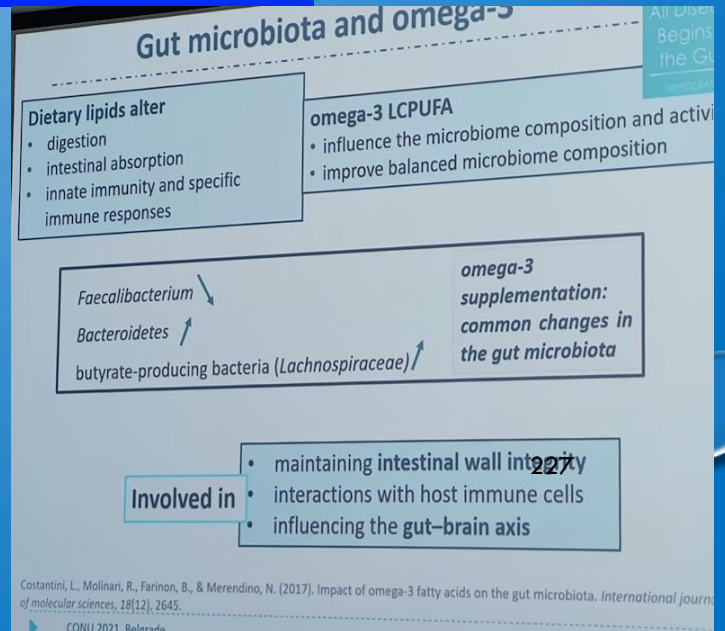
Personalized dosage should also be considered, which requires further studies



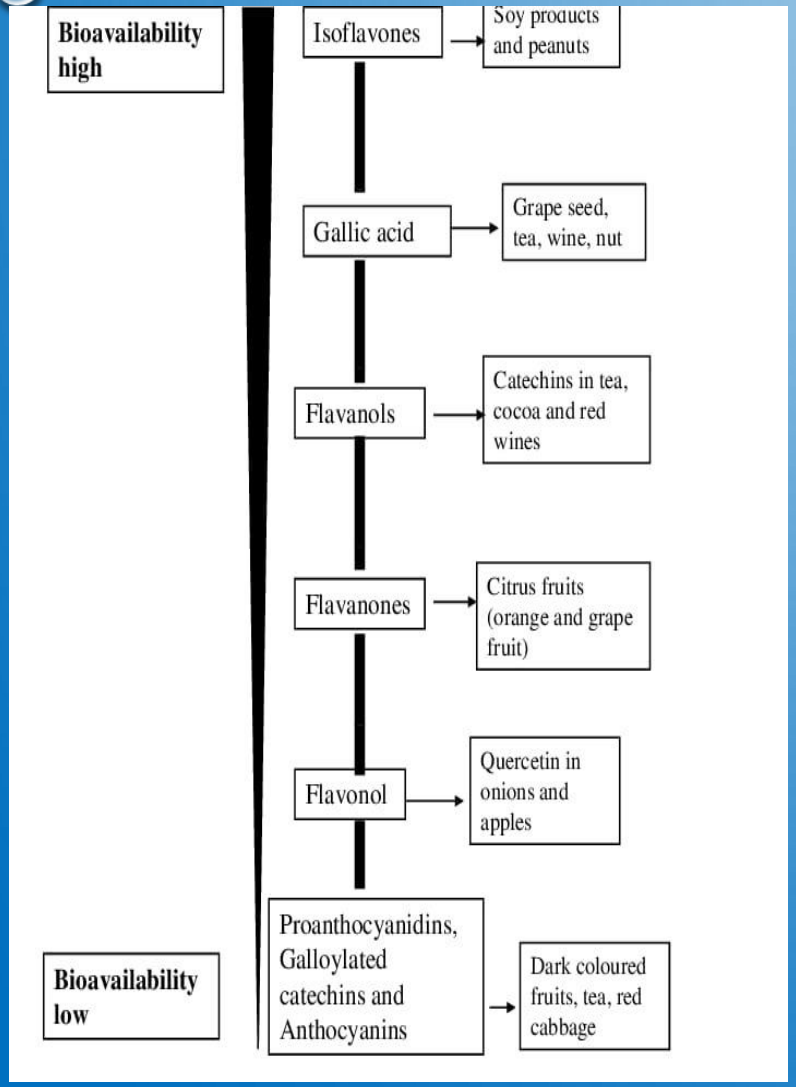
Marine ω3 increase insulin sensitivity in people with metabolic disorders

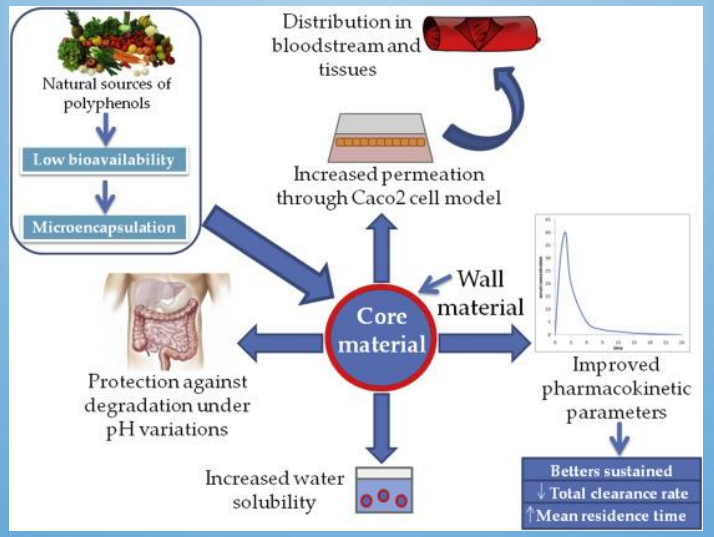
Table 3 Subgroup analysis of fish oil consumption and insulin sensitivity

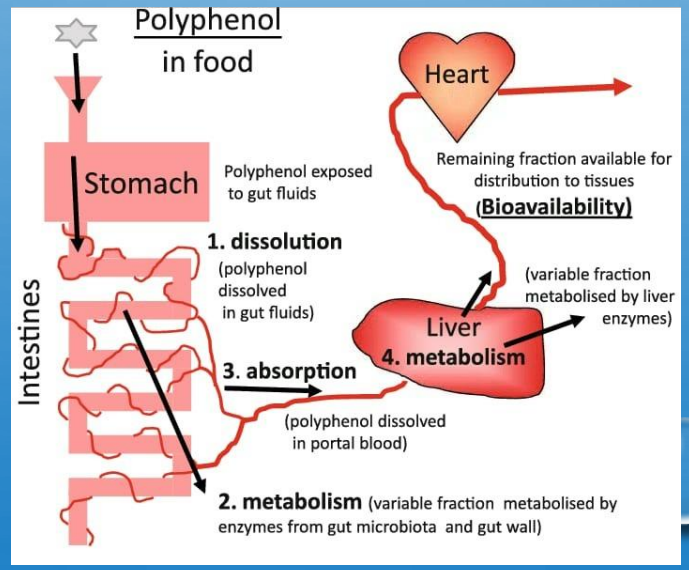
Subgroup	No. Of studies	SMD (95%IC)	*P* value
Methods of insulin sensitivity			
Clamps	4	0.10(−0.18–0.44)	0.41
HOMA	9	0.28(−0.08–0.63)	0.13
QUICKI	3	0.15(−0.68–0.97)	0.73
Glucose tolerance	1	0.19(−0.05–0.42)	0.79
Population			
T2DM	8	0.12(−0.22–0.45)	0.50
Metabolic disorders	5	0.53(0.17–0.88)	<0.001
Healthy people	4	−0.15(−0.53–0.24)	0.46
Dose			
≥2 g	14	0.17(−0.11–0.46)	0.24
< 2 g	3	0.26(−0.04–0.56)	0.09
Duration			
≥12w	9	0.09(−0.25–0.44)	0.60
<12w	8	0.31(−0.01–0.61)	0.04

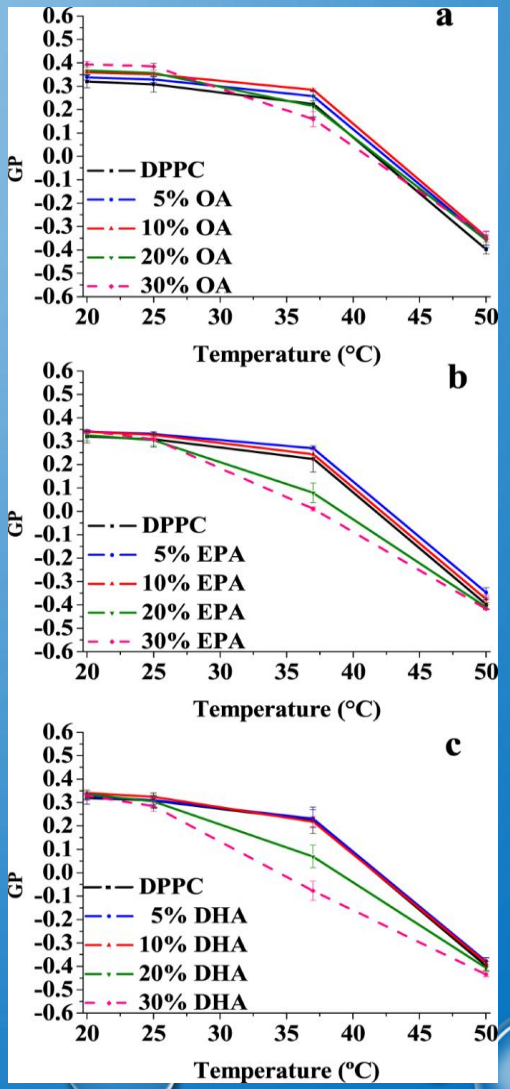


BIOAVAILABILITY, STABILITY









EXERCISE INHIBITS SENESCENCE

1606 Diabetes Volume 65, June 2016

Marissa J. Schafer,[1,2] Thomas A. White,[1] Glenda Evans,[1] Jason M. Tonne,[3] Grace C. Verzosa,[4] Michael B. Stout,[1,5] Daniel L. Mazula,[1] Allyson K. Palmer,[1] Darren J. Baker,[1,6] Michael D. Jensen,[7] Michael S. Torbenson,[8] Jordan D. Miller,[1,4] Yasuhiro Ikeda,[3] Tamara Tchkonia,[1] Jan M. van Deursen,[1,9] James L. Kirkland,[1,5] and Nathan K. LeBrasseur[1,2]

Exercise Prevents Diet-Induced Cellular Senescence in Adipose Tissue

Diabetes 2016;65:1606–1615 | DOI: 10.2337/db15-0291

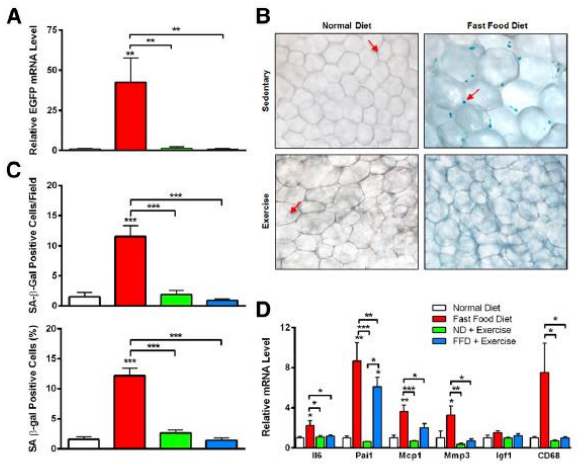


Figure 4—Exercise prevents diet-induced cellular senescence and the SASP within visceral adipose tissue. *A*: Compared with the ND, the FFD caused a marked increase in the activity of the senescence-associated $p16^{INK4a}$ promoter, as measured by EGFP expression. *B*: Representative images show the abundance of cells positive for SA-β-gal (arrow) in harvested visceral adipose tissue further validated the pro- and antisenescent effects of nutrient excess and exercise, respectively (summary data, *C*). *D*: The expression of SASP and inflammatory factors was also increased in response to FFD, and these increases were attenuated by exercise. For all analyses, $n = 6–7$ mice/group. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

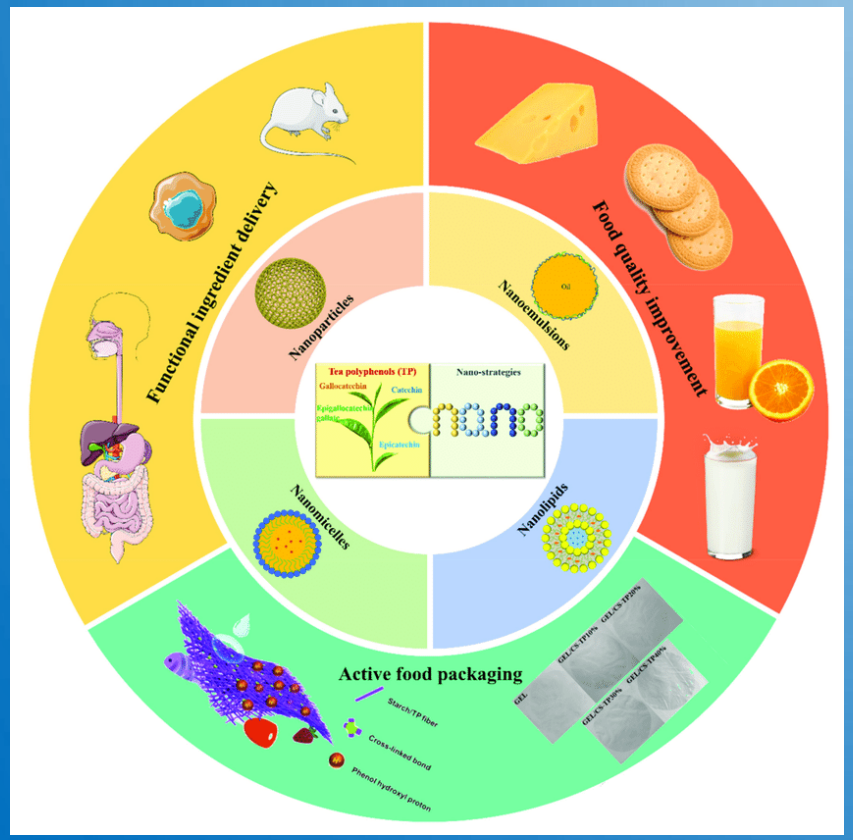
Nutrition and Healthy Aging 4 (2016) 95–99
DOI 10.3233/NHA-1614
IOS Press

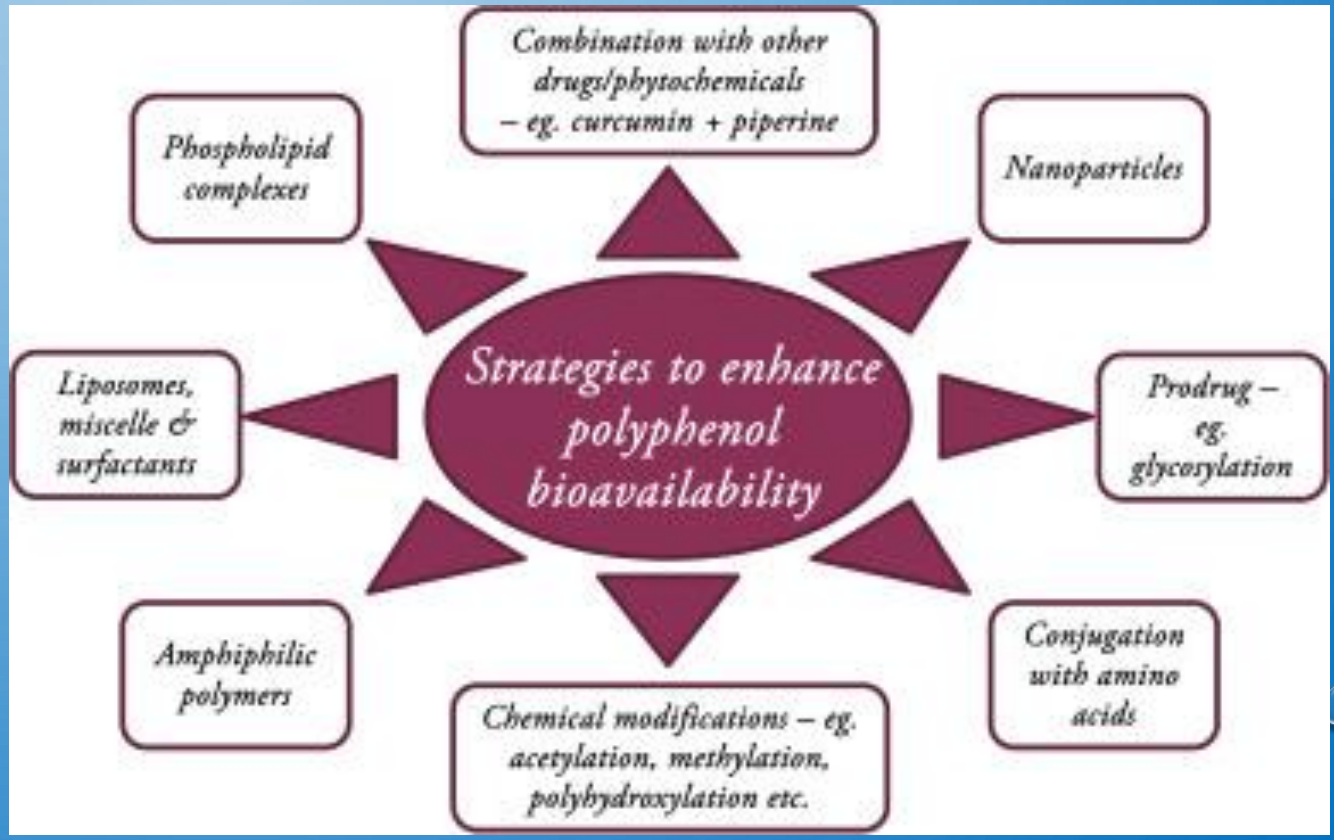
Short Communication

Diet-induced weight loss is sufficient to reduce senescent cell number in white adipose tissue of weight-cycled mice

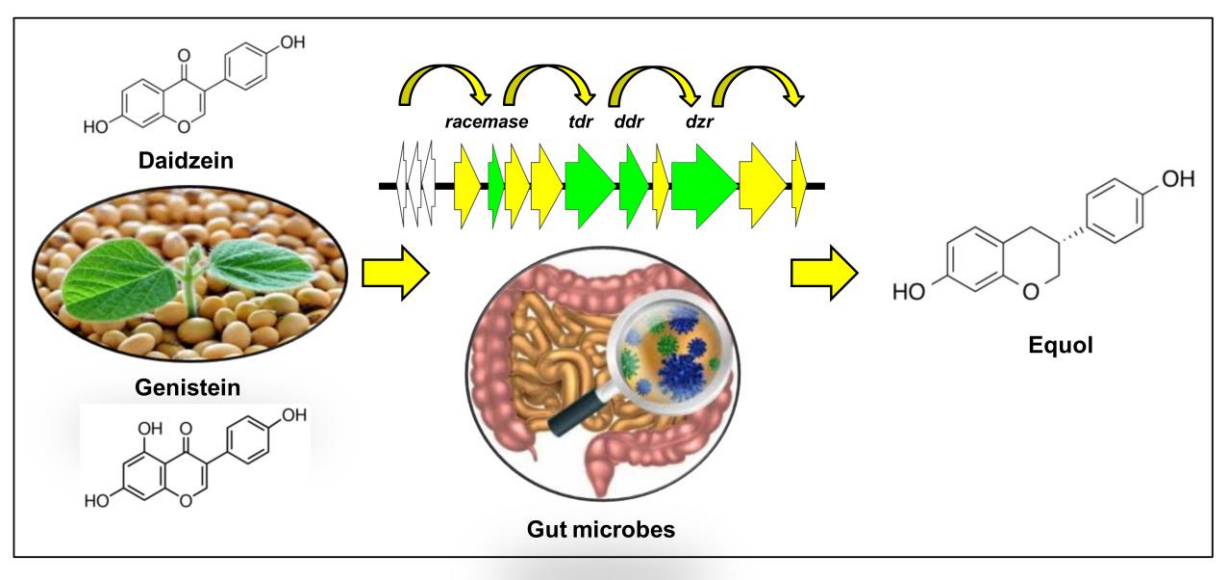
Edward O. List[a,b,c,*], Elizabeth Jensen[a], Jesse Kowalski[a], Mathew Buchman[a], Darlene E. Berryman[a,c,d] and John J. Kopchick[a,c,d]

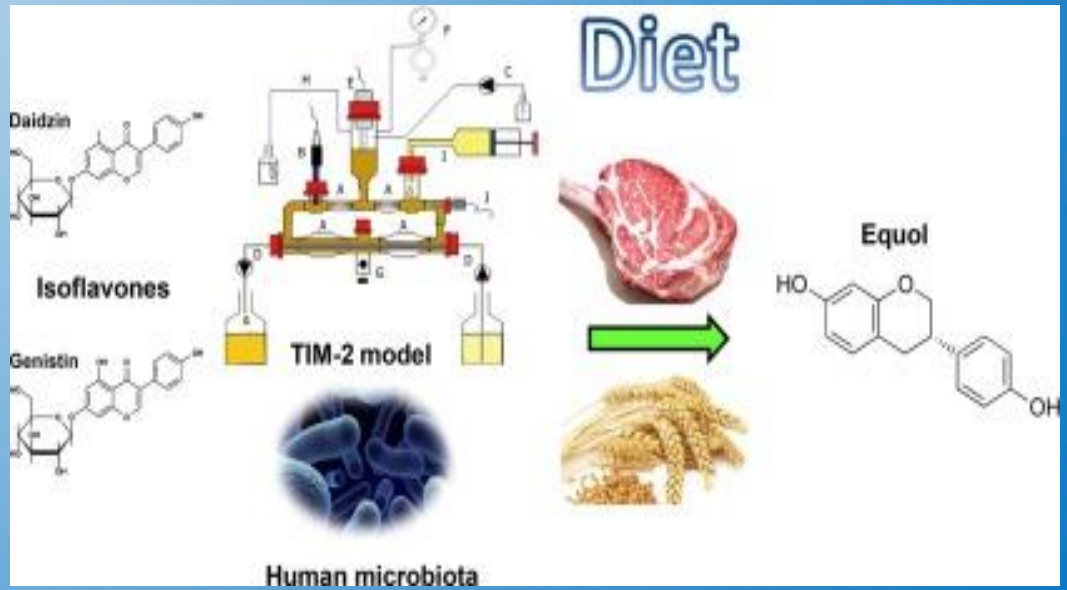
IMPROVEMENT OF STABILITY POLYPHENOLS, LIPOSOMES, NANOPARTICLES

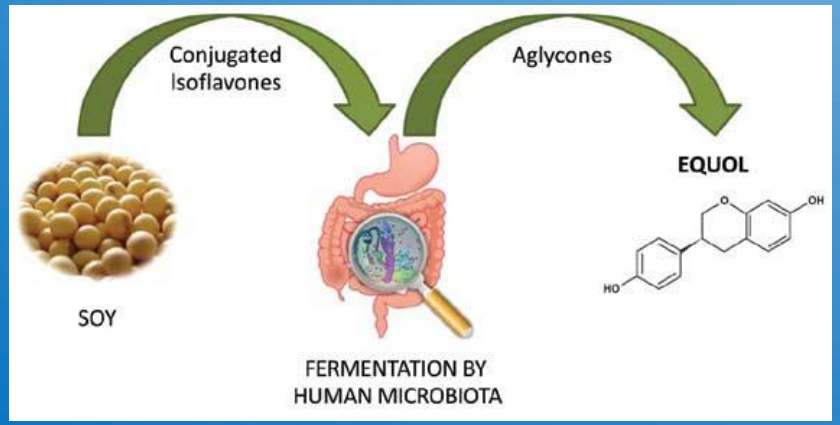


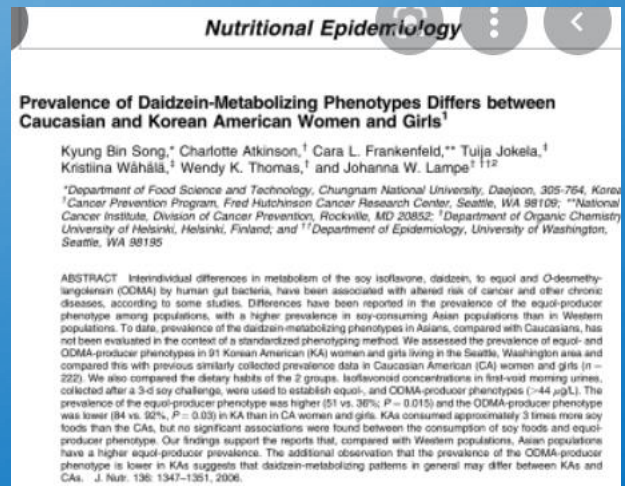


SOY, GENISTEIN, EQUOL, E.R., MICROBIOTA, ETHNIC








Nutritional Epidemiology

Prevalence of Daidzein-Metabolizing Phenotypes Differs between Caucasian and Korean American Women and Girls[1]

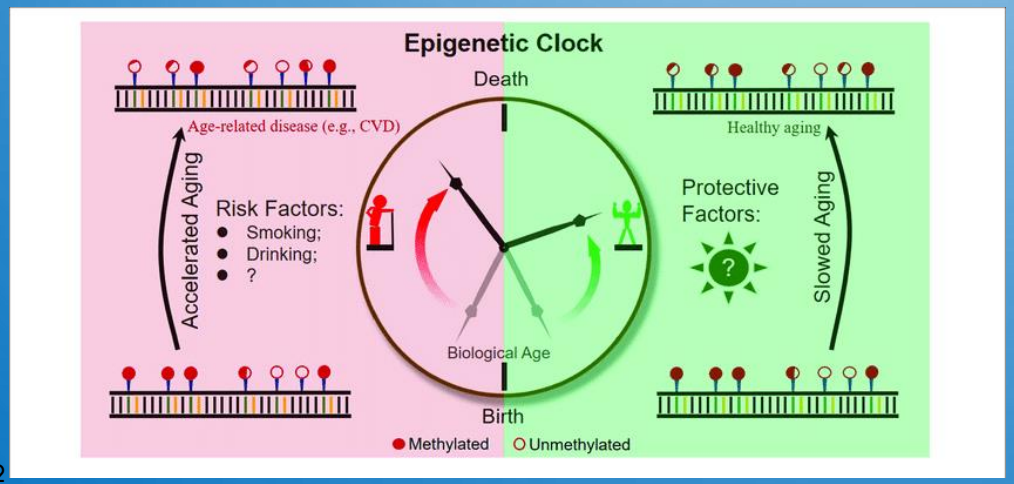
Kyung Bin Song,* Charlotte Atkinson,† Cara L. Frankenfeld,** Tuija Jokela,‡ Kristiina Wähälä,‡ Wendy K. Thomas,† and Johanna W. Lampe†[11]2

*Department of Food Science and Technology, Chungnam National University, Daejeon, 305-764, Korea †Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; **National Cancer Institute, Division of Cancer Prevention, Rockville, MD 20852; ‡Department of Organic Chemistry University of Helsinki, Helsinki, Finland; and ††Department of Epidemiology, University of Washington, Seattle, WA 98195

ABSTRACT Interindividual differences in metabolism of the soy isoflavone, daidzein, to equol and O-desmethylangolensin (ODMA) by human gut bacteria, have been associated with altered risk of cancer and other chronic diseases, according to some studies. Differences have been reported in the prevalence of the equol-producer phenotype among populations, with a higher prevalence in soy-consuming Asian populations than in Western populations. To date, prevalence of the daidzein-metabolizing phenotypes in Asians, compared with Caucasians, has not been evaluated in the context of a standardized phenotyping method. We assessed the prevalence of equol- and ODMA-producer phenotypes in 91 Korean American (KA) women and girls living in the Seattle, Washington area and compared this with previous similarly collected prevalence data in Caucasian American (CA) women and girls (n = 222). We also compared the dietary habits of the 2 groups. Isoflavonoid concentrations in first-void morning urines, collected after a 3-d soy challenge, were used to establish equol-, and ODMA-producer phenotypes (>44 μg/L). The prevalence of the equol-producer phenotype was higher (51 vs. 36%; $P = 0.015$) and the ODMA-producer phenotype was lower (84 vs. 92%, $P = 0.03$) in KA than in CA women and girls. KAs consumed approximately 3 times more soy foods than the CAs, but no significant associations were found between the consumption of soy foods and equol-producer phenotype. Our findings support the reports that, compared with Western populations, Asian populations have a higher equol-producer prevalence. The additional observation that the prevalence of the ODMA-producer phenotype is lower in KAs suggests that daidzein-metabolizing patterns in general may differ between KAs and CAs. J. Nutr. 136: 1347–1351, 2006.

CR, FASTING AND FASTING MIMETICS

Caloric restriction improves healthy aging, role for epigenetic regulation as seen in epigenetic clock



Also true for mi RNA- marker

CALORIC RESTRICTION AND AGING CHANGE EPIGENETIC CPG -METHYLATION STRUCTURE

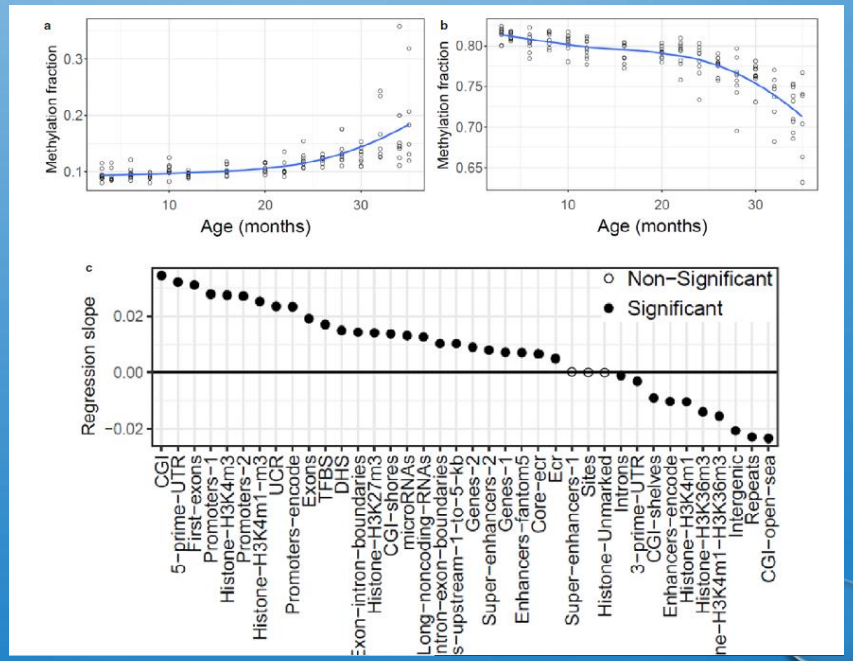
Accepted: 23 January 2018
DOI: 10.1111/acel.12738

ORIGINAL ARTICLE

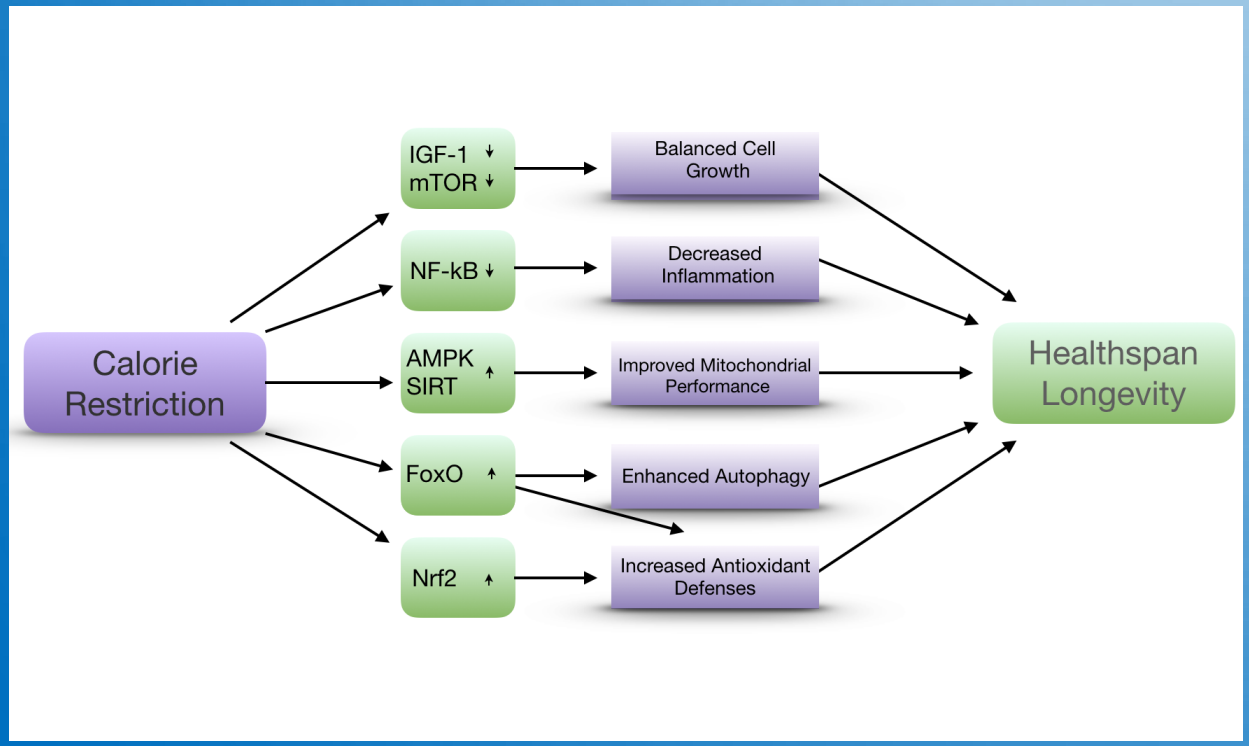
WILEY Aging Cell

Global remodeling of the mouse DNA methylome during aging and in response to calorie restriction

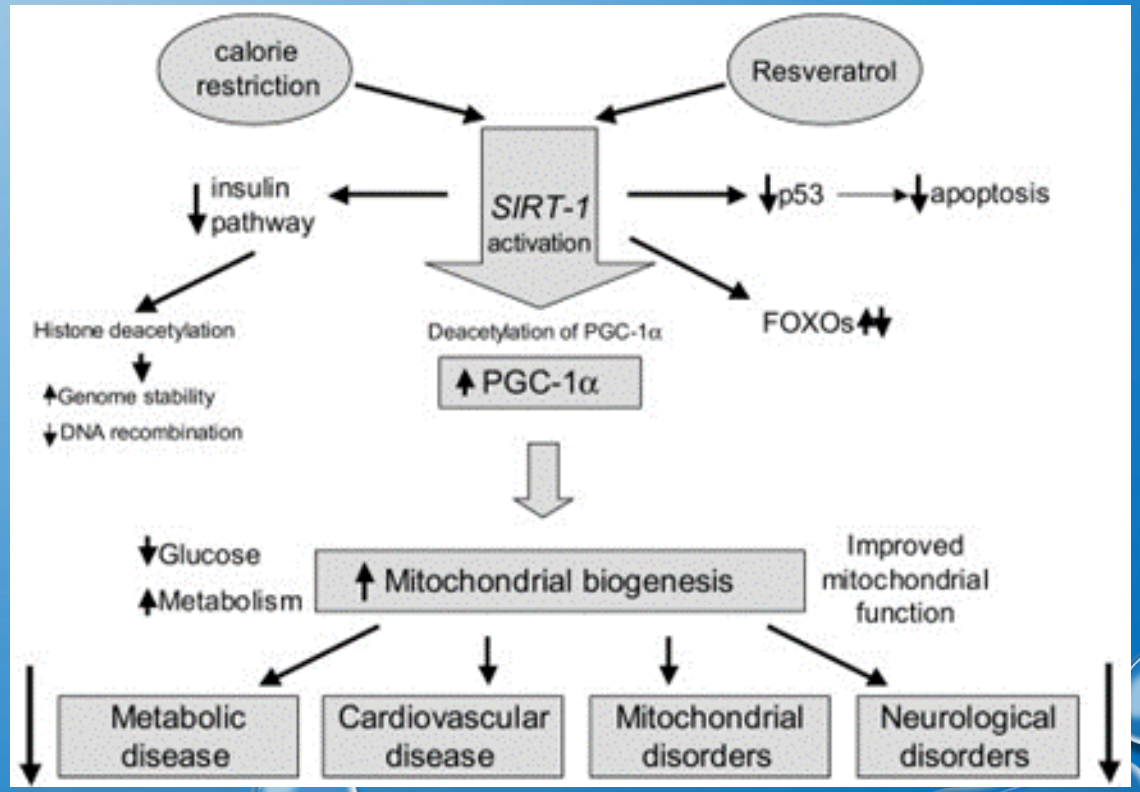
András Sziráki[1] | Alexander Tyshkovskiy[1,2] | Vadim N. Gladyshev[1]



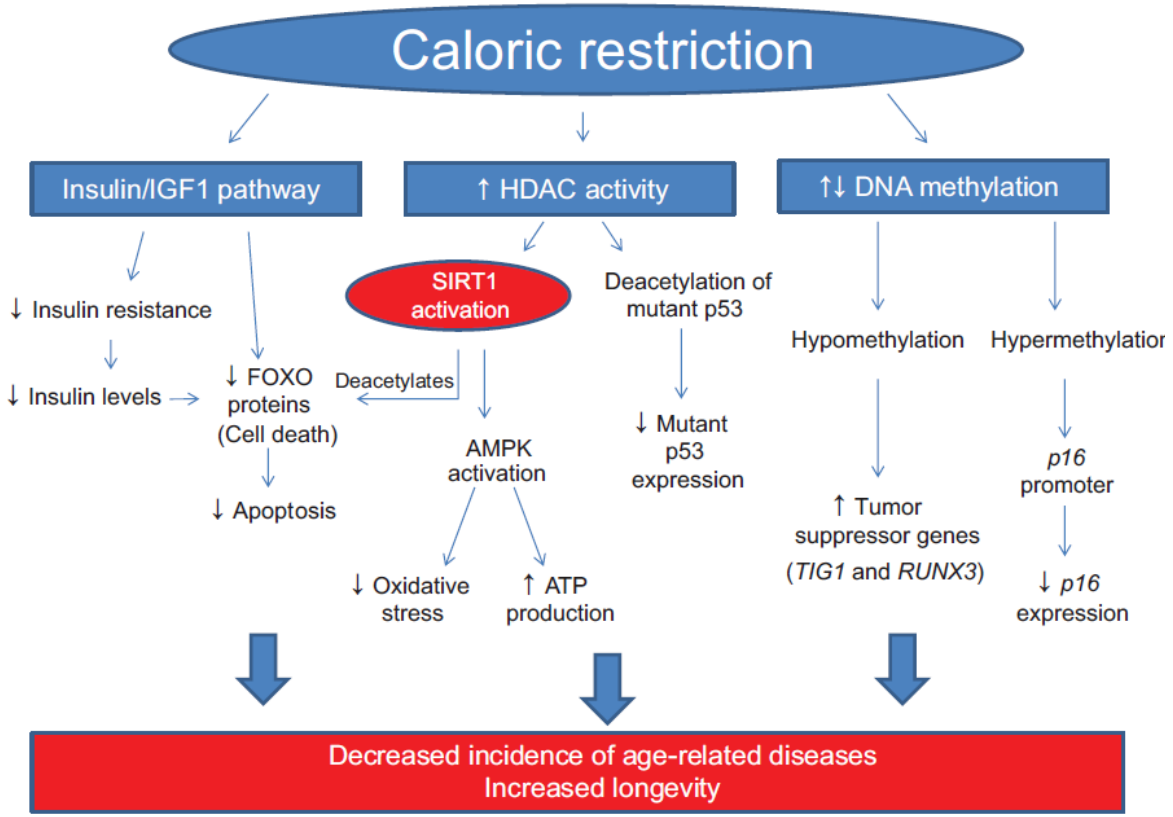
CR, FASTING PATHWAYS

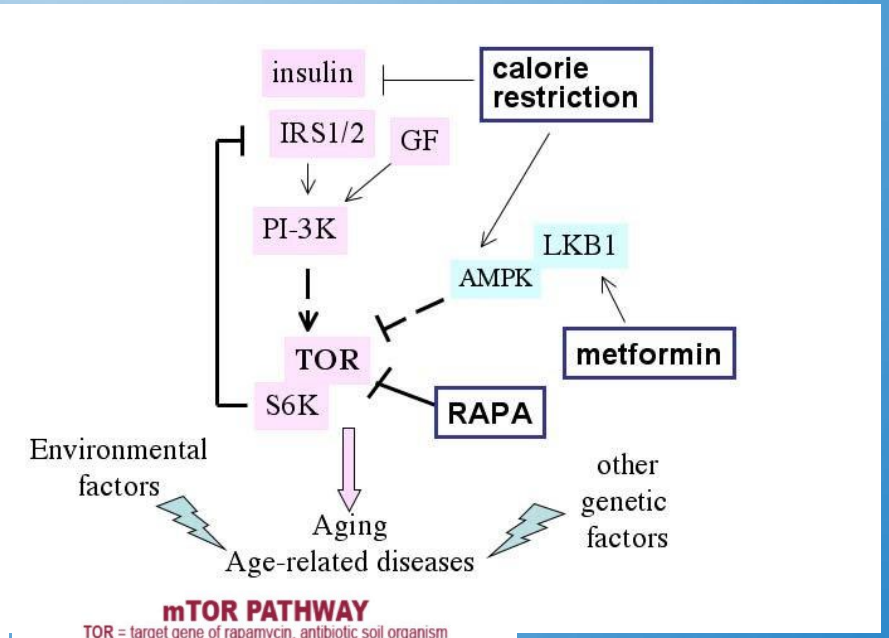


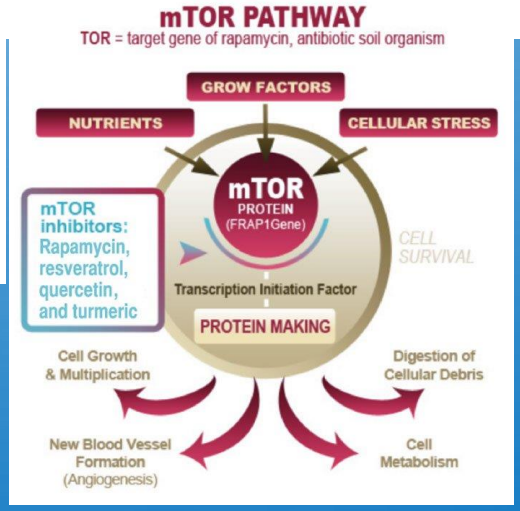
Haslberger 2022



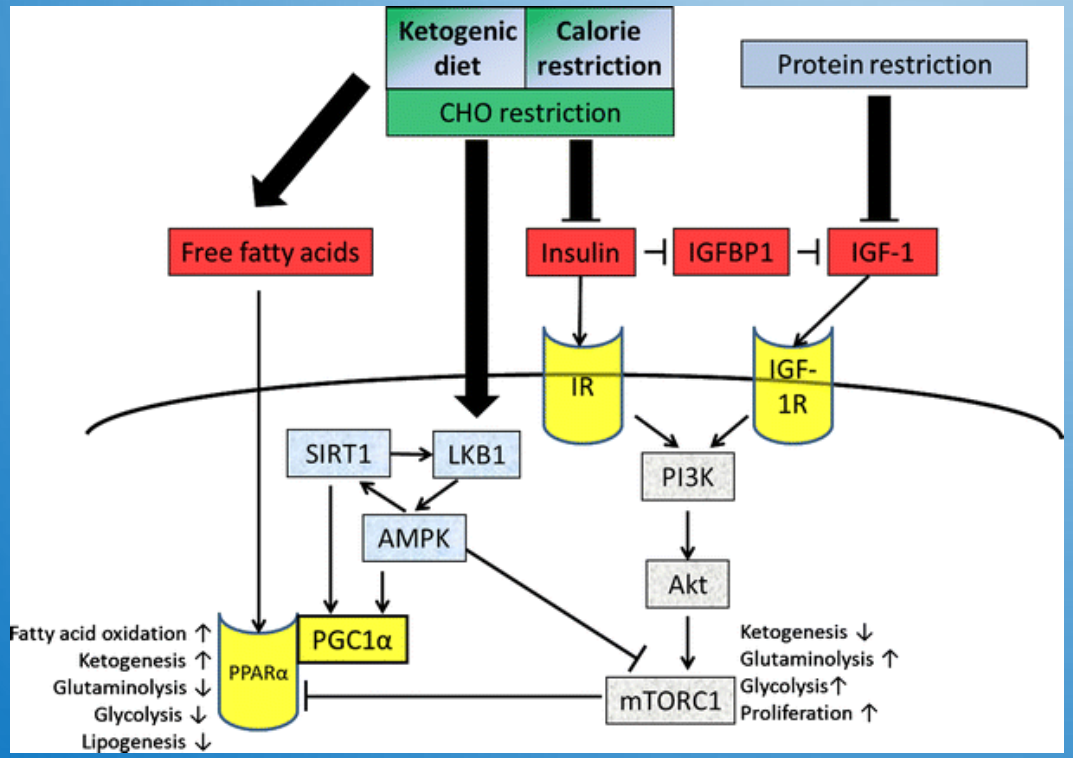
FASTING PATHWAYS: SIRT, MTOR PATHWAYS







CALORIC RESTRICTION, KETOGENIC DIET INVOLVE SIRTS (+NAD, CLOCK GENES) + MTOR PATHWAYS (METFORMIN).



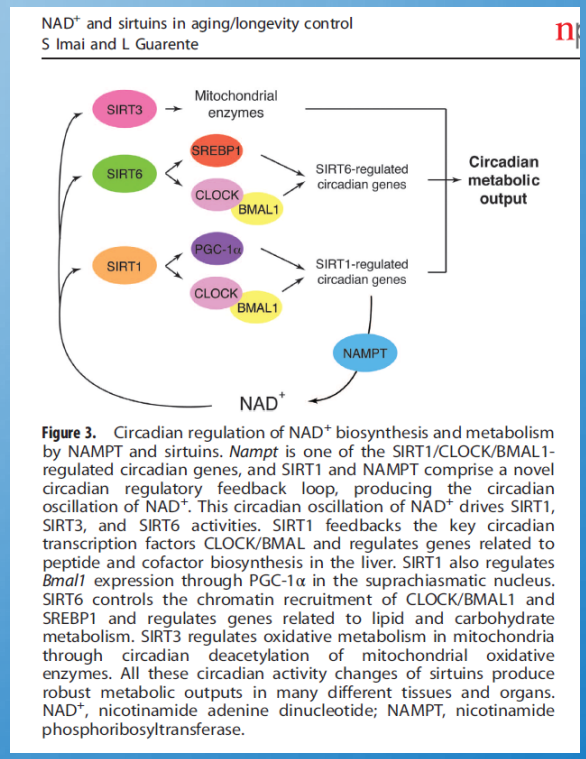


Figure 3. Circadian regulation of NAD$^+$ biosynthesis and metabolism by NAMPT and sirtuins. *Nampt* is one of the SIRT1/CLOCK/BMAL1-regulated circadian genes, and SIRT1 and NAMPT comprise a novel circadian regulatory feedback loop, producing the circadian oscillation of NAD$^+$. This circadian oscillation of NAD$^+$ drives SIRT1, SIRT3, and SIRT6 activities. SIRT1 feedbacks the key circadian transcription factors CLOCK/BMAL and regulates genes related to peptide and cofactor biosynthesis in the liver. SIRT1 also regulates *Bmal1* expression through PGC-1α in the suprachiasmatic nucleus. SIRT6 controls the chromatin recruitment of CLOCK/BMAL1 and SREBP1 and regulates genes related to lipid and carbohydrate metabolism. SIRT3 regulates oxidative metabolism in mitochondria through circadian deacetylation of mitochondrial oxidative enzymes. All these circadian activity changes of sirtuins produce robust metabolic outputs in many different tissues and organs. NAD$^+$, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase.

Front Psychol. 2015; 6: 27. PMCID: PMC4313585
Published online 2015 Feb 2. doi: 10.3389/fpsyg.2015.00027

Ketosis, ketogenic diet and food intake control: a complex relationship

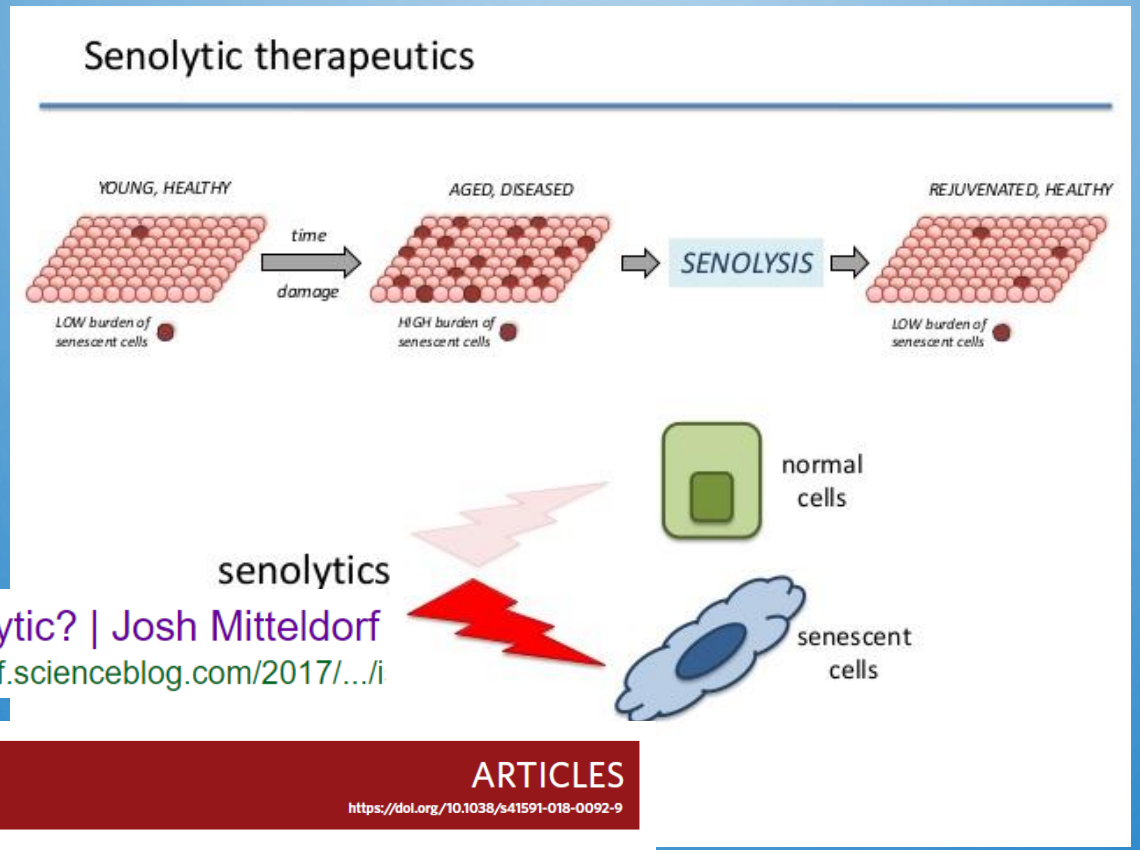
Antonio Paoli,[1,*] Gerardo Bosco,[1] Enrico M. Camporesi,[2,3] and Devanand Mangar[3,4]

npj | Aging and Mechanisms of Disease
www.nature.com/npjam
REVIEW ARTICLE OPEN

It takes two to tango: NAD$^+$ and sirtuins in aging/longevity control

Shin-ichiro Imai[1] and Leonard Guarente[2,3]

CALORIC RESTRICTION: REJUVENETION BY SENOLYSIS? ROLE FOR AUTOPHAGY ?



Is fasting senolytic? | Josh Mitteldorf
https://joshmitteldorf.scienceblog.com/2017/.../i

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0092-9

Senolytics improve physical function and increase lifespan in old age

Ming Xu[1,2*], Tamar Pirtskhalava[1], Joshua N. Farr[1], Bettina M. Weigand[1,3], Allyson K. Palmer[1],

83rd ICREA Colloquium, 2018

FASTING AND MICROBIOTA

Wien Klin Wochenschr (2015) 127:394–398
DOI 10.1007/s00508-015-0755-1

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Increased gut microbiota diversity and abundance of *Faecalibacterium prausnitzii* and *Akkermansia* after fasting: a pilot study

Marlene Remely · Berit Hippe · Isabella Geretschlaeger · Sonja Stegmayer · Ingrid Hoefinger · Alexander Haslberger

Received: 2 October 2014 / Accepted: 20 January 2015 / Published online: 13 March 2015

FERNSEHEN TVTHEK RADIO DEBATTE ÖSTERREICH WETTER SPORT IPTV NEWS

SCIENCE ORF.at

Forscher/innen schreiben | Linktipps

ERNÄHRUNG 20.11.2014

Fastenkuren sind gut für den Darm

Studien aus der Tierwelt haben schon öfters bewiesen, dass Fasten das Leben verlängern kann. Untersuchungen zu Menschen gibt es vergleichsweise wenig. Ein Wiener Forscher hat nun aber 60 Probanden im Dienste der Wissenschaft fasten lassen. Ergebnis: Neben allgemeinem Wohlbefinden konnte sich auch die Darmflora erholen.

Why Your Gut Microbes Love Intermittent Fasting

Did you know that most of the cells that make up your body aren't human at all? Some of them are microbial… and when you fast with the LIFE Fasting Tracker app, they fast too.

Conclusions Our results show that caloric restriction affects gut microbiota by proliferating mucin-degrading microbial subpopulations. An additional intervention with a probiotic formula increased probiotic-administered gut microbial populations.

CALORIC RESTRICTION- LONGEVITY FASTING MIMETICS AND SENOLYTICS ?

Functional Foods in Health and Disease 2020; 10(10):439-455 www.ffhdj.com Page 439 of 455

Research Article Open Access

FFHD
Functional Foods in Health and Disease

Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition

Stephanie Lilja[1], Angelika Pointner[1], Hanna Bäck[1], Kalina Duszka[1], Berit Hippe[1], Lucia Suarez[1], Ingrid Höfinger[2], Tewodros Debebe[3], Jürgen König[1], Alexander G. Haslberger[1]

[1]Department of Nutritional Sciences, University of Vienna, 1090 Vienna, Austria, [2]Monastory, Pernegg, [3]Biomes NGS GmbH, Germany

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

METABOLIC DISEASE

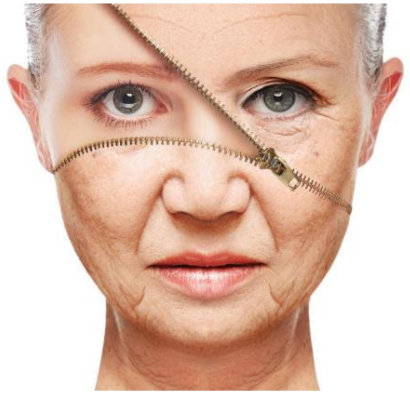
Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Min Wei,[1]* Sebastian Brandhorst,[1]* Mahshid Shelehchi,[1] Hamed Mirzaei,[1] Chia Wei Cheng,[1] Julia Budniak,[1] Susan Groshen,[2] Wendy J. Mack,[2] Esra Guen,[1] Stefano Di Biase,[1] Pinchas Cohen,[1] Todd E. Morgan,[1] Tanya Dorff,[3] Kurt Hong,[4] Andreas Michalsen,[5] Alessandro Laviano,[6] Valter D. Longo[1,7]†

Fastenmimetika aktivieren Reparaturmechanismen, die den Alterungsprozess der Zelle bremsen können.

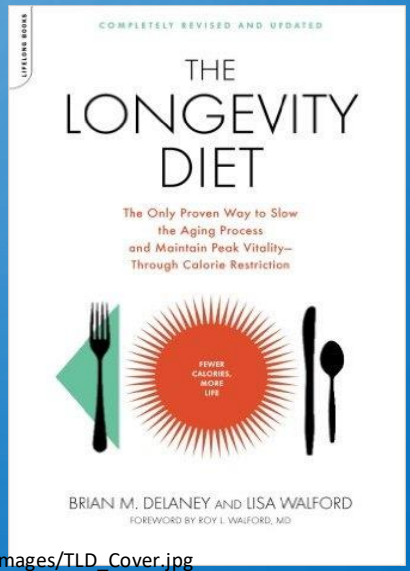
Univ.-Prof Dr. Alexander Haslberger

Mit einer Pille Lebensstil-Sünden verhindern



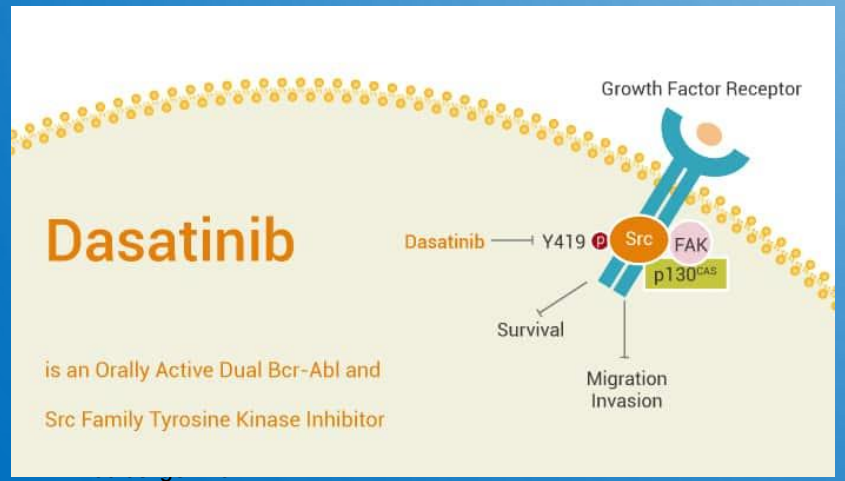
Symbolbild© Bild: Getty Images/iStockphoto/evgenyatamanenko/iStockphoto

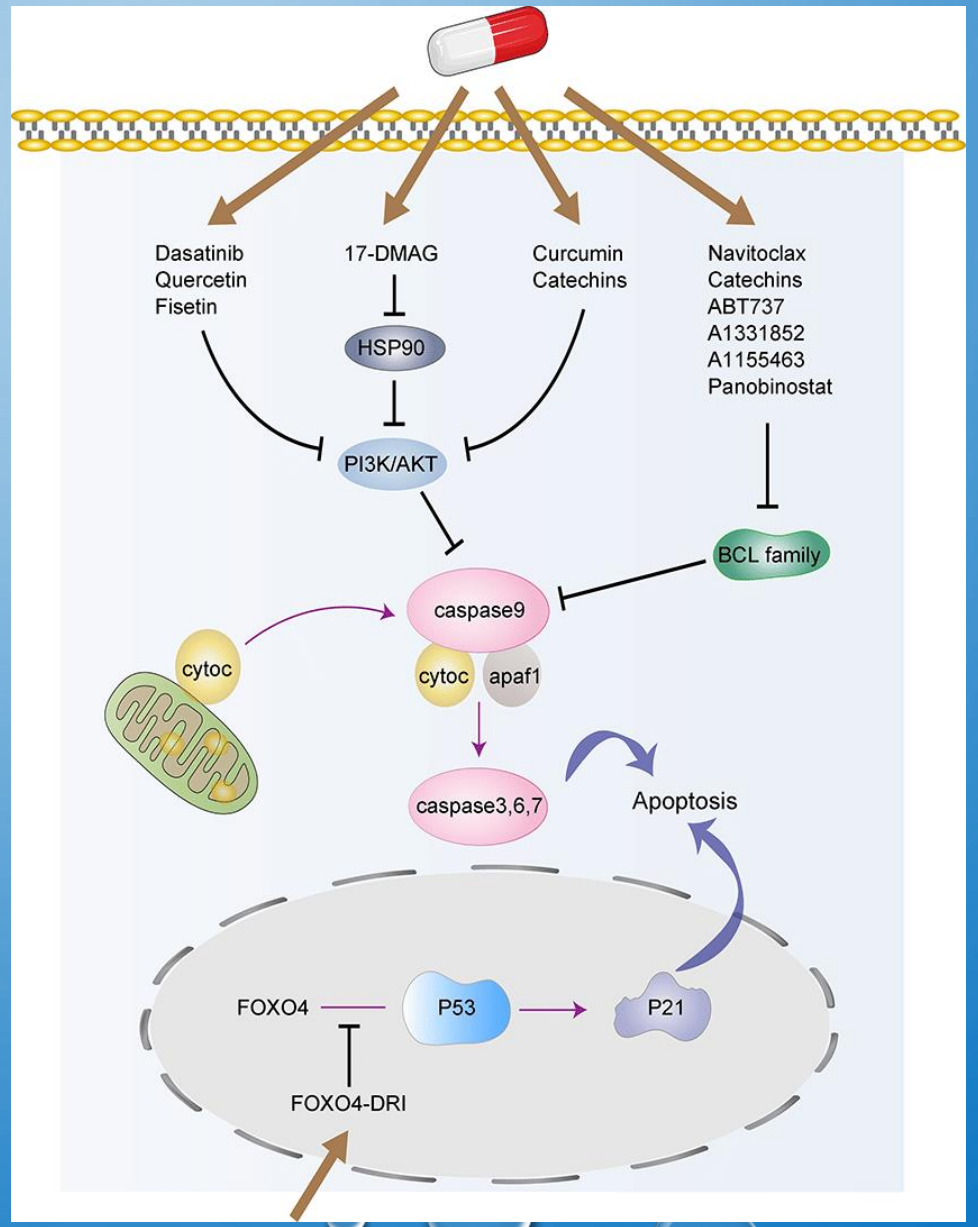
Für immer jung? Nährstoff-Kombination soll helfen, DNA-Schäden zu reparieren. Experten sind skeptisch.



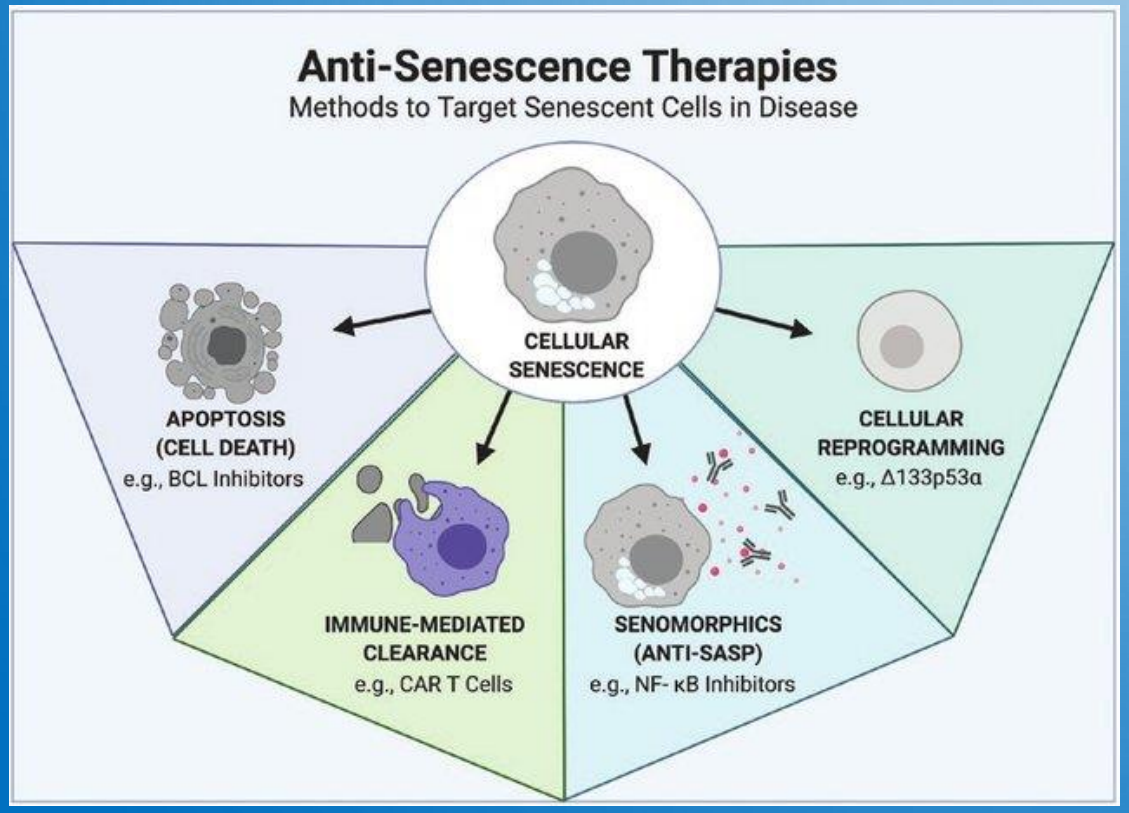
/images/TLD_Cover.jpg

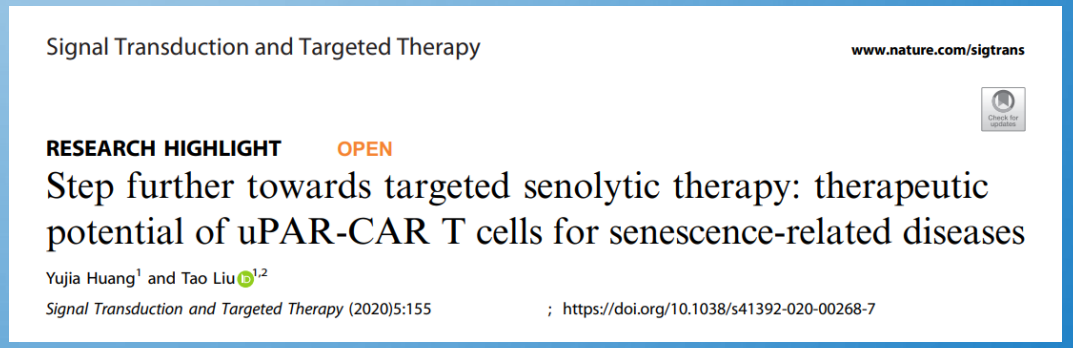
SENOLYTICS QUECETIN,CURCUMIN, CATECHINS, FISETIN,… + DASATINIB MARKETS





ANTI SENESCENCE STRATEGIES




Signal Transduction and Targeted Therapy www.nature.com/sigtrans

RESEARCH HIGHLIGHT OPEN

Step further towards targeted senolytic therapy: therapeutic potential of uPAR-CAR T cells for senescence-related diseases

Yujia Huang[1] and Tao Liu[1,2]

Signal Transduction and Targeted Therapy (2020)5:155 ; https://doi.org/10.1038/s41392-020-00268-7

CR- MIMETICS

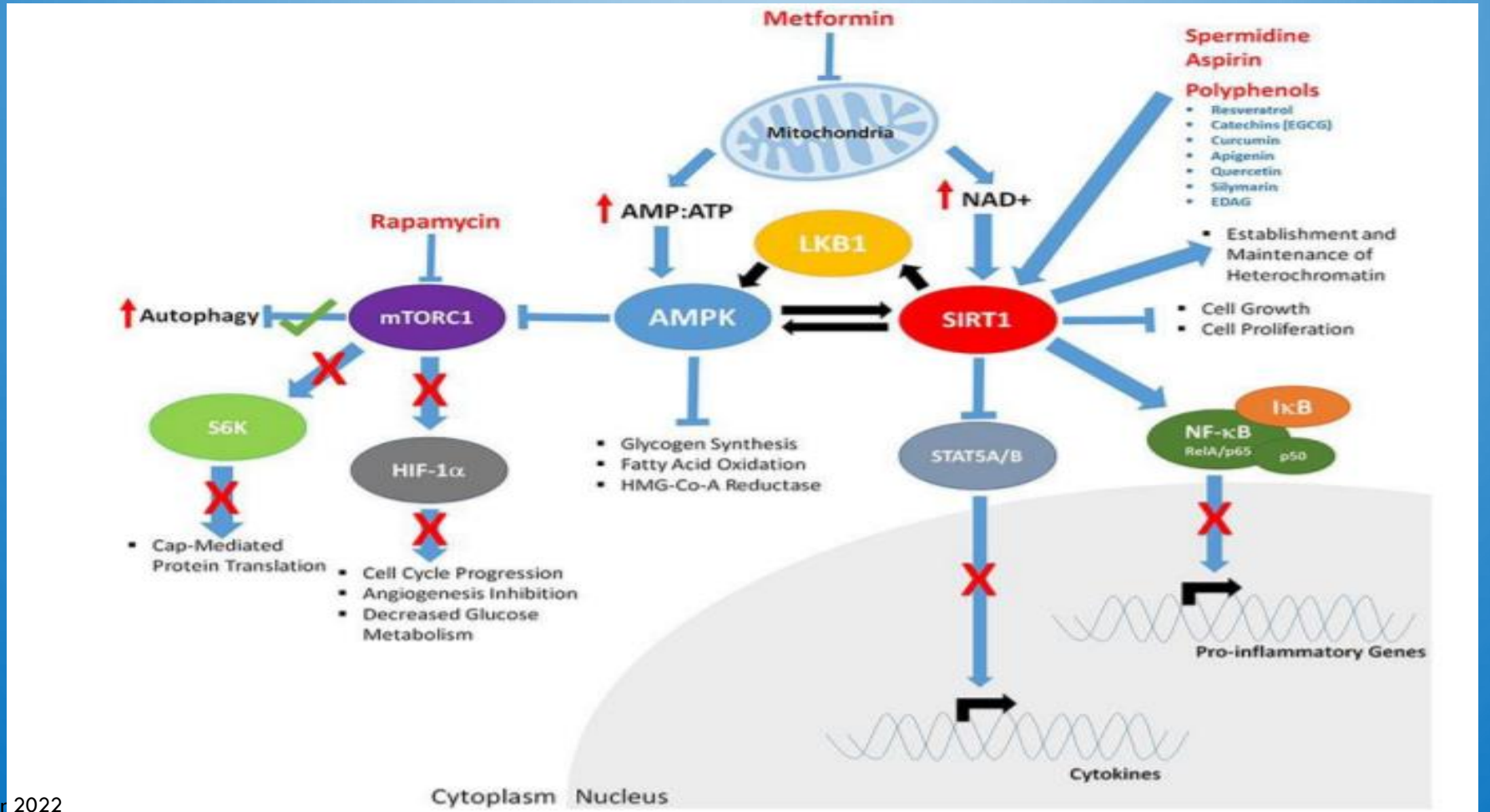


Figure 20. The downstream effects of CR mimetics and nutraceuticals on key aging mediators AMPK and SIRT1 [177].

STUDY SENOLYTICS, SENESCENCE MARKERS IN BRDU TREATED PRE-ADIPOCYTES, ADIPOCYTES, 3T3

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2020, Article ID 4793125, 13 pages
https://doi.org/10.1155/2020/4793125

Hindawi

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

Stephanie Lilja,[1] Julia Oldenburg,[1] Angelika Pointner,[1] Laura Dewald,[1] Mariam Lerch,[1] Berit Hippe,[2] Olivier Switzeny,[2] and Alexander Haslberger[1]

Stem Cells. Author manuscript; available in PMC 2015 Aug 19.
Published in final edited form as:
Stem Cells. 2008 Dec; 26(12): 3218–3227.
Published online 2008 Sep 18. doi: 10.1634/stemcells.2008-0299

Bromodeoxyuridine Induces Senescence

EGCG Uji-XP™

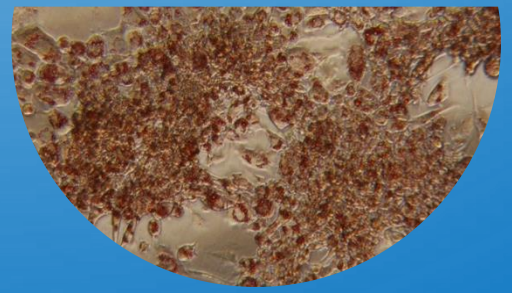
Anthocyanins-Bluezones®

Ayurvedic Spermidine Bluezones®

BLUEZONES™ RESVERATROL

Phloretin, BHB, Butyrate (Merck)

B-Gal, senescence



Adipocytes, fat droplets

CASE STUDY: COMPARING FASTING AND A FASTING MIMETIC SIRT-FOOD SHOT: MICROBIOTA, EPIGENETICS

STOFF	WIRKSTOFF	MENGE / 25ML	Wirkstoff
Blueberry Extract	Anthocyanins/ Anthocyanidin..	40 mg	14mg 10mg
Broccoli Extract	Sulpharapane, Glucoraphin..	30 mg	
Apfel extract	Phlorentin, Quercetin..	50 mg	
Citrus extract	Naringin..	40 mg	
Nikotinamid	Nikotinamid ribosid	24 mg	
Zinkgluconat	Zink	7.5 mg	

Wasser, Stevia, Erythrit

Buchinger Fasting < 120 kcal/day
n: 22 in Pernegg Monastery

Feces , blood spots, before and
After the end, first sold feces

Active (N. 131) Placebo (n: 30)
Intervention 3 months

Feces, Blood spots before, after 1,3 month

Illuminia sequencing, Line 1 methylation bisulfite qPCR, HR-MCA, RNA, MiRNA RT QPCRi

BUCHINGER FASTING RESULTED IN A RISE IN THE DISTRIBUTION OF PROTEOBACTERIA, INCREASED MICROBIOTA DIVERSITY AND A SIGNIFICANT INCREASE IN CHRISTENSENELLA

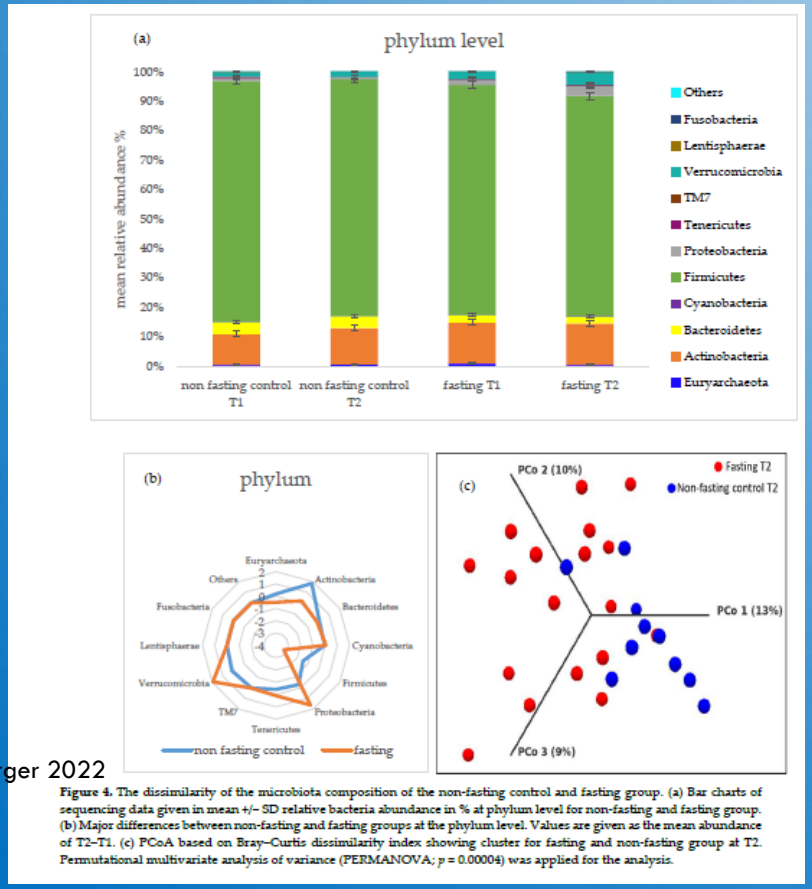


Figure 4. The dissimilarity of the microbiota composition of the non-fasting control and fasting group. (a) Bar charts of sequencing data given in mean +/− SD relative bacteria abundance in % at phylum level for non-fasting and fasting group. (b) Major differences between non-fasting and fasting groups at the phylum level. Values are given as the mean abundance of T2–T1. (c) PCoA based on Bray–Curtis dissimilarity index showing cluster for fasting and non-fasting group at T2. Permutational multivariate analysis of variance (PERMANOVA; $p = 0.00004$) was applied for the analysis.

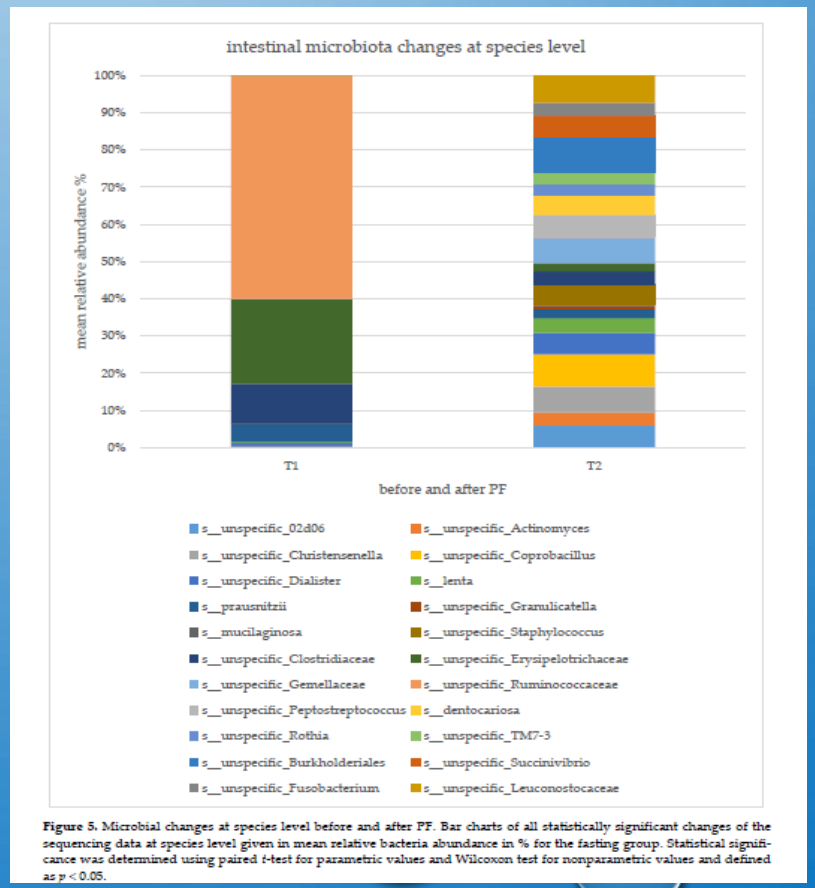


Figure 5. Microbial changes at species level before and after PF. Bar charts of all statistically significant changes of the sequencing data at species level given in mean relative bacteria abundance in % for the fasting group. Statistical significance was determined using paired *t*-test for parametric values and Wilcoxon test for nonparametric values and defined as $p < 0.05$.

3M SIRT INDUCING DRINK INCREASED *ACTINOBACTERIA*. FIRMICUTES/*BACTEROIDETES* RATIO DECREASED AND CORRELATED WITH BMI. ONLY FASTING INCREASED BUTYRATE SIGNIFICANTLY

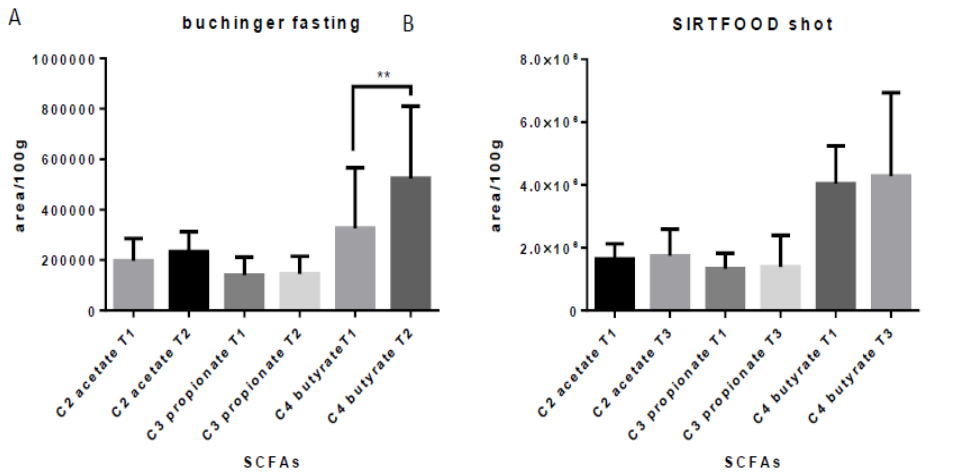


Figure 7: Amount of SCFAs produced given as area/100g stool for buchinger fasting (A) and SIRTFOOD shot (B) interventions. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

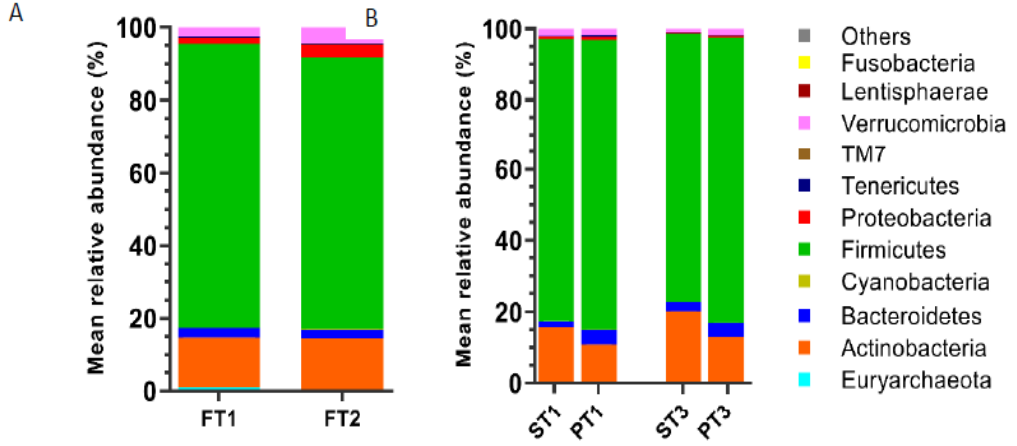


Figure 6: Abundance microbiota by phyla for fasting group (A), SIRTFOOD shot (ST1 vs ST3) (B) and placebo group (PT1 vs PT3) (B). Results are expressed in percentage of the mean of relative abundance for the different phyla. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

POSITIVE CORRELATION OF THE ABUNDANCE OF BUTYRATE-PRODUCING *BACTEROIDETES* WITH MIR125, SIRT-1 EXPRESSION, TELOMERE LENGTH

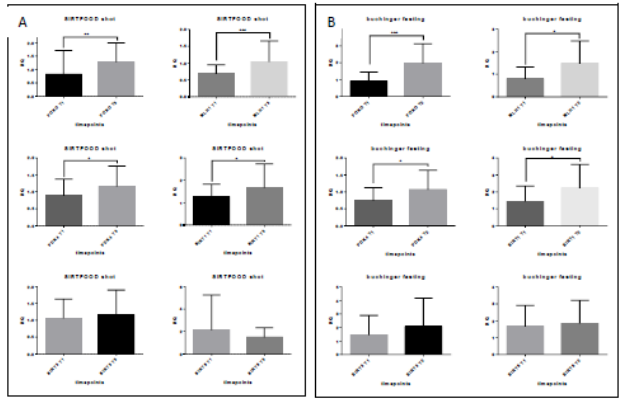


Figure 4: RQ selected mRNA gene expression (*FoxO1, MLH1, PDK4, SIRT1, SIRT3, SIRT6*) SIRTFOOD shot and buchinger fasting. The results are expressed as mean +/- SD. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

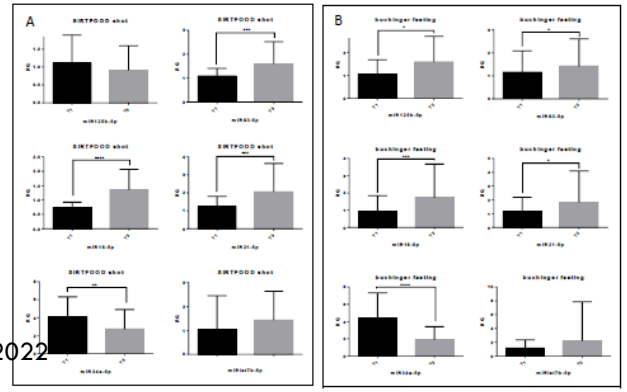


Figure 5: RQ selected miRNA gene expression (*miR125b-5p, miR93-5p, miR16-5p, miR21-5p, miR34a-5p, miRlet7b-5p*) SIRTFOOD shot and buchinger fasting. The results are expressed as mean +/- SD. Statistical significance between timepoint 1 (T1) and end (T2 or T3) of the intervention was determined using paired t-test for parametric values and Wilcoxon test for nonparametric values.

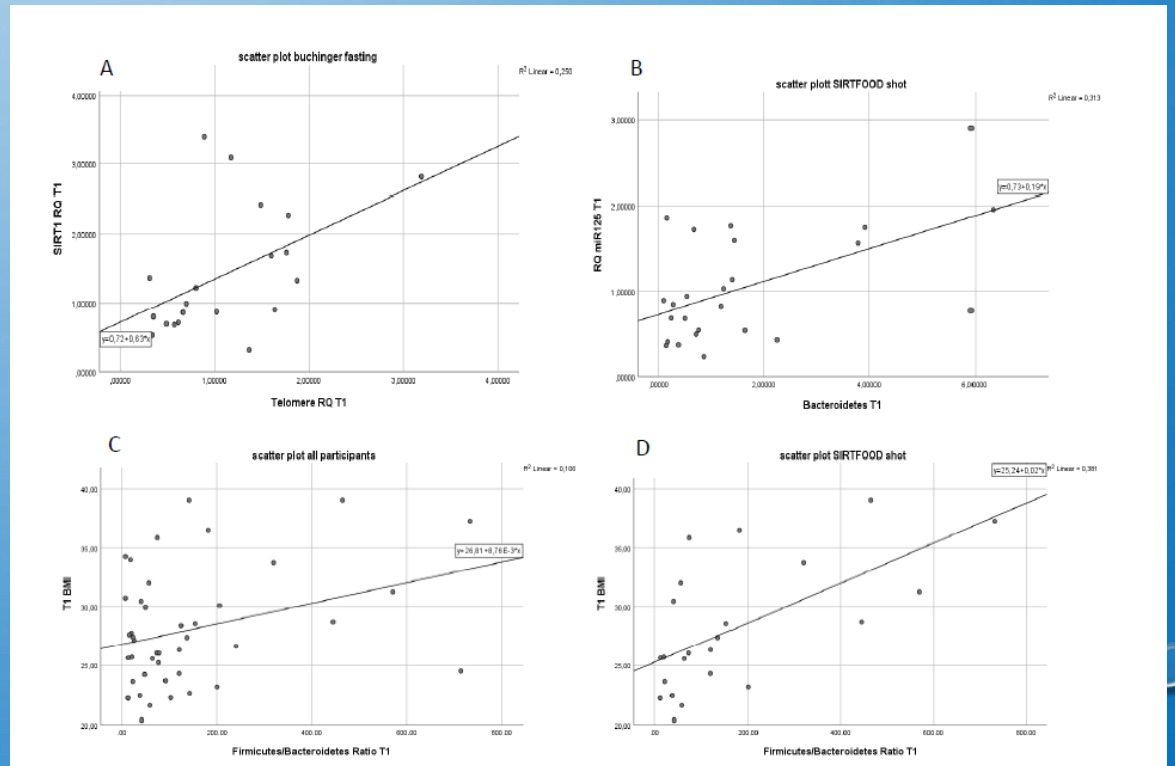
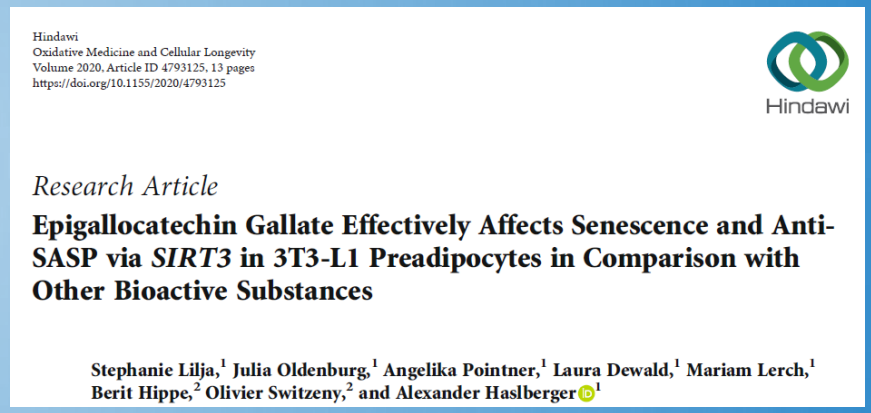


Figure 8: spss output scatter plots. (A) shows a positive correlation between telomere length and SIRT1 expression for buchinger fasting at baseline. Bacteroidetes and miR125b-5p positively correlated in the SIRTFOOD shot intervention at baseline(B). For all participants the ratio of Firmicutes/Bacteroidetes increased with higher BMI (C), which was also seen for the SIRTFOOD shot intervention Discussion (D). Statistical significance was defined as $p < 0.05$.

CONCLUSIONS

In conclusion fasting and to some extend fasting mimetics result in beneficial modulation of microbiota (e.g diversity, SCFA, BHP) and metabolism (e.g SIRTS, mtDNA, telomer length)

Microbiota structure seems to interfere with the expression of Sirtuins and metabolism relevant miRNAs


Hindawi
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Hindawi

Research Article

Epigallocatechin Gallate Effectively Affects Senescence and Anti-SASP via *SIRT3* in 3T3-L1 Preadipocytes in Comparison with Other Bioactive Substances

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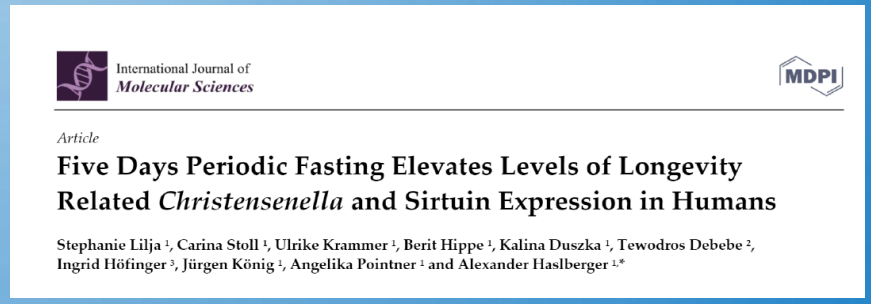

International Journal of *Molecular Sciences*

MDPI

Article

Five Days Periodic Fasting Elevates Levels of Longevity Related *Christensenella* and Sirtuin Expression in Humans

Stephanie Lilja [1], Carina Stoll [1], Ulrike Krammer [1], Berit Hippe [1], Kalina Duszka [1], Tewodros Debebe [2], Ingrid Höfinger [3], Jürgen König [1], Angelika Pointner [1] and Alexander Haslberger [1,*]


Online ISSN: 2160-3855, Print ISSN: 2378-7007

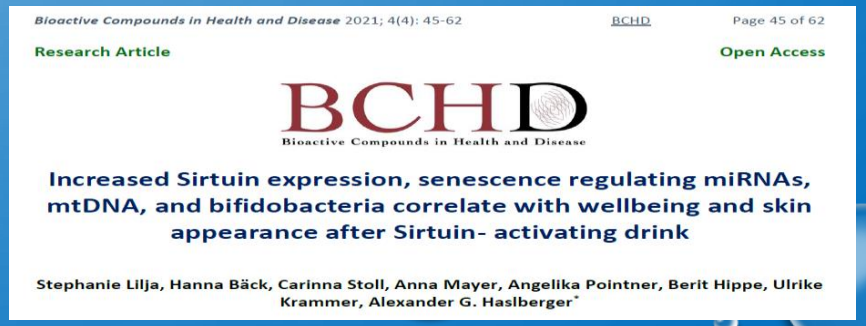
Functional Foods in Health and Disease

Home Editorial Team Iss

Home > Vol 10, No 10 (2020) > Lilja

Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition

Stephanie Lilja, Hanna Bäck, Kalina Duszka, Berit Hippe, Lucia Suarez, Ingrid Höfinger, Tewodros Debebe, Jürgen König, Alexander Haslberger


Bioactive Compounds in Health and Disease 2021; 4(4): 45-62 BCHD Page 45 of 62

Research Article Open Access

BCHD

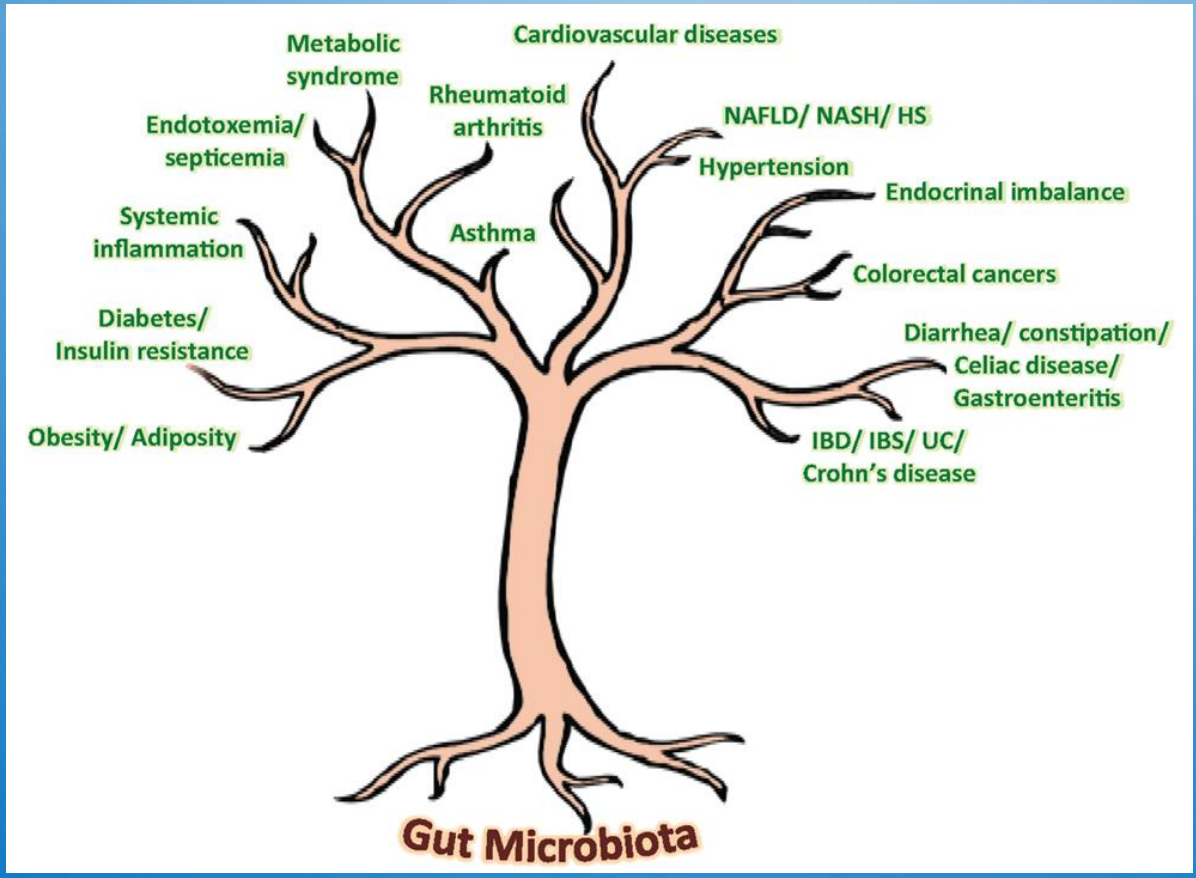
Bioactive Compounds in Health and Disease

Increased Sirtuin expression, senescence regulating miRNAs, mtDNA, and bifidobacteria correlate with wellbeing and skin appearance after Sirtuin- activating drink

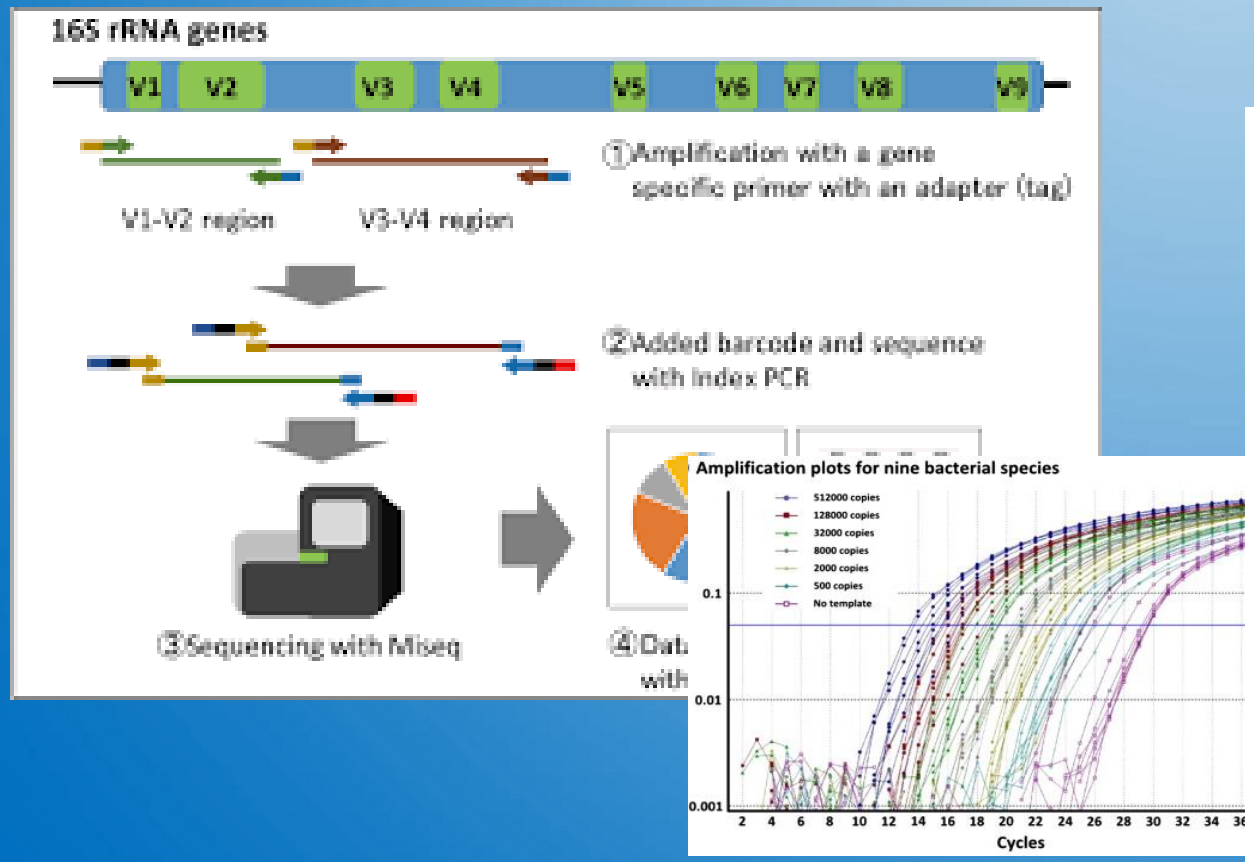
Stephanie Lilja, Hanna Bäck, Carinna Stoll, Anna Mayer, Angelika Pointner, Berit Hippe, Ulrike Krammer, Alexander G. Haslberger*

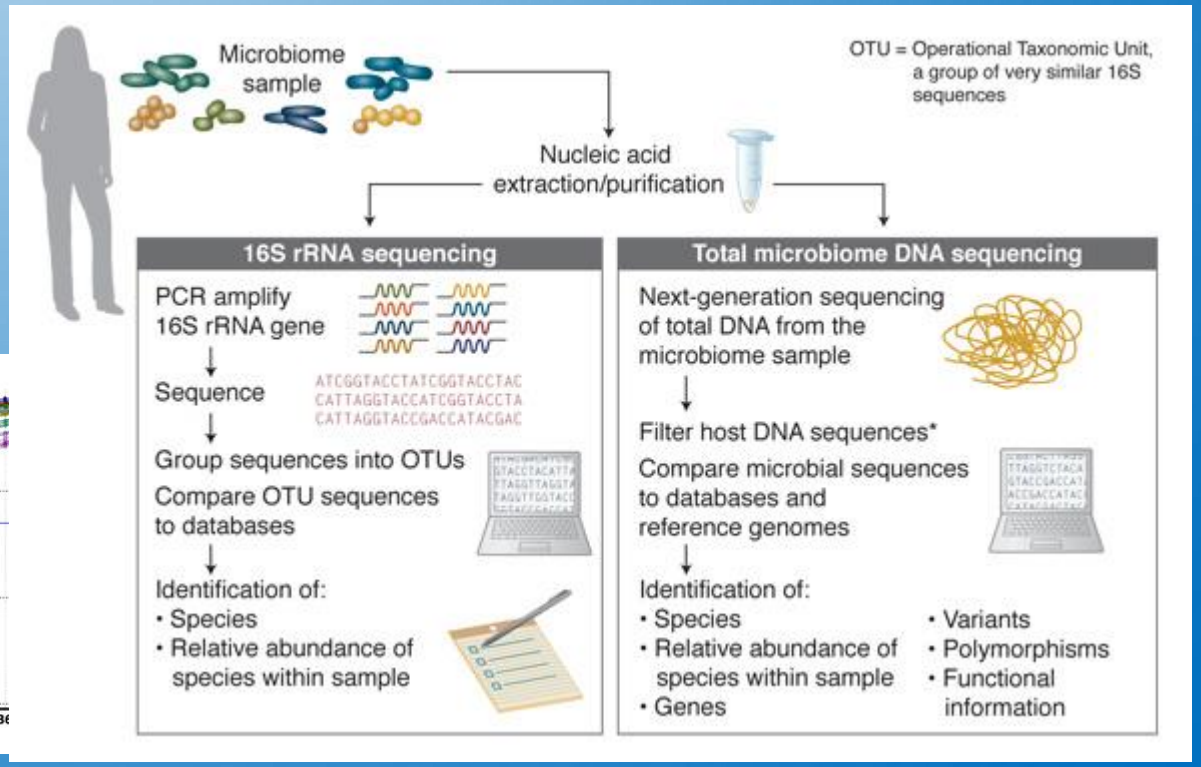
MICROBIOTA

MICROBIOTA IN MOST COMPLEX DISEASES INVOLVED ?

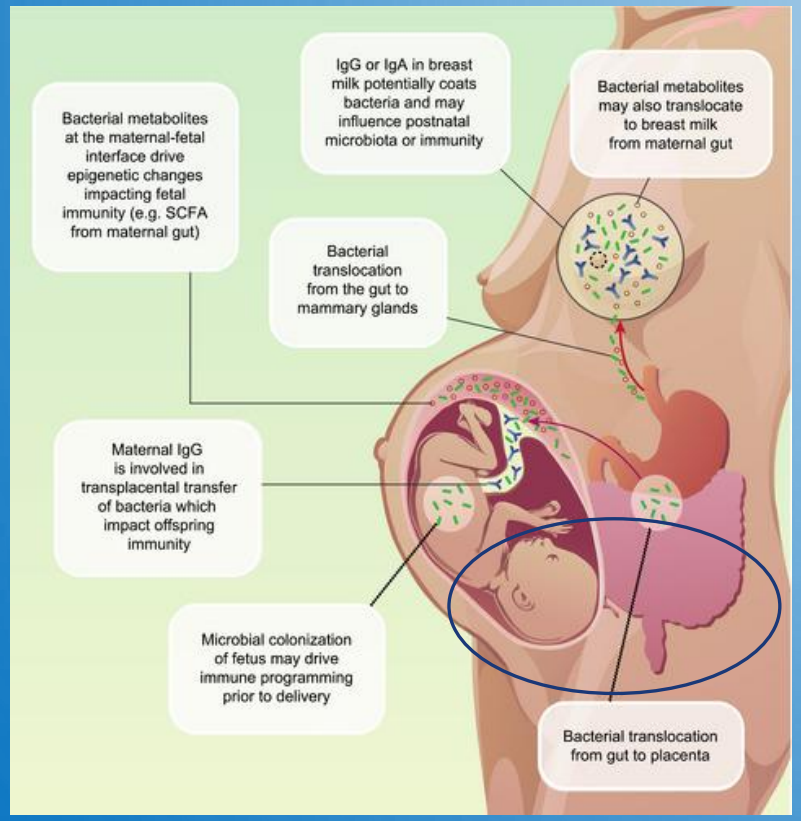


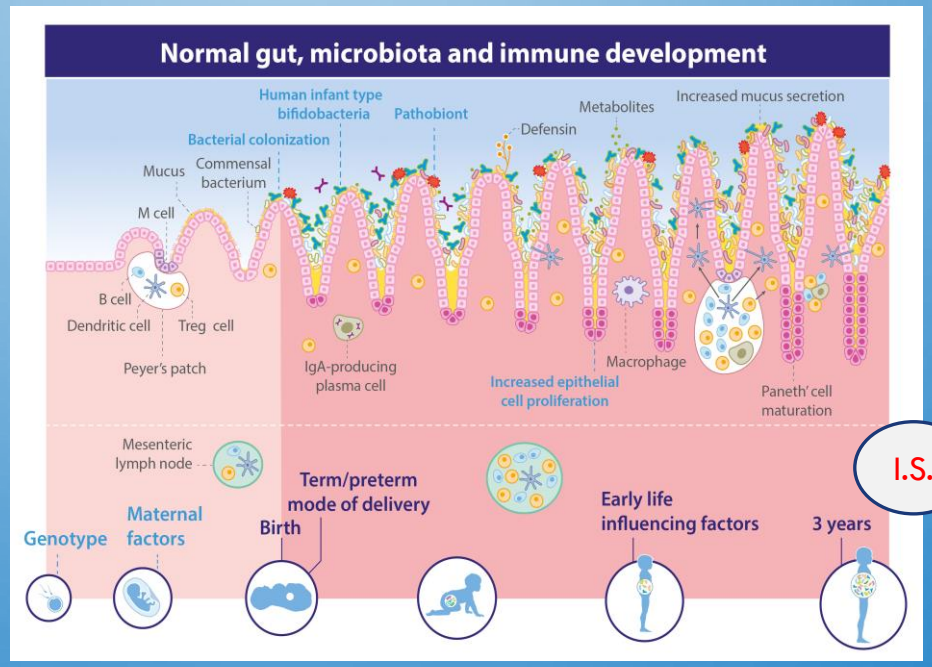
BACTERIA, CULTIVATION : 16S $_R$RNA IDENTIFICATION



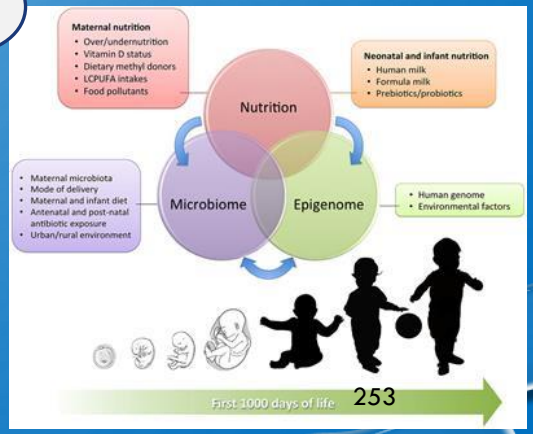


DEVELOPMENT OF MICROBIOTA, I.S., AND EPIGENETIC SYSTEM, IMPRINTING





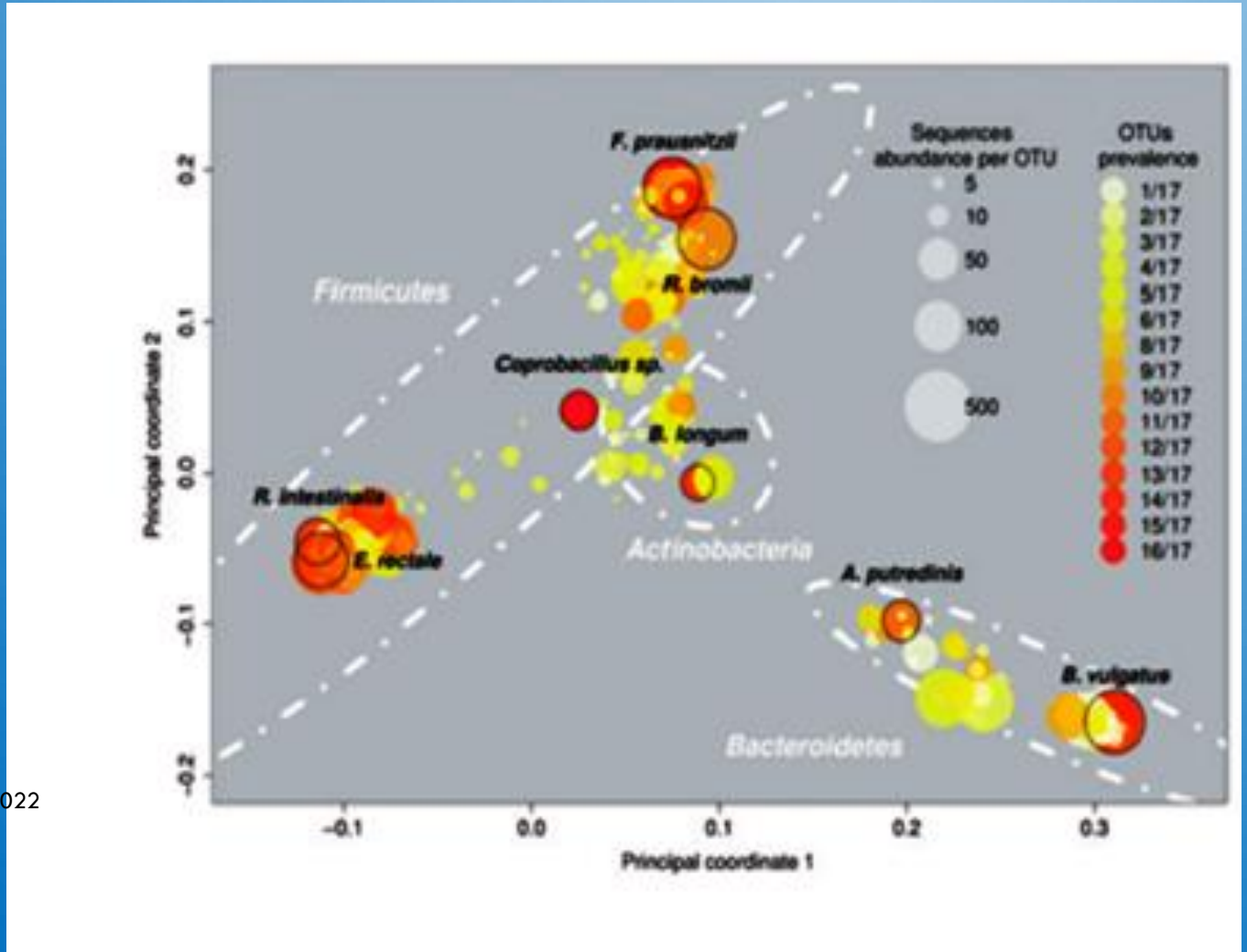
I.S.



Development prenatal, Interaction with I.S., epigenetic maternal factors, Diversity:delivery, breastfeeding, imprinting in 1000 days of life

Haslberger 2022

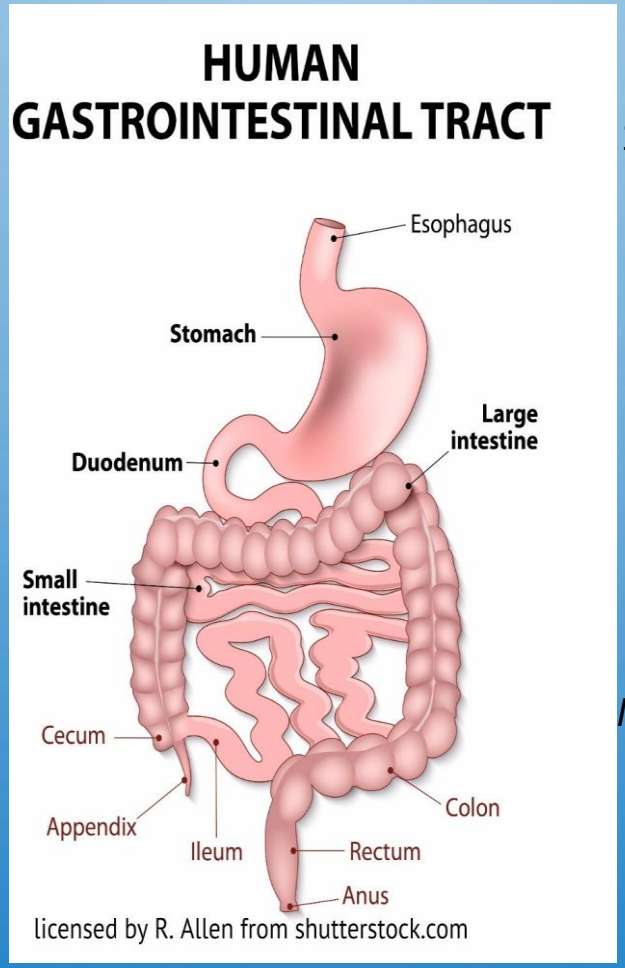
MICROBIOTA: THE ROLE OF THE DISTRIBUTION OF GROUPS (AND THEIR FUNCTIONS ?)



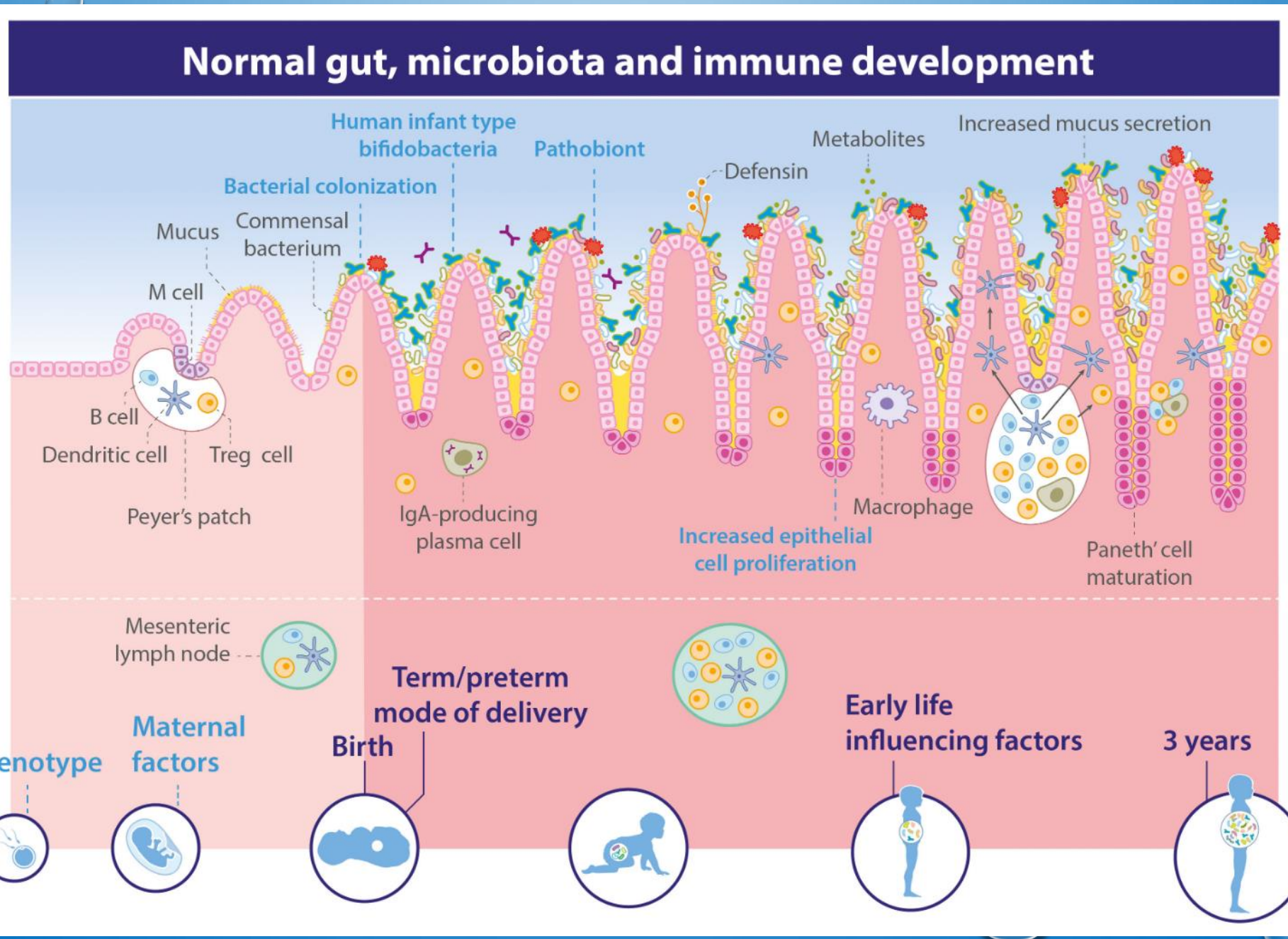
GUT MICROBIOTA

Stomach & Duodenum
10^1– 10^2 CFU/mL
Helicobacter
Streptococcus

Jejunum & Ileum
10^4 – 10^8 CFU/mL
Bacteroides
Streptococcus
Lactobacillius
Bifidobacteria
Fusobacteria

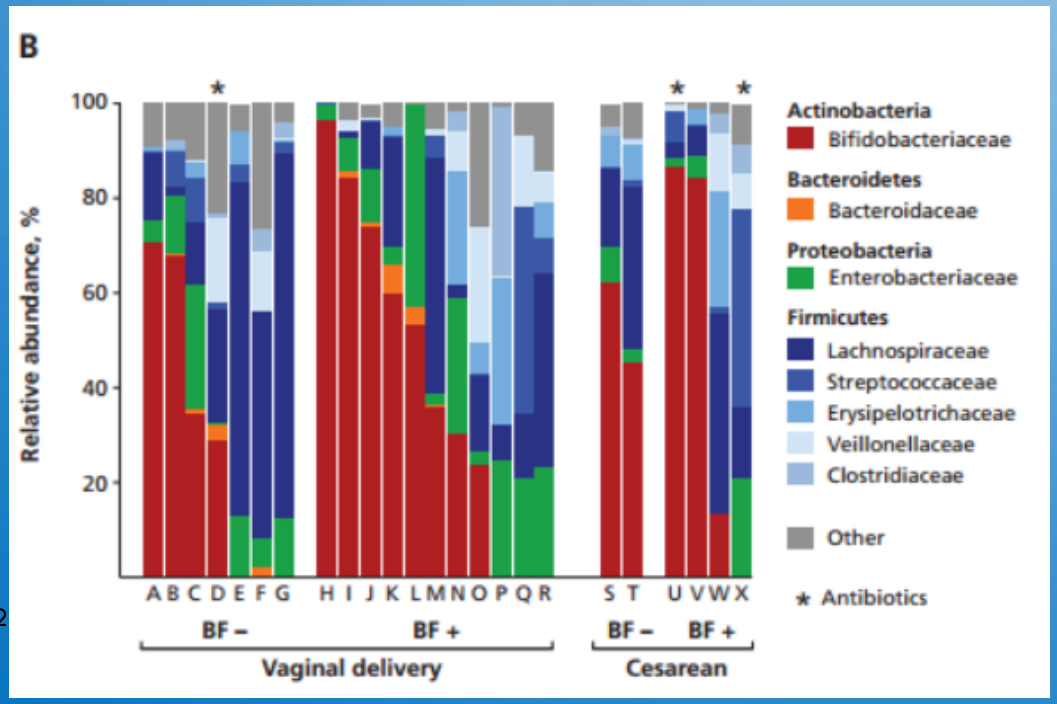


Colon
10^{10} – 10^{12} CFU/mL
Bacteroides
Prevotella
Facaelbacterium
Ruminococcus
Roseburia
Clostridium
Bifidobacteria
Collinsella
Desulfovibrio
Bilophila
Akkermansia
Methanobrevibacter


Normal gut, microbiota and immune development
Human infant type bifidobacteria
Pathobiont
Bacterial colonization
Mucus
Commensal bacterium
M cell
B cell
Dendritic cell
Treg cell
Peyer's patch
IgA-producing plasma cell
Defensin
Metabolites
Increased mucus secretion
Macrophage
Increased epithelial cell proliferation
Paneth' cell maturation
Mesenteric lymph node
Genotype
Maternal factors
Birth
Term/preterm mode of delivery
Early life influencing factors
3 years

WAYS OF DELIVERY AND MICROBIOTA: A LONG LASTING DIFFERENCE

INFANTS BORN BY ELECTIVE CESAREAN DELIVERY HAD PARTICULARLY LOW BACTERIAL RICHNESS AND DIVERSITY. FORMULA-FED INFANTS HAD INCREASED RICHNESS OF SPECIES, WITH OVERREPRESENTATION OF *CLOSTRIDIUM DIFFICILE*.



CHILD involves more than 10 000 people, including 3 500 infants

CMAJ March 19, 2013 vol. 185 no. 5 First published February 11, 2013, doi: 10.1503/cmaj.121189

Research

Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months

Meghan B. Azad, PhD, Theodore Konya, MPH, Heather Maughan, PhD, David S. Guttman, PhD, Catherine J. Field, PhD, Radha S. Chari, MD, Malcolm R. Sears, MB, Allan B. Becker, MD, James A. Scott, PhD, Anita L. Kozyrskyj, PhD† on behalf of the CHILD Study Investigators

CORE MICROBIOTA

- *BACTEROIDETES* (22,9 %)
- *FIRMICUTES* (64 %)

  (32 % OF C. *CLUSTER IV*, 36 % OF C. *CLUSTER XIVA* AND 5 % OF *LACTOBACILLI*)

  (MARIAT ET AL., 2009)

- *ACTINOBACTERIA* (1- 4 %)
- VERRUMICROBIALES (1- 4 %)
- ARCHAEAL DOMAIN (1- 2,5 %)
- EUKARYOTIC MICROORGANISMS (< 0,1 %)

  (GERRITSEN ET AL., 2011)

MICROBIOTA FUNCTIONS

- Protective functions
- Structural functions /
- Metabolic functions /
- Fermenting dietary fiber into
- short-chain fatty acids
- Synthesizing vitamins

- *BACTEROIDETES* (22,9 %)
- *FIRMICUTES* (64 %)

  (32 % OF C. *CLUSTER IV*, 36 % OF C. *CLUSTER XIVA* AND 5 % OF *LACTOBACILLI*)
- *ACTINOBACTERIA* (1- 4 %)
- VERRUMICROBIALES (1- 4 %)
- ARCHAEAL DOMAIN (1- 2,5 %)
- EUKARYOTIC MICROORGANISMS (< 0,1 %)

(GERRITSEN ET AL., 2011)

Grenham S, Front Physiol, 2011

VARIATION IN MICROBIOTA STRUCTURE IS HIGH

Despite high variation, GI microbiota depend on :

1. Individuum
2. Area and lifestyle
3. Diet
4. Interventions

GI MICROBIOTA: DIVERSITY OF GROUPS AND FUNCTIONS IMPORTANT FOR HEALTH

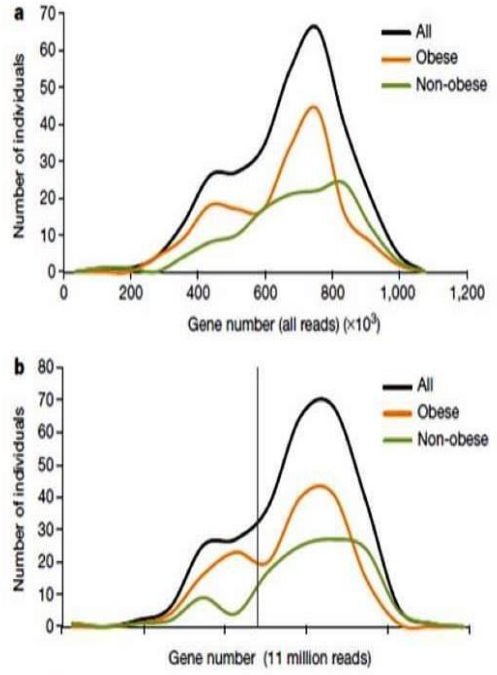
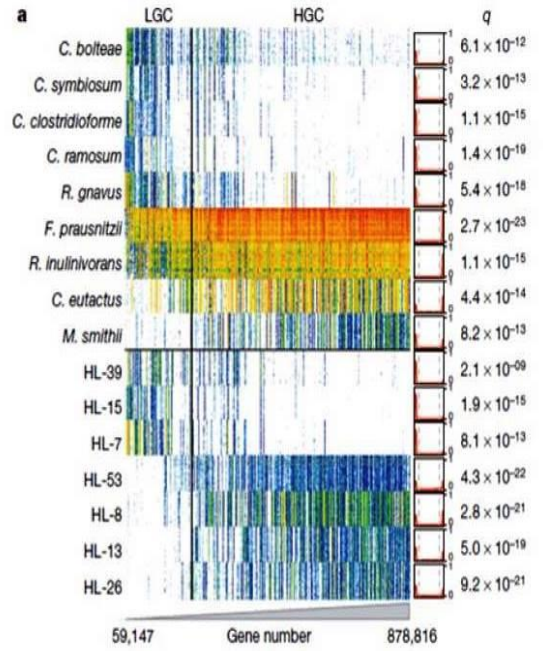
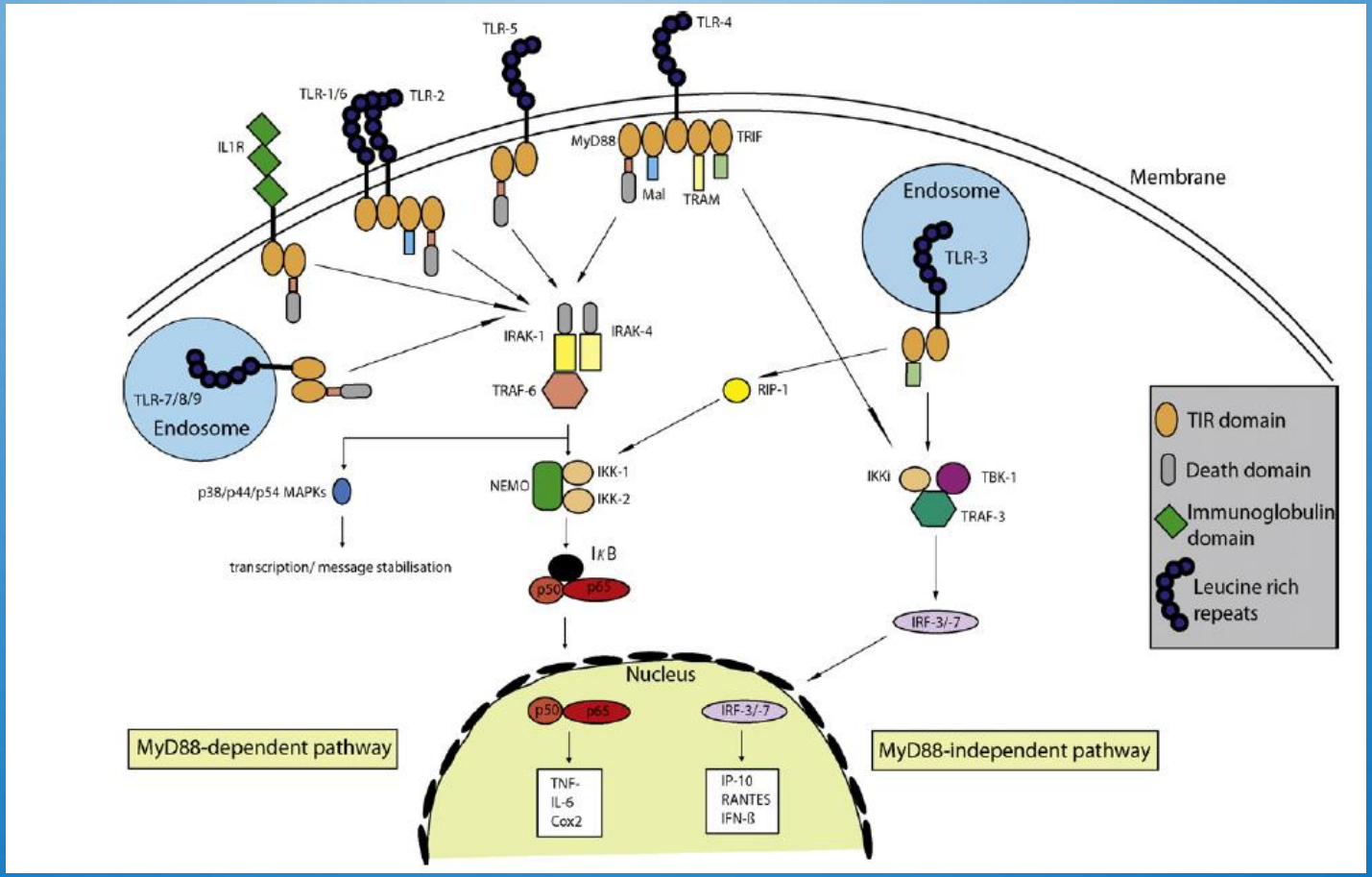


Figure 1 | Distribution of low and high gene count individuals ($n = 292$). a, Gene counts from all uniquely matched reads. b, Gene counts adjusted to 11 million uniquely mapped reads per individual. Vertical line indicates the threshold of the LGC and the HGS individuals; the observed bimodal distribution was not statistically significant by the dip-test.

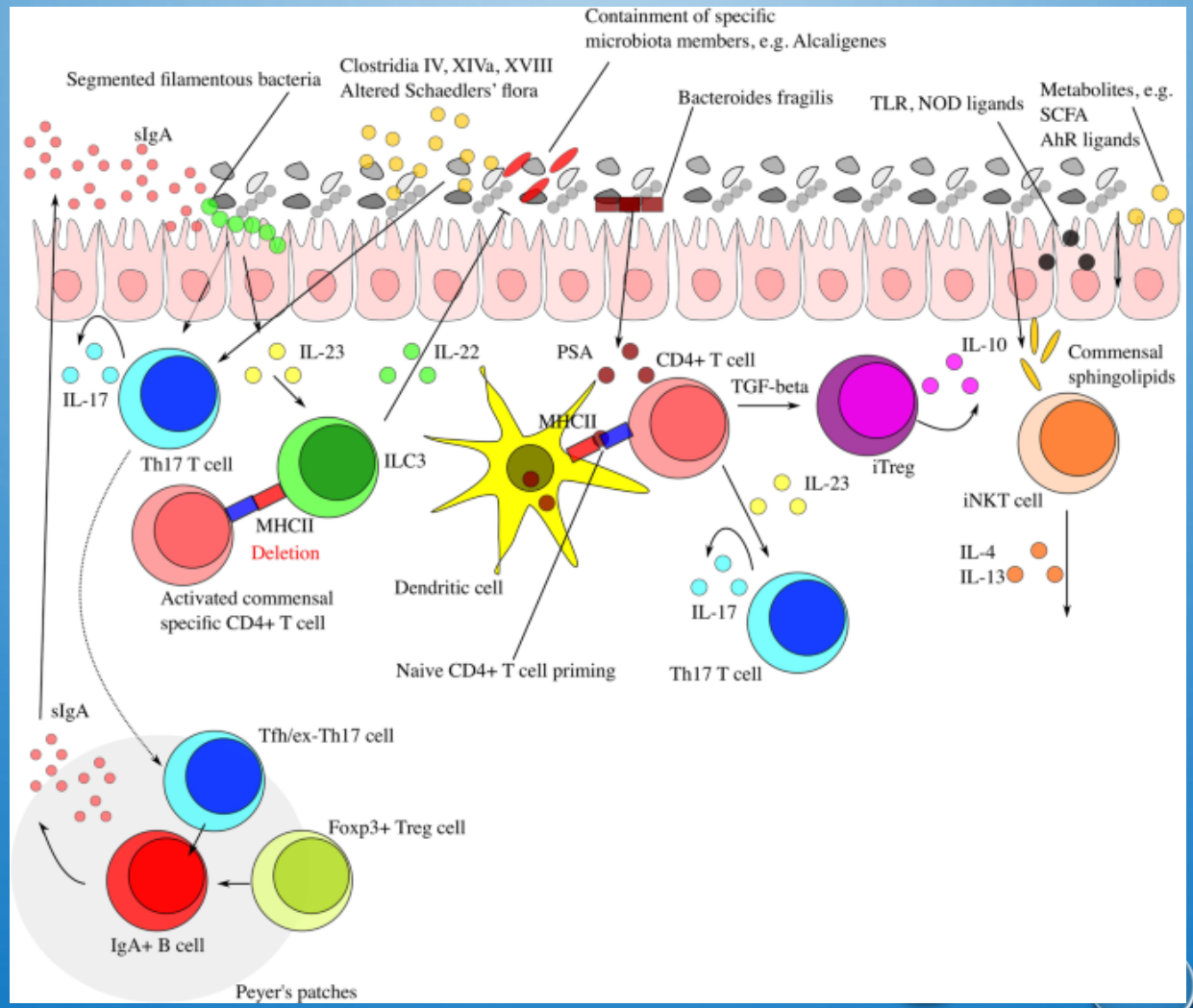


(Le Chatelier E. et al., 2013)
MetaHitConsortium

COOPERATION BETWEEN MICROBIOTA AND THE I.S.: PAMPS , TLRS, ADAPTOR MOLECULES



INTERACTION MICOBIOTA IMMUNE SYSTEM, IS



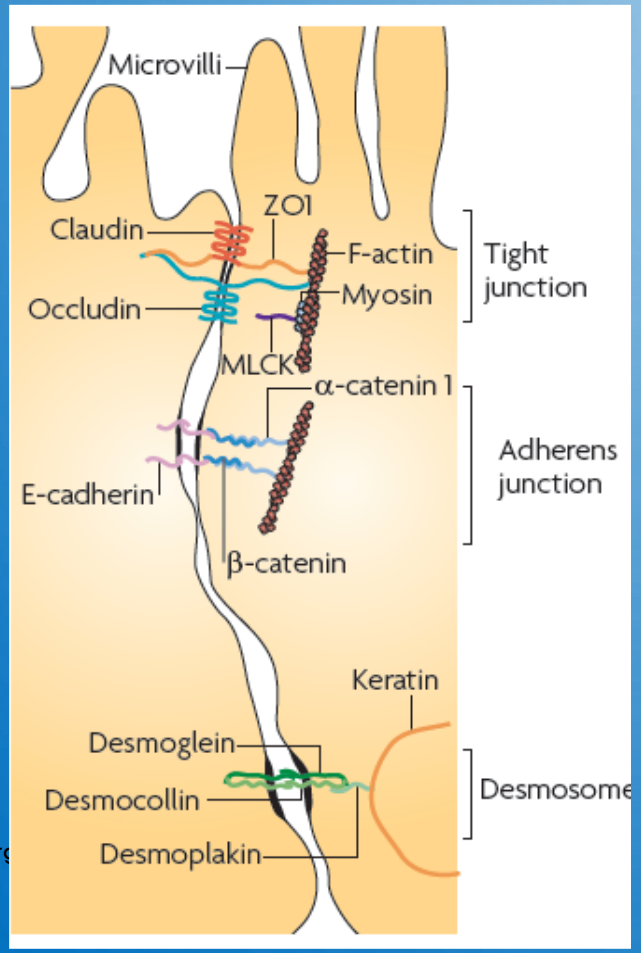
TOLL-LIKE AND NOD-LIKE RECEPTORS

PATTERN RECOGNITION RECEPTORS (PRRS)

- PRRS RECOGNIZE PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPS) SUCH AS
  LIPOPOLYSACCHARIDE, FLAGELLIN, BACTERIAL DNA AND RNA

- PRRS FALL INTO THREE FAMILIES
  - TOLL-LIKE RECEPTORS (TLRS)
  - NOD-LIKE RECEPTORS (NLRS)
  - RETINOICACID-INDUCIBLE GENE I (RIG-I)-LIKE RECEPTORS (RLRS)

TIGHT JUNCTIONS. LEAKY GUT



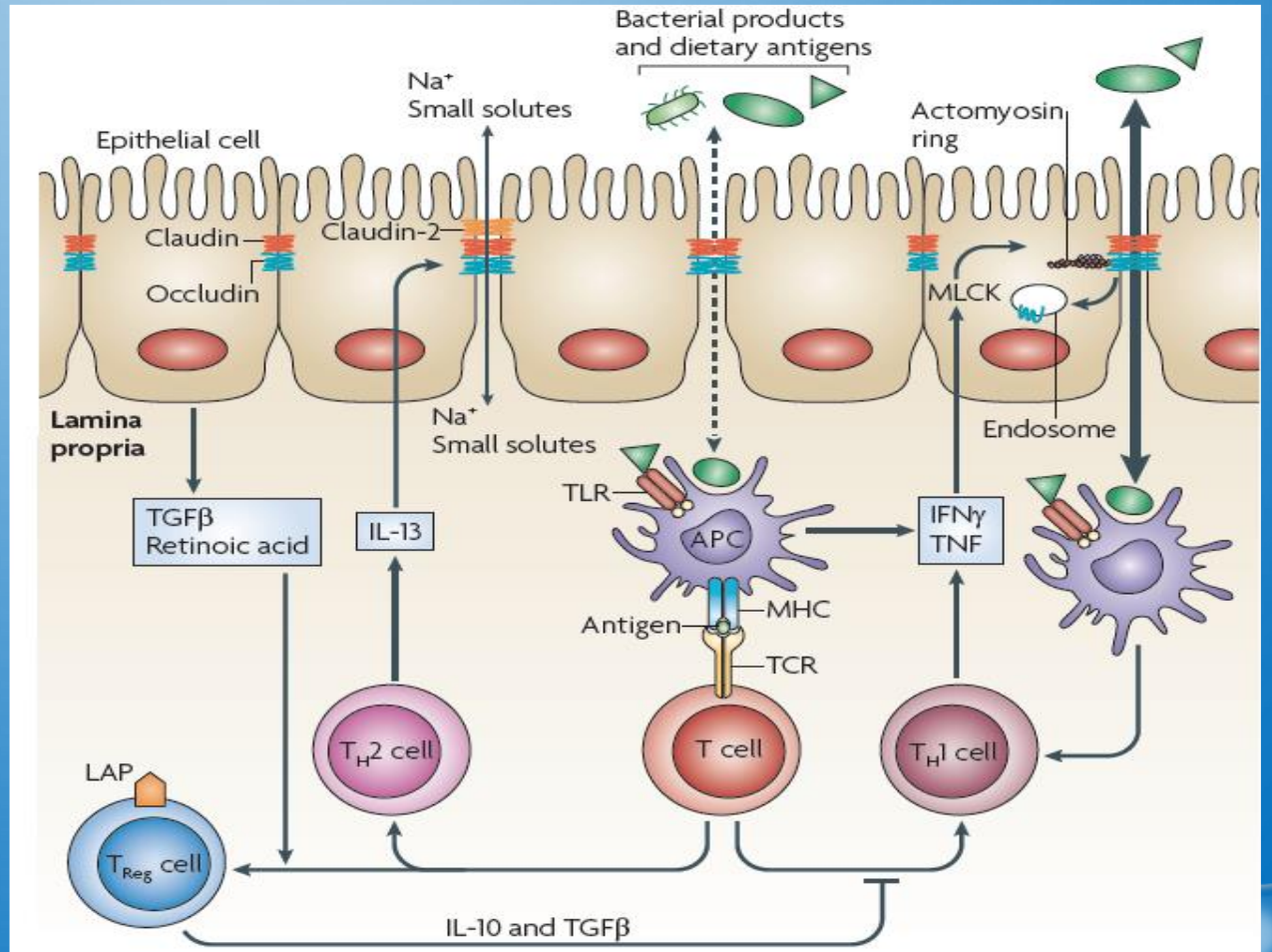
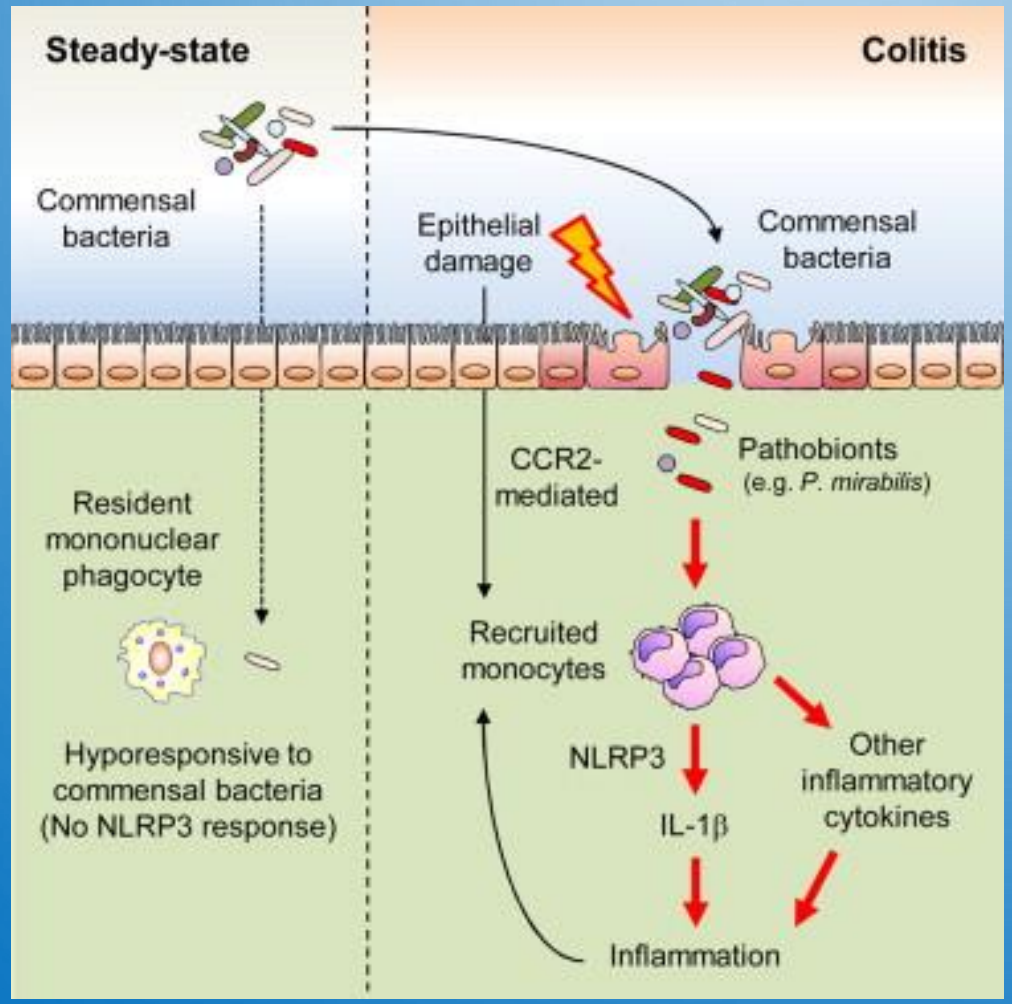
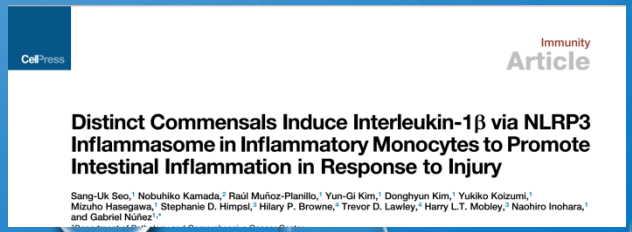


Figure 3 | **The epithelium and tight junction as integrators of mucosal homeostasis.**

DAMAGE OF GUT WALL: MICROBIOTA INDUCE NRLP3 INFLAMMASOME AND INFLAMMATION

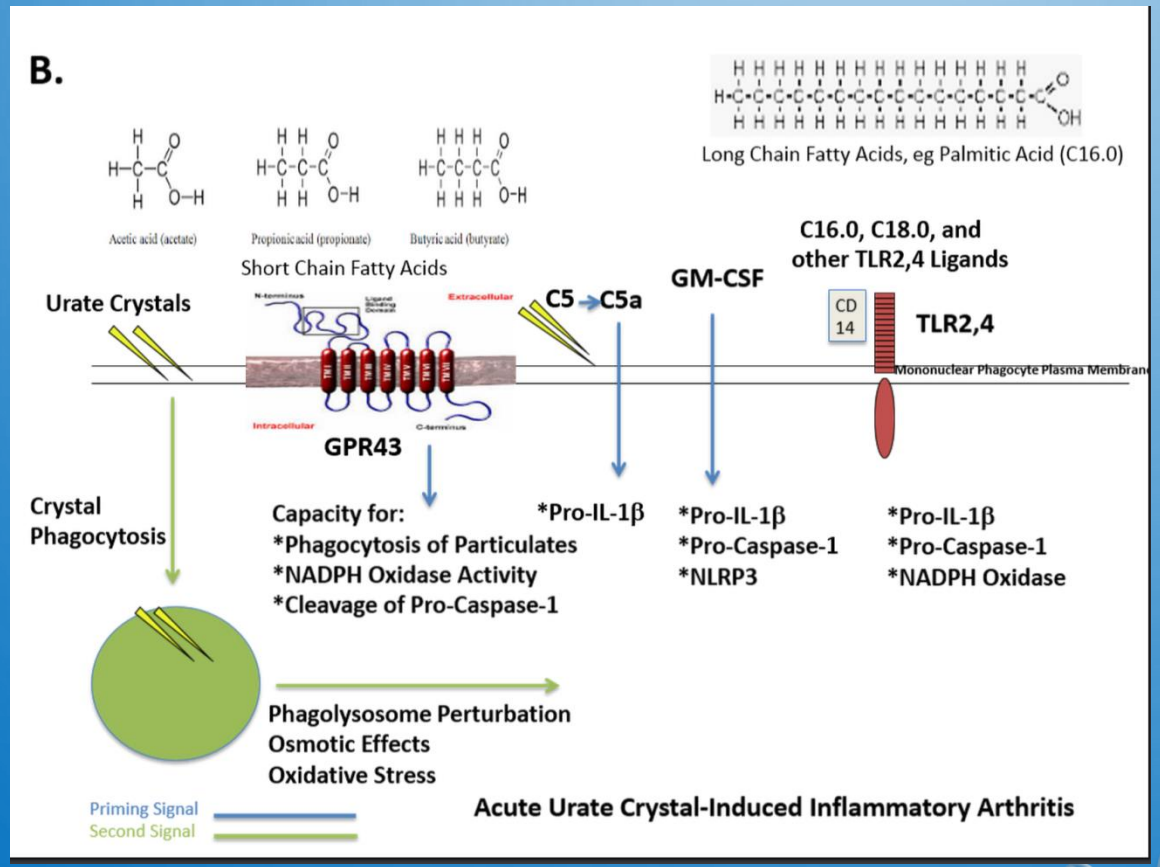


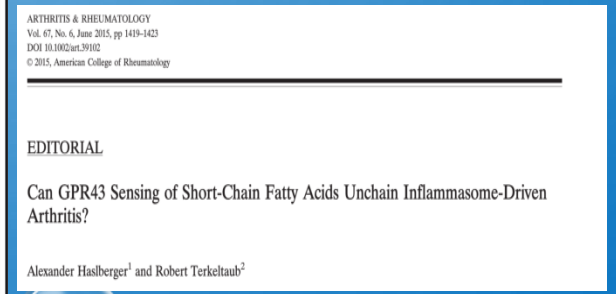

Immunity
Article

Distinct Commensals Induce Interleukin-1β via NLRP3 Inflammasome in Inflammatory Monocytes to Promote Intestinal Inflammation in Response to Injury

Sang-Uk Seo,[1] Nobuhiko Kamada,[2] Raúl Muñoz-Planillo,[1] Yun-Gi Kim,[1] Donghyun Kim,[1] Yukiko Koizumi,[1] Mizuho Hasegawa,[1] Stephanie D. Himpsl,[3] Hilary P. Browne,[4] Trevor D. Lawley,[4] Harry L.T. Mobley,[3] Naohiro Inohara,[1] and Gabriel Núñez[1,*]

TLR2, TLR4 LIGANDS (ENDOTOXINS, LONG CHAIN FATTY ACID) TRIGGER INFLAMMATION, GPR43 INTERFERS?





ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 6, June 2015, pp 1419–1423
DOI 10.1002/art.39102
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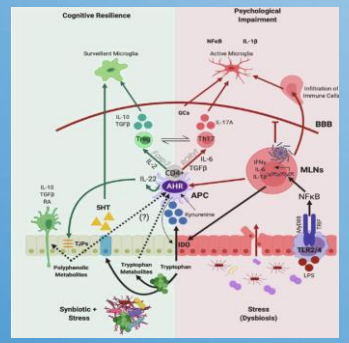
EDITORIAL

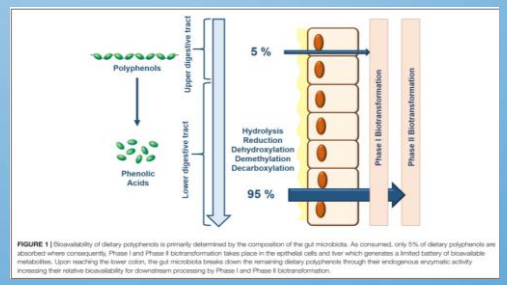
Can GPR43 Sensing of Short-Chain Fatty Acids Unchain Inflammasome-Driven Arthritis?

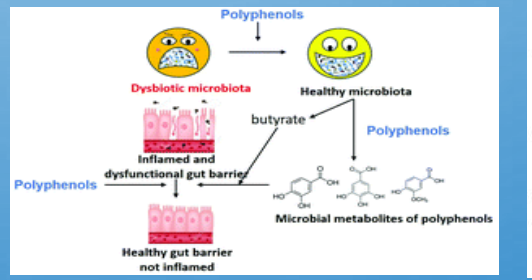
Alexander Haslberger[1] and Robert Terkeltaub[2]

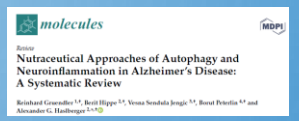
MICROBIAL METABOLITES REGULATE TREG-TH17 BALANCE, COGNITIVE RESILIENCE, MICROBIOTA AND METABOLITES



Scheme of Synbiotic-Derived Metabolites' Action on AHR-Mediated Treg/Th17 Ratios for the Promotion of Cognitive Resilience in Response to Stress. Synbiotic-derived metabolites promote cognitive resilience to stress-induced anxiety and depression by altering tryptophan metabolism, modulating aryl hydrocarbon receptor (AHR) activity and/or affecting the inflammatory activity of antigen presenting cells

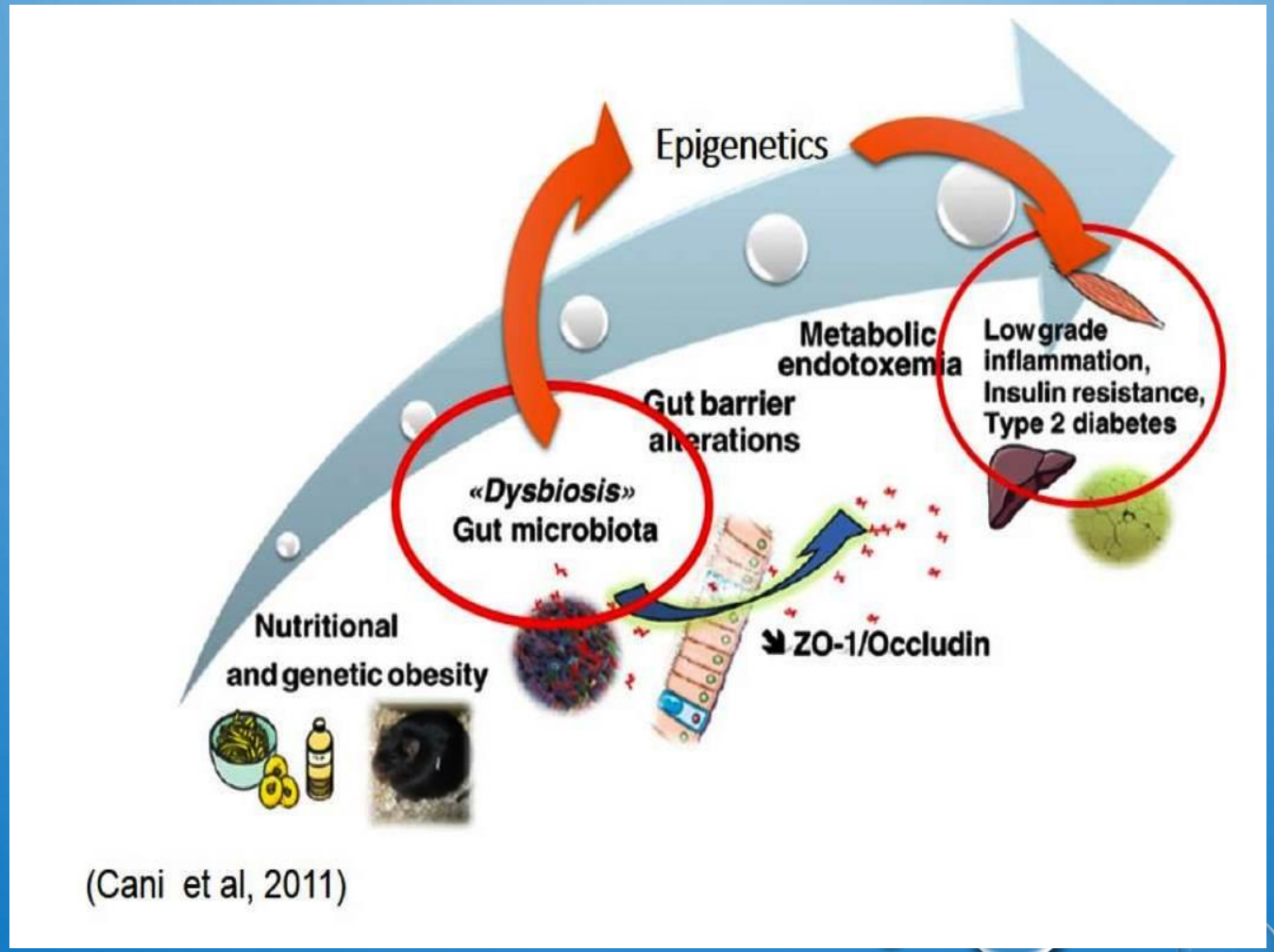






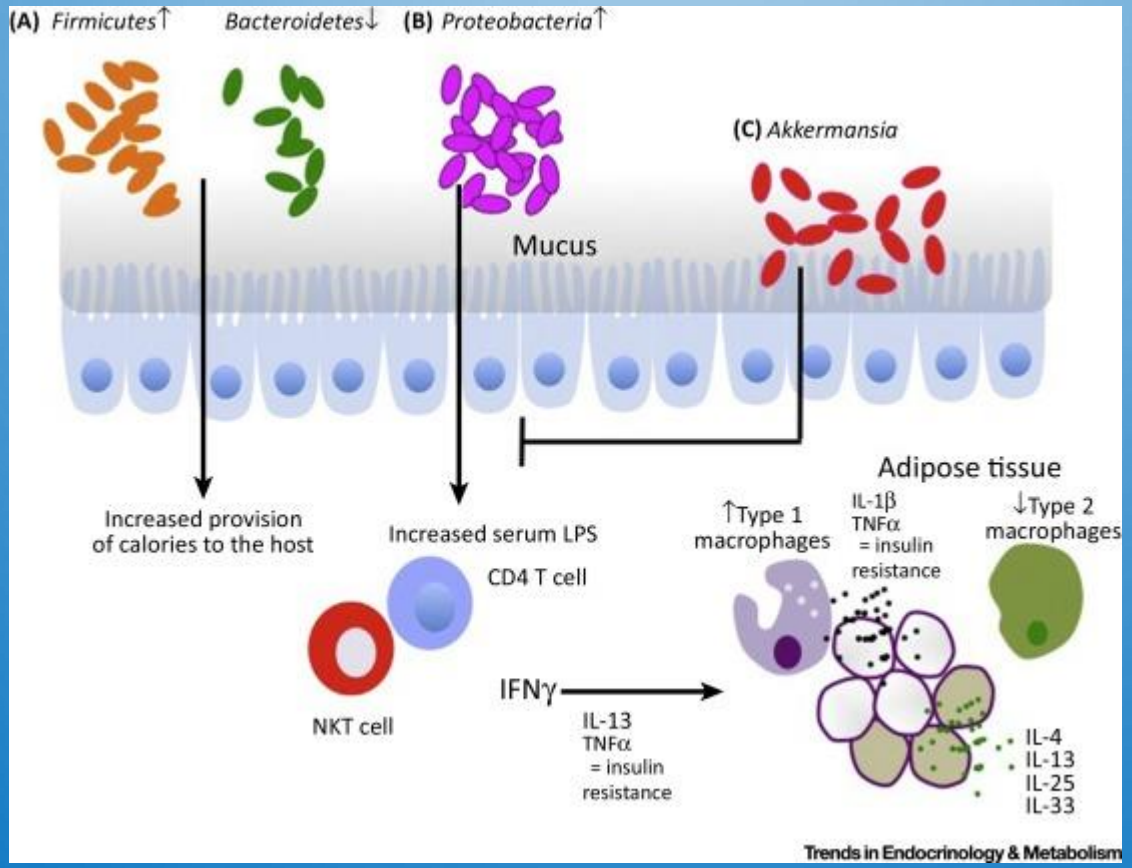
The gut brain axis: microbiota regulate bio-availability of polyhenol metabolites and their activity in neurological disorders, ***Giulio M Pasinetti***, *Icahn School of Medicine at Mount Sinai, USA*

Bacterial cell wall components and Inflammation: dysbiosis, LPS and gut permeability; obesity as a model

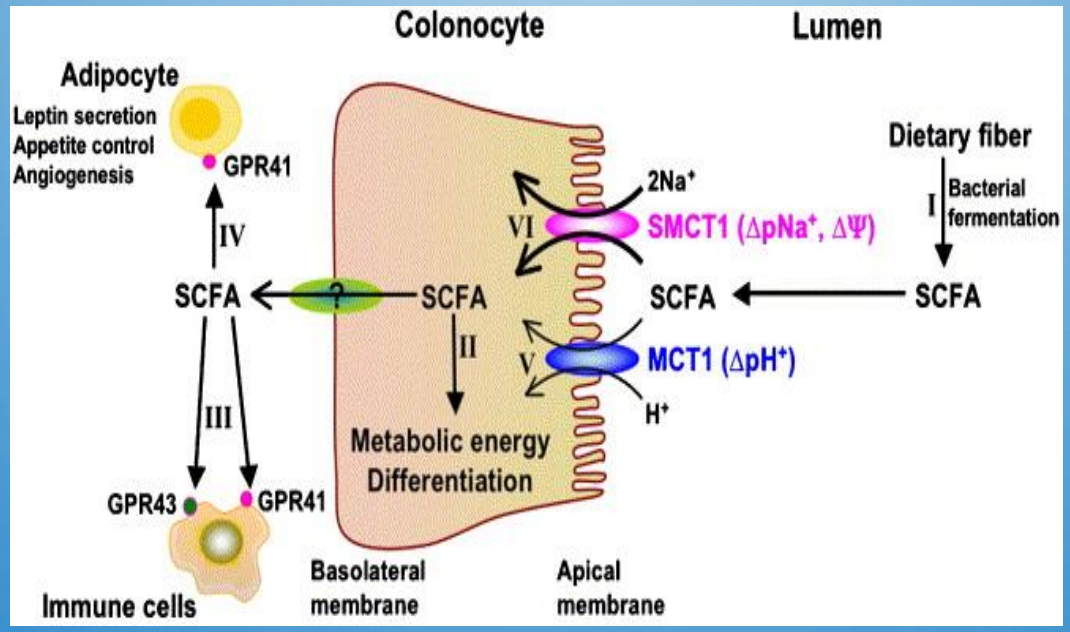


(Cani et al, 2011)

OBESITY: FIRMICUTES: BACTEROIDETES; AKKERMANSIA AND THE CELL WALL



MICROBIOTA METABOLITES: SCFAS BIND TO G-PROTEIN-RECEPTORS GPR 41/43 (FFARS)



Anti-inflammatory;

Inhibition of NFκB

(Huster et al., 2013; Flint et al., 2009, Nature Rev)

MICROBIOTA AND FERMENTATION PRODUCTS E.G. SCFAS

Clostridial cluster IV (Rumminococaceae)	*Clostridial cluster XIVa (Lachnospiraceae)*
Faecalibacterium prausnitzii *Butyricoccus* *Clostridium Leptum*	*Eubacterium hallii* *Anaerostipes coli* *Roseburia spp.* *E. rectale spp.*
Resistent starch	*Non starch Polysaccharides*

(Louis and Flint, 2009, FEMS)

PATHWAYS AND CROSS FEEDING FOR SCFAS/ BUTYRATE

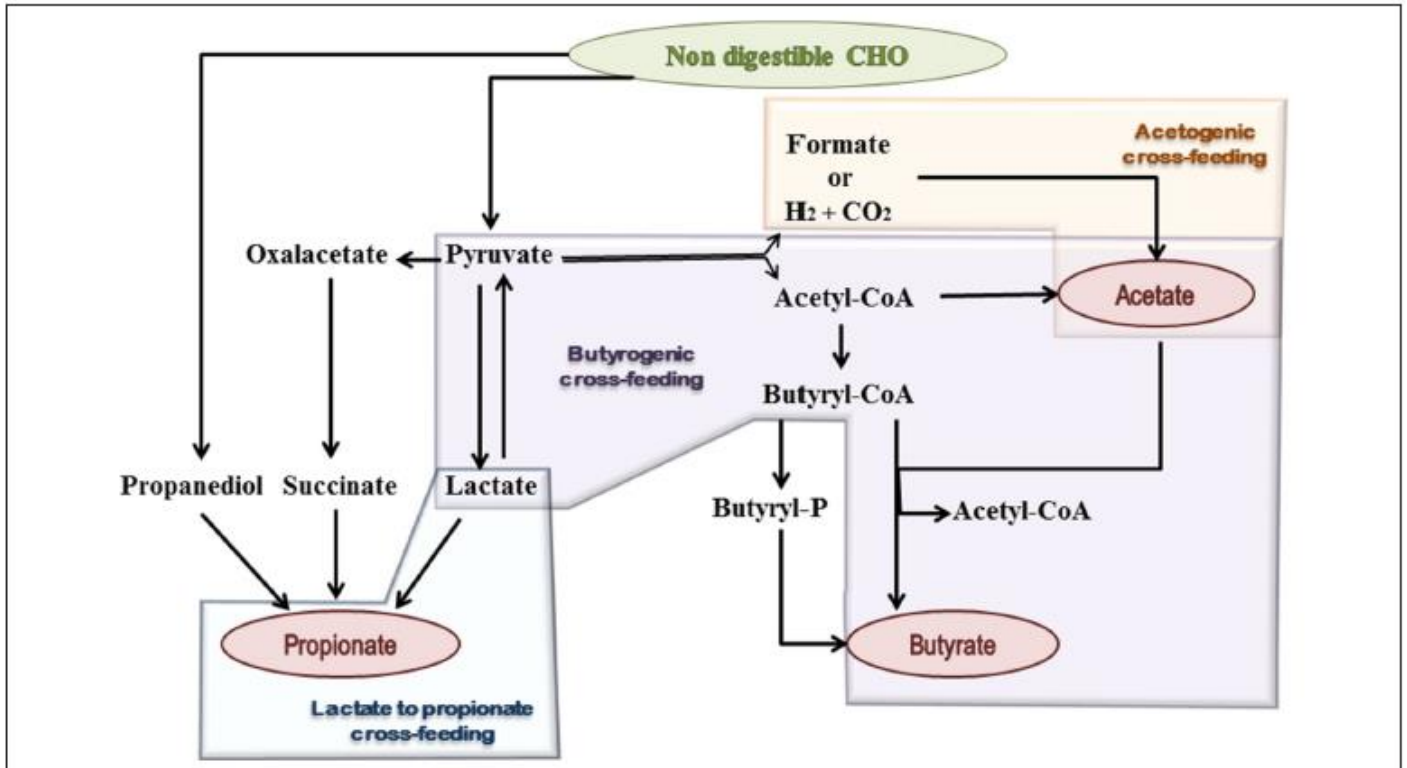


FIGURE 1 | Schematic representation of microbial metabolic pathways and cross-feeding mechanisms, contributing to SCFA formation in the human gut. Shaded geometric shapes summarize routes of formation for each of the three main SCFA: acetate, propionate, and butyrate.

BUTYRATE AND EPIGENETICS

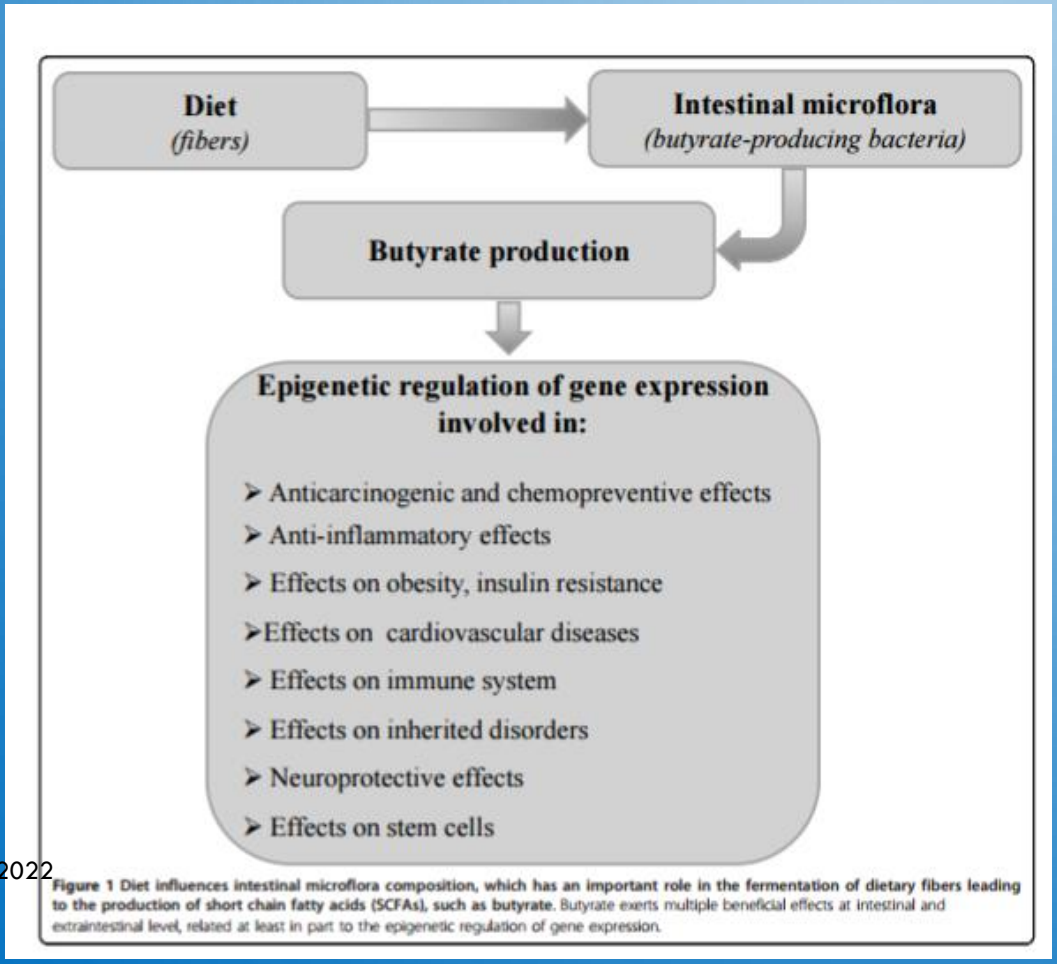


Figure 1 Diet influences intestinal microflora composition, which has an important role in the fermentation of dietary fibers leading to the production of short chain fatty acids (SCFAs), such as butyrate. Butyrate exerts multiple beneficial effects at intestinal and extraintestinal level, related at least in part to the epigenetic regulation of gene expression.

BUTYRATE: APOPTOSIS, AUTOPHAGY, MI- RNAS REGULATING INFLAMMATION, VITRO

Table 1. Anti-cancer properties of butyrate through regulating miRNA and gene expression.

TREATMENT	TYPE OF STUDY	METHODS	CANCER CELLS	TARGETS	EFFECT OF BUTYRATE	CITATIONS
NaB	In vitro	PCR	HT-29 (human CRC cells)	MUC2 gene	NaB can inhibit MUC2 gene expression	39
NaB	In vitro	RT-PCR	HCT-116, AW480 (human CRC cells)	Dynamin-related protein 1 (DRP1)	NaB induces apoptosis in CRC	40
NaB, EGCG	In vitro	PCR	HCT-116, RKO, HT-29 (human CRC cells)	P21, P53, NF-kB-p65, HDAC1, DNMT1, survivin	NaB promotes apoptosis and inhibits DNA damage, cell cycle arrest in CRC cells	41
NaB	In vitro	RT-PCR, Western blot assay, MTT proliferation assay	DU145, PC3 cells (human prostate cancer cells)	ANXA1	NaB inhibits proliferation and cell survival in DU145 cells and upregulates ANXA1 expression in prostate cancer	42
Butyrate, TSA	In vitro	Northern blot analyses, H-thymidine assay, DNA transfer analysis	HT-29, HT-116 (human CRC cells)	P21 mRNA	Butyrate induces P21 mRNA expression in an immediate early fashion	43
NaB	In vitro	Western blot assay, qRT-PCR	Burkitt lymphoma cell line Raji	c-Myc protein	Butyrate upregulates miR-143, miR-145, and miR-101	44
NaB	In vitro	Western blot analyses, PCR	MDA-MB-231 and MCF7 (human breast cancer cells)		NaB upregulates miR-31	45

Abbreviations: ANXA1, lipocortin 1; DNMT 1, DNA (cytosine-5)-methyltransferase 1; HDACi, histone deacetylase inhibitors; MUC 2, mucin 2; NaB, sodium butyrate; NF-κB, nuclear factor κB; PCR, polymerase chain reaction; qRT-PCR, reverse-transcription quantitative PCR; RT-PCR, real-time PCR; TSA, trichostain A (histone hyperacetylating agent).

Epigenetic Regulation of Gene Expression Induced by Butyrate in Colorectal Cancer: Involvement of MicroRNA

Karen S Bishop[1], Huawen Xu[2] and Gareth Marlow[3]

[1]Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University

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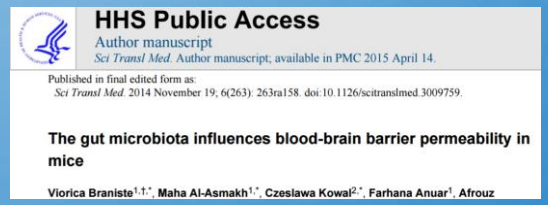
DOI: 10.1177/1179237X17729900
SAGE

BUTYRATE: WHERE AND HOW MUCH ?

For good reason it is not possible with current technologies to perform direct measurements of the variation in the butyrate concentration in the portal vein of human subjects, but short-chain fatty acid levels in portal blood from sudden-death victims, subjects undergoing emergency surgery or planned surgery have indicated a higher gut production and absolute and relative concentration of butyrate in non-fasted as compared with fasted human subjects



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Published in final edited form as:

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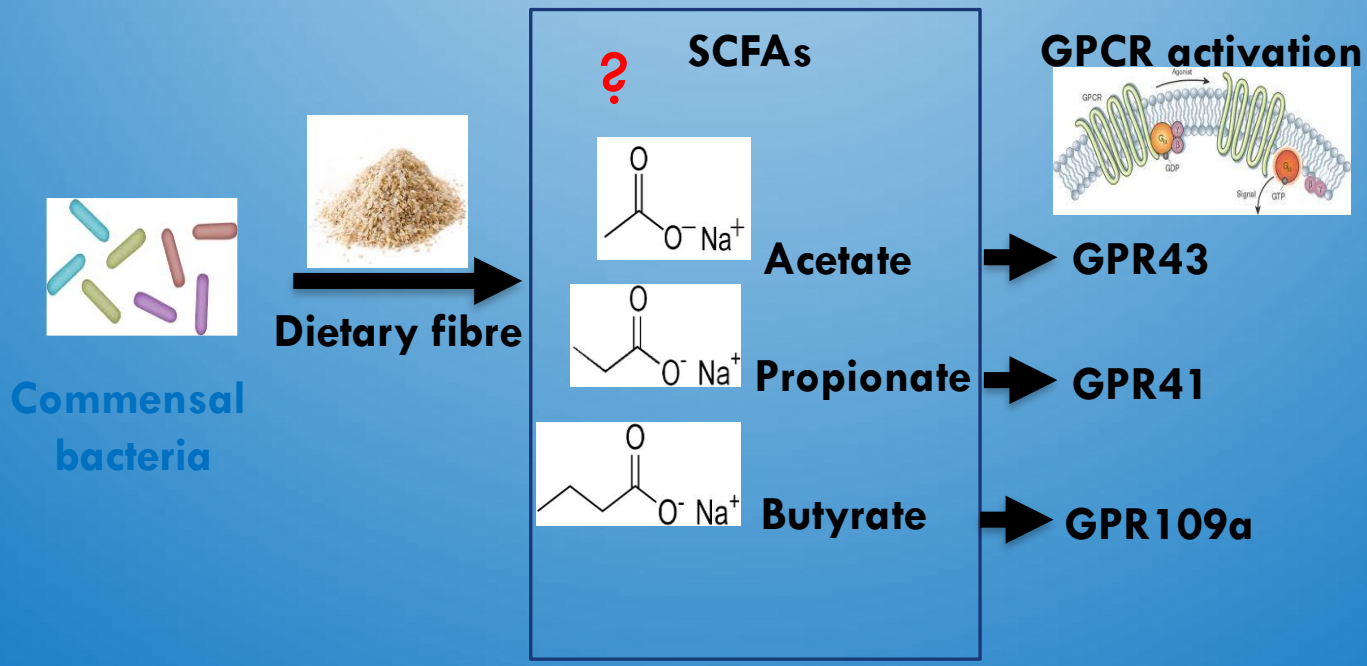
The gut microbiota influences blood-brain barrier permeability in mice

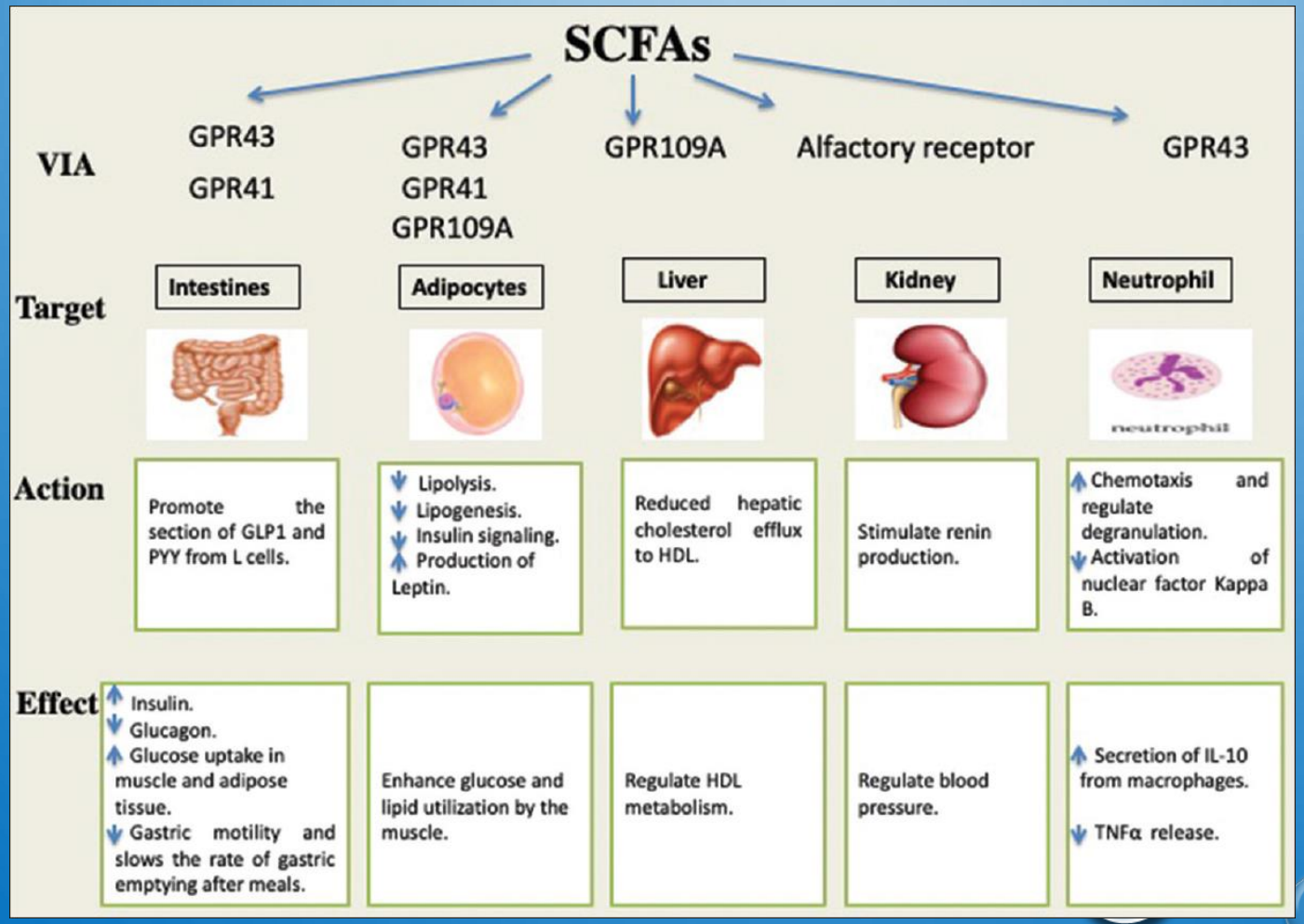
Viorica Braniste[1,†,*], Maha Al-Asmakh[1,*], Czeslawa Kowal[2,*], Farhana Anuar[1], Afrouz

MECHANISM OF ACTION OF FIBRE: SHORT-CHAIN FATTY ACIDS (SCFAS)?

- SCFAS ARE MAJOR METABOLITES PRODUCED BY THE MICROBIOTA



GPR RECEPTORS



GPRS AND THERAPY, STILL MANY UNCLEAR

TABLE 1 | Contradictory findings on the inflammation phenotypes of *Gpr43*$^{-/-}$ and *Gpr41*$^{-/-}$ mice.

***Gpr43*$^{-/-}$ mice display increased chronic inflammation**	
Maslowski et al. (29)	Exacerbated colitis, arthritis, and asthma Reduced neutrophil recruitment
Smith et al. (32)	Exacerbated colitis Reduced Treg cell count
Masui et al. (33)	Exacerbated colitis
Macia et al. (44)	Exacerbated colitis Reduced IL-18 expression presumably due to reduced inflammasome activation in epithelial cells
***Gpr43*$^{-/-}$ mice display reduced chronic inflammation**	
Sina et al. (30)	Reduced colitis Increased neutrophil recruitment
Kim et al. (31)	Reduced colitis Reduced ERK and p38 activation in epithelial cells
Vieira et al. (45)	Reduced joint inflammation in mouse model of gout Impaired inflammasome formation in macrophages
***Gpr43*$^{-/-}$ mice display increased obesity markers**	
Ge et al. (38)	Increased lipolysis and plasma free fatty acids
Tolhurst et al. (35)	Impaired glucagon-like peptide-1 secretion and glucose tolerance
Kimura et al. (36)	Increased fat accumulation and obesity on a normal diet
McNelis et al. (39)	Glucose intolerance due to defective insulin secretion Reduced beta cell mass and expression of differentiation genes
Priyadarshini et al. (40)	Marginal reduction in glucose-stimulated insulin secretion
***Gpr43*$^{-/-}$ mice display reduced obesity markers**	
Bjursell et al. (34)	Improved glucose control and reduced body fat mass on a high-fat diet
***Gpr41*$^{-/-}$ mice display increased inflammation**	
Trompette et al. (37)	Exacerbated asthma Impaired dendritic cell generation
***Gpr41*$^{-/-}$ mice display reduced inflammation**	
Kim et al. (31)	Reduced colitis Reduced ERK and p38 activation in epithelial cells
***Gpr41*$^{-/-}$*Gpr43*$^{-/-}$ mice display reduced obesity markers**	
Tang et al. (46)	Increased insulin secretion and improved glucose tolerance in type 2 diabetes

GPR41 AND GPR43 EXPRESSION IS TISSUE-SPECIFIC

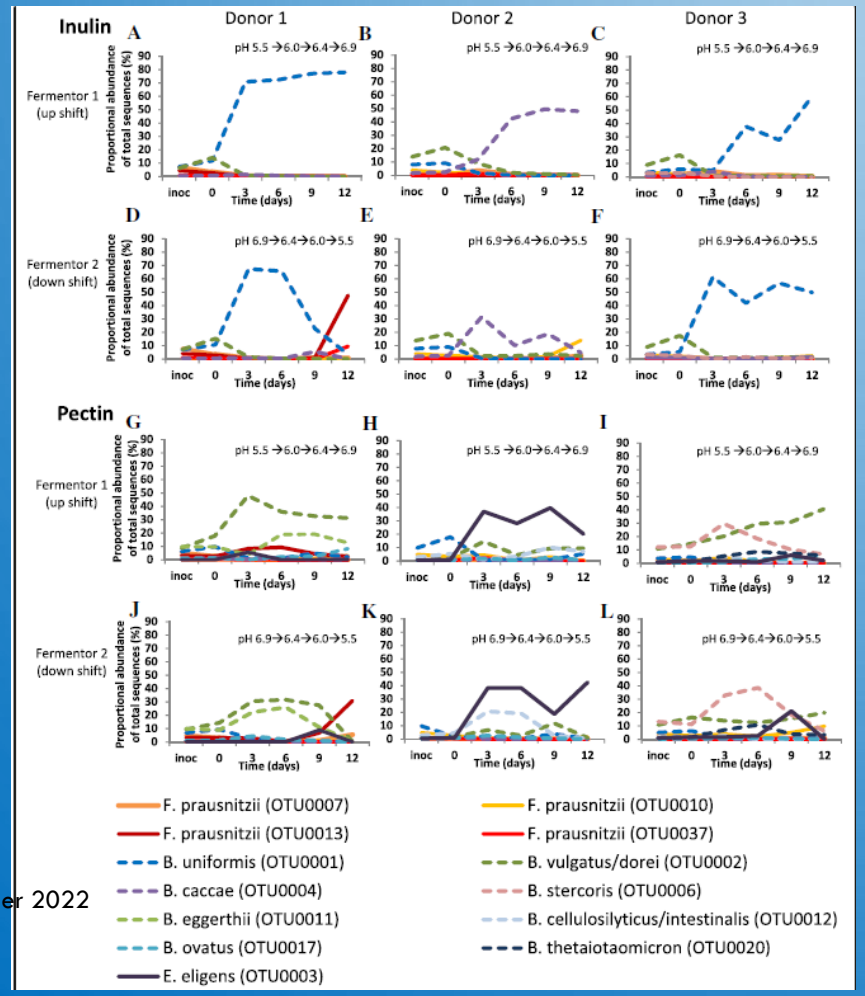
GPR41 AND GPR43 AS POTENTIAL THERAPEUTIC TARGETS FOR OBESITY, COLITIS, ASTHMA, AND ARTHRITIS

REPORTS ON GPR41 AND GPR43 KNOCKOUT MICE PHENOTYPES ARE IN CONSISTENT

*Zhiwei Ang and Jeak Ling Ding**
Front. Imm. 2016

Haslberger 2022

MICROBIOTA AND SCFA RESPONSES VARY VERY INDIVIDUALLY



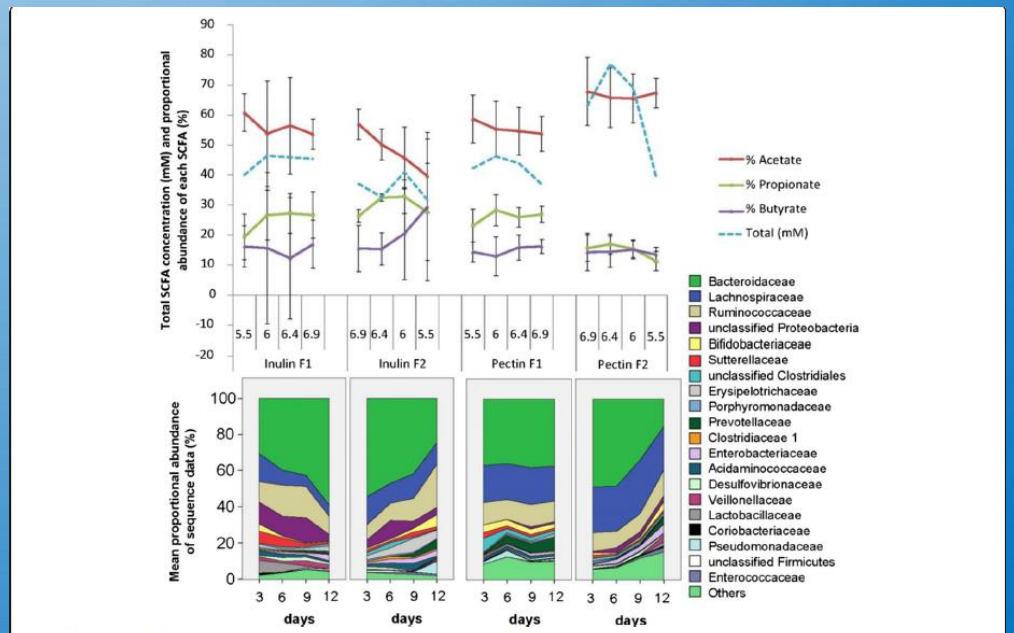
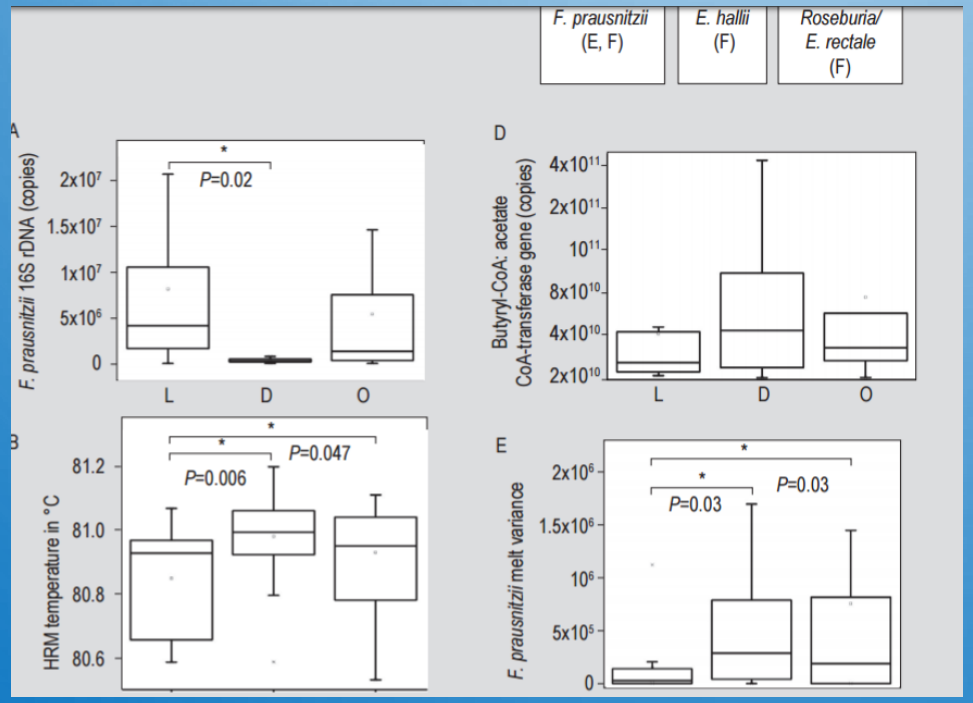


Fig. 7 Short chain fatty acids (SCFA) in upshift and downshift fermentors. Mean SCFA values (means and standard deviations) and proportional abundance of bacterial families based on sequence analysis of 16S rRNA gene amplicons are shown for the 16 fermentor runs described in Fig. 3. Significant changes in % SCFA (from ANOVA) are discussed in the text. ANOVA revealed significant decreases in % Bacteroidaceae between pH 6.9 and pH 5.5 in inulin fermentors F1 ($P = 0.015$) and F2 ($P = 0.012$), but with pectin only for the F2 (downshift) fermentors ($P = 0.0001$). % Bifidobacteriaceae and % Lachnospiraceae increased significantly at pH 5.5 compared with pH 6.9 in F2 inulin ($P = 0.007$) and F1 inulin ($P = 0.025$) fermentors, respectively

SCFAS PRODUCERS, PHYLOTYPES DIFFER IN OBESE, DIABETES



Beneficial Microbes, 2016; 7(4): 511-517

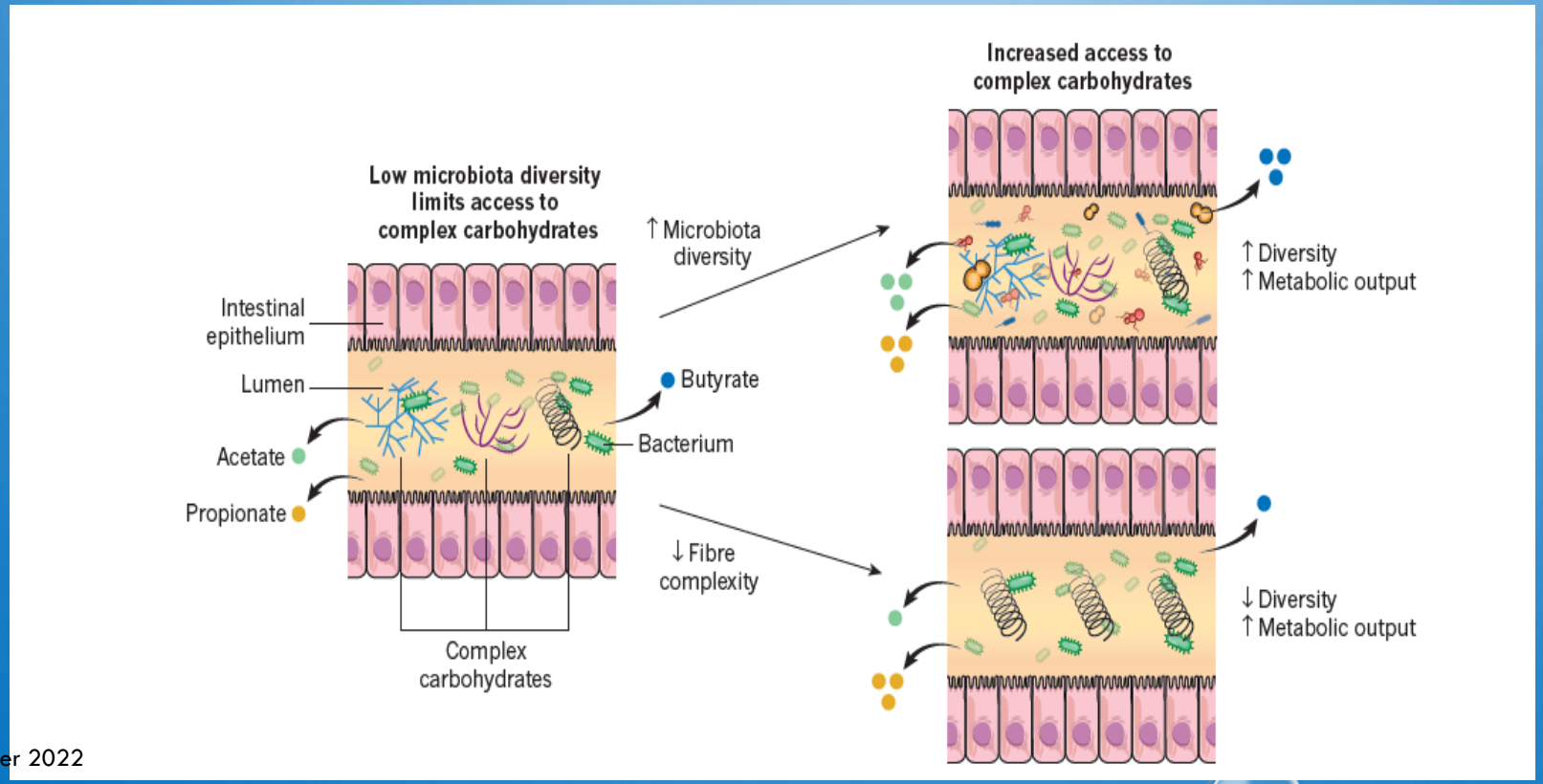
Wageningen Academic Publishers

***Faecalibacterium prausnitzii* phylotypes in type two diabetic, obese, and lean control subjects**

B. Hippe, M. Remely, E. Aumueller, A. Pointner, U. Magnet and A.G. Haslberger*

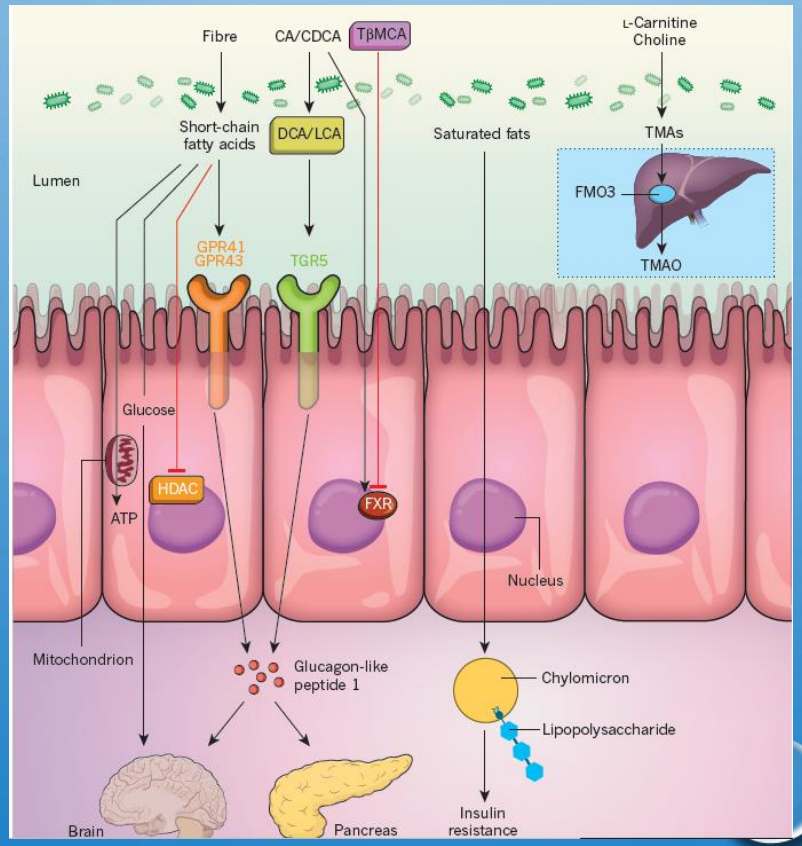
Institute of Nutritional Sciences, Althanstr. 14, UZA 2, 1090 Vienna, Austria; alexander.haslberger@univie.ac.at

DIET DICTATES THE PRODUCTION OF SCFAS, DIVERSITY OF THE MICROBIOTA, MANY TYPES OF COMPLEX CARBS

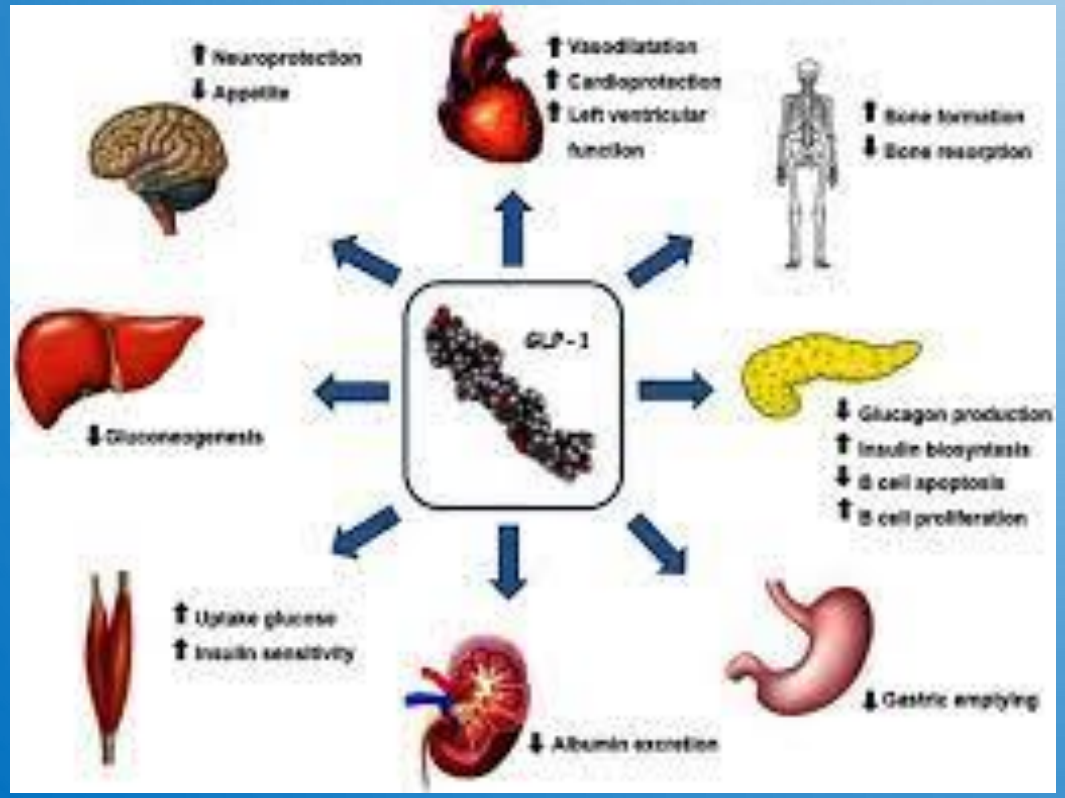


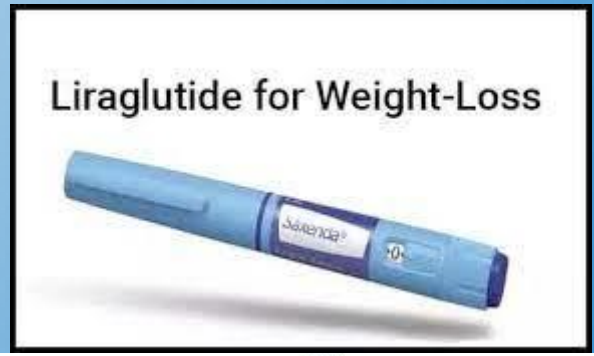
ENDOTOXINS, SATURATED FATS/ CHYLOMICRONS TRIGGER INFLAMMATION, INSULIN RESISTANCE; SCFAS MAY TRIGGER GLP1 ACTIVATION

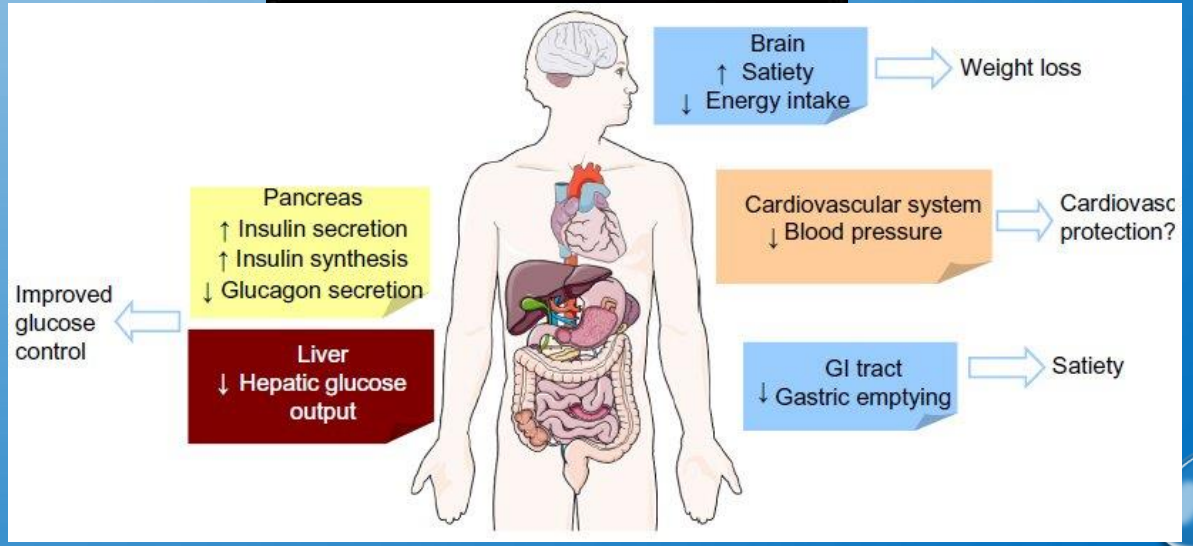
GLP1: incretin improves DMII and obesity



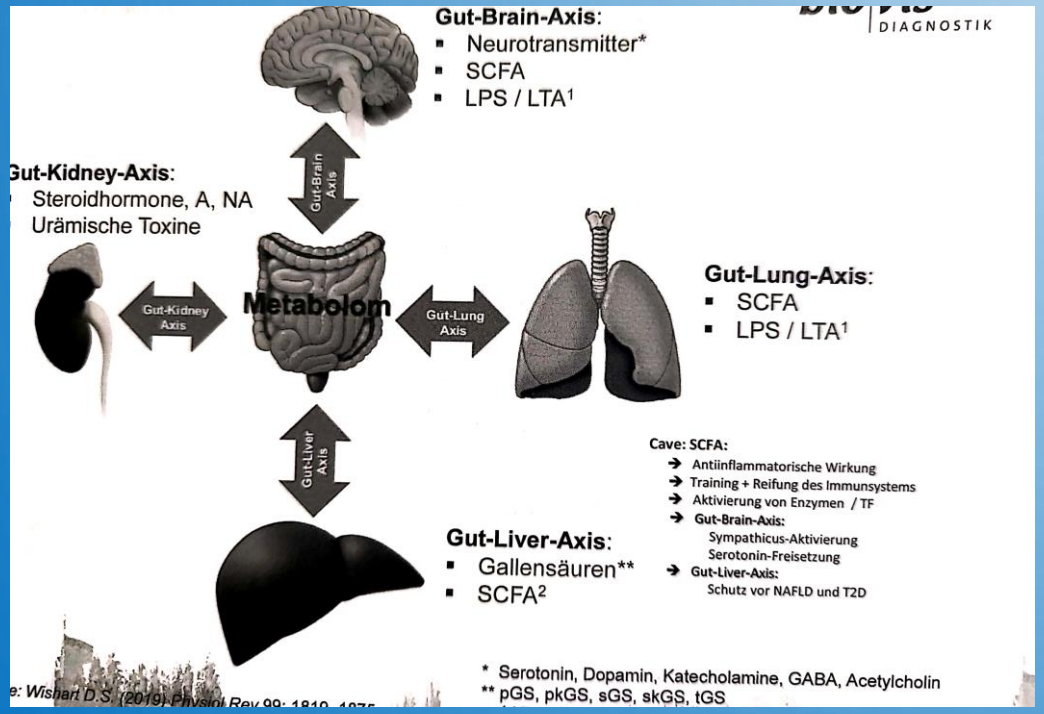
GLP1, ANALOGS

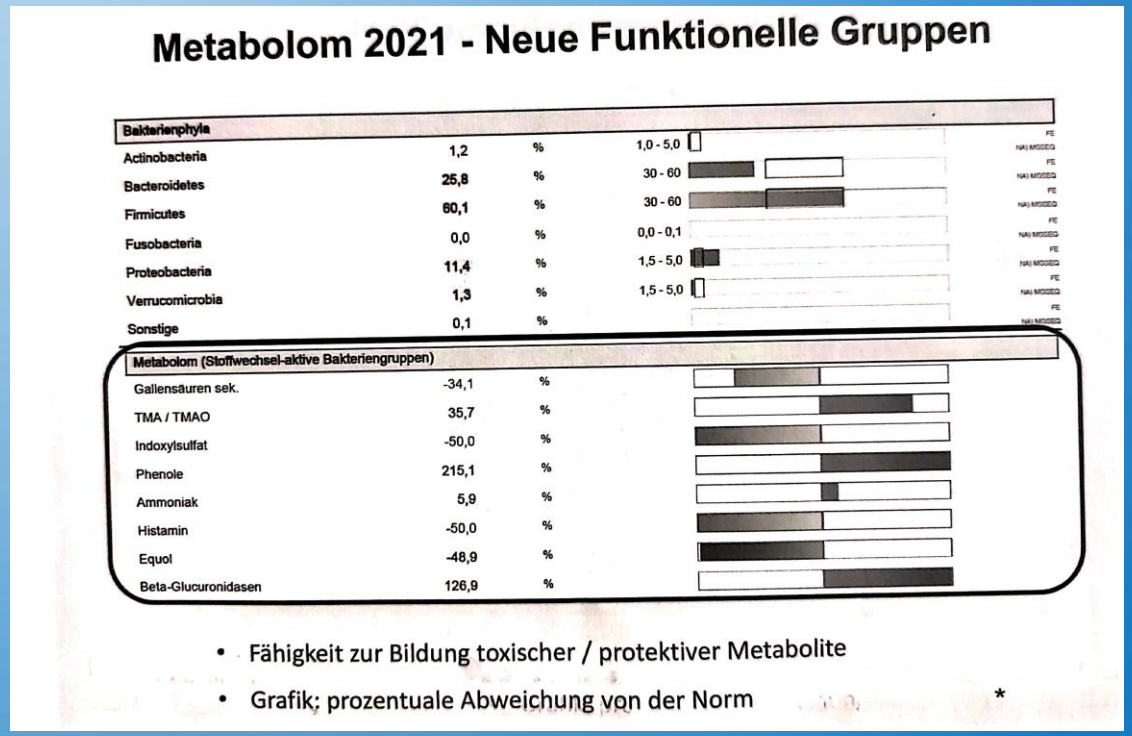


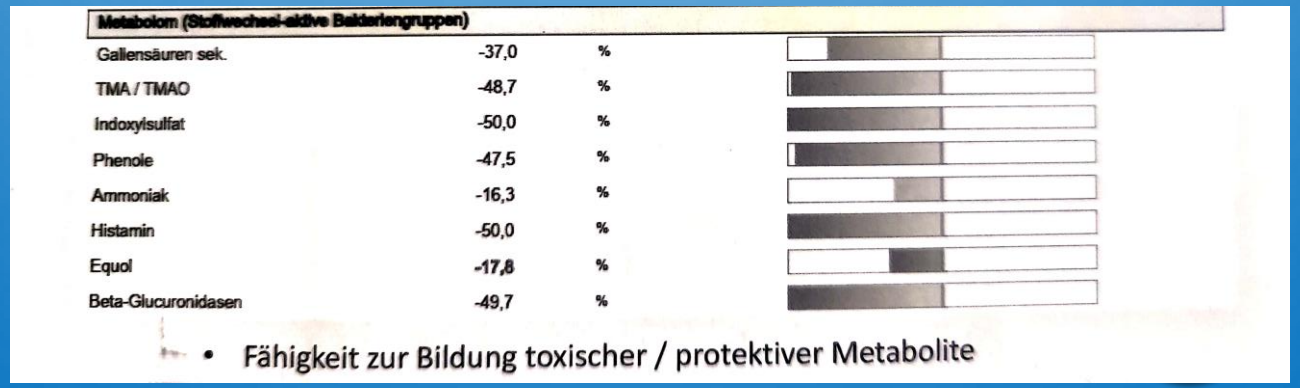




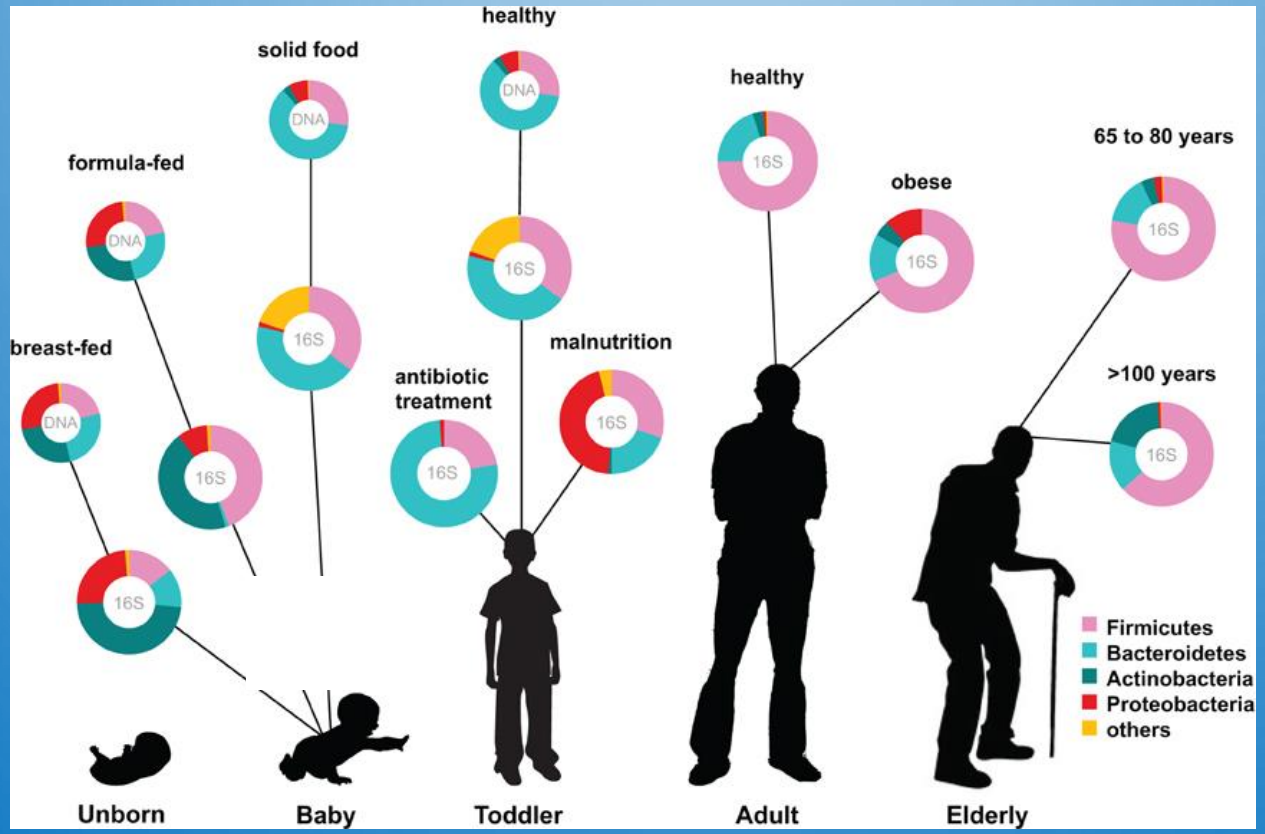
MICROBIOTA AND METABOLOMICS



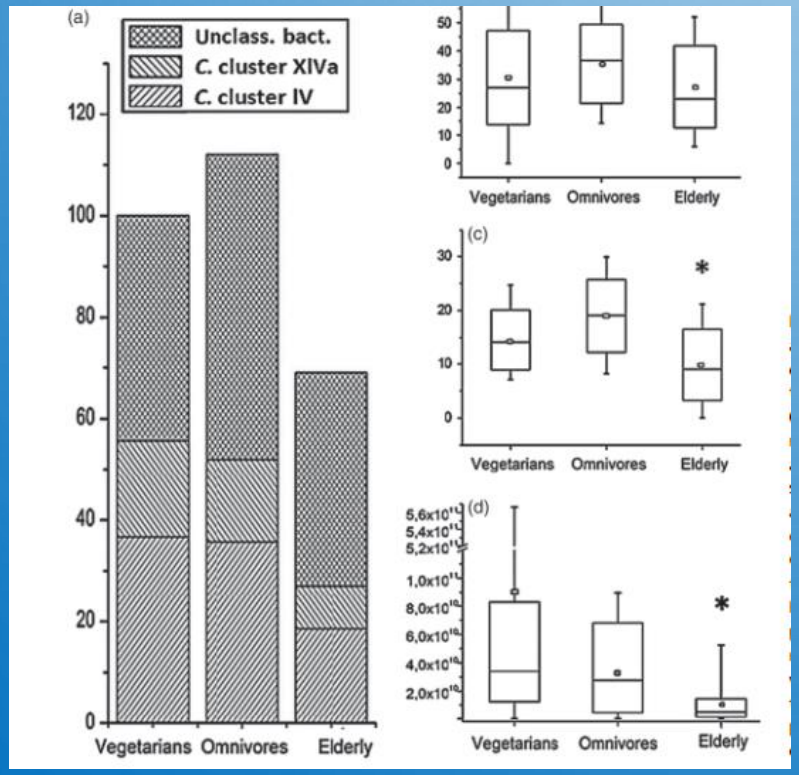


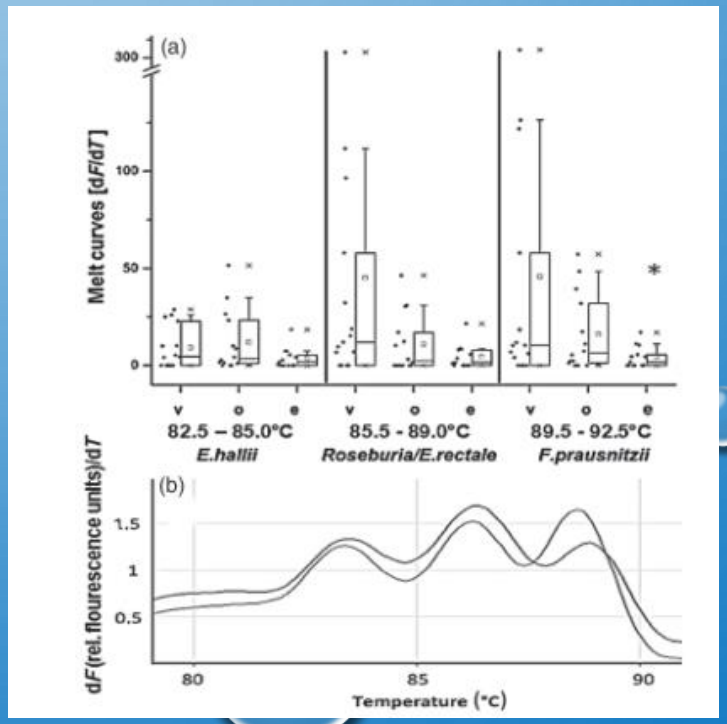


AGING AND MICROBIOTA

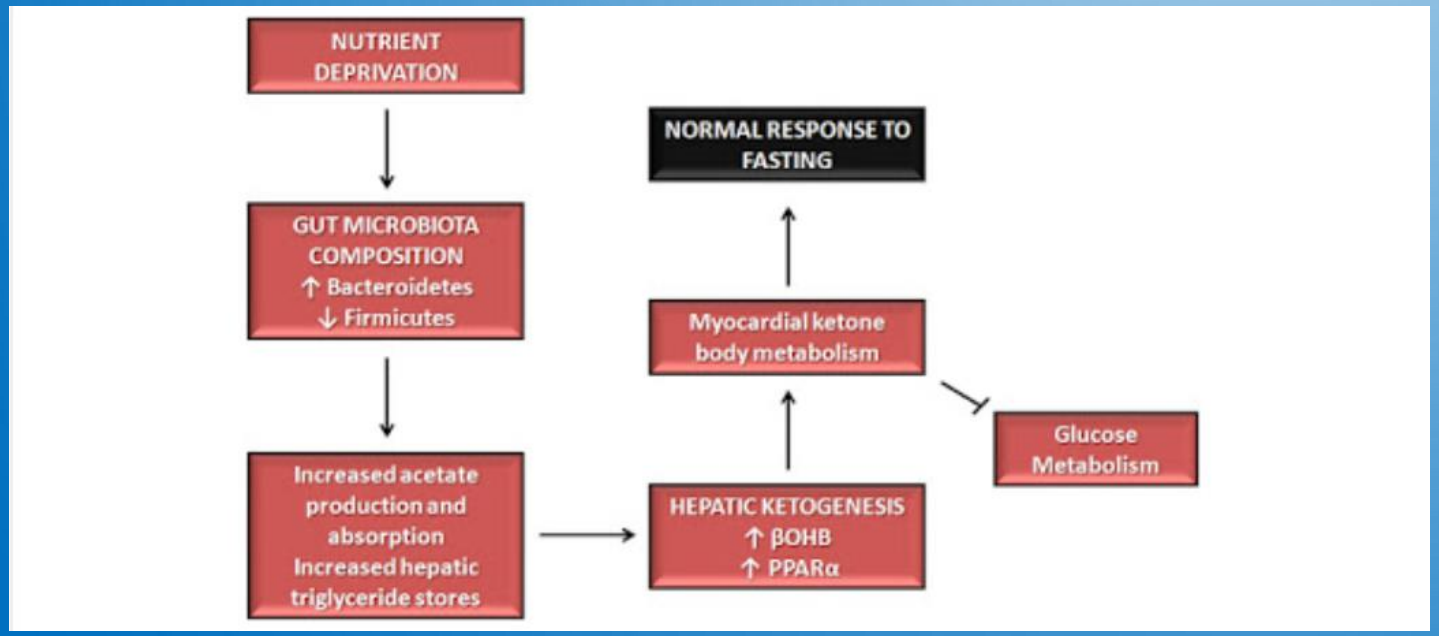


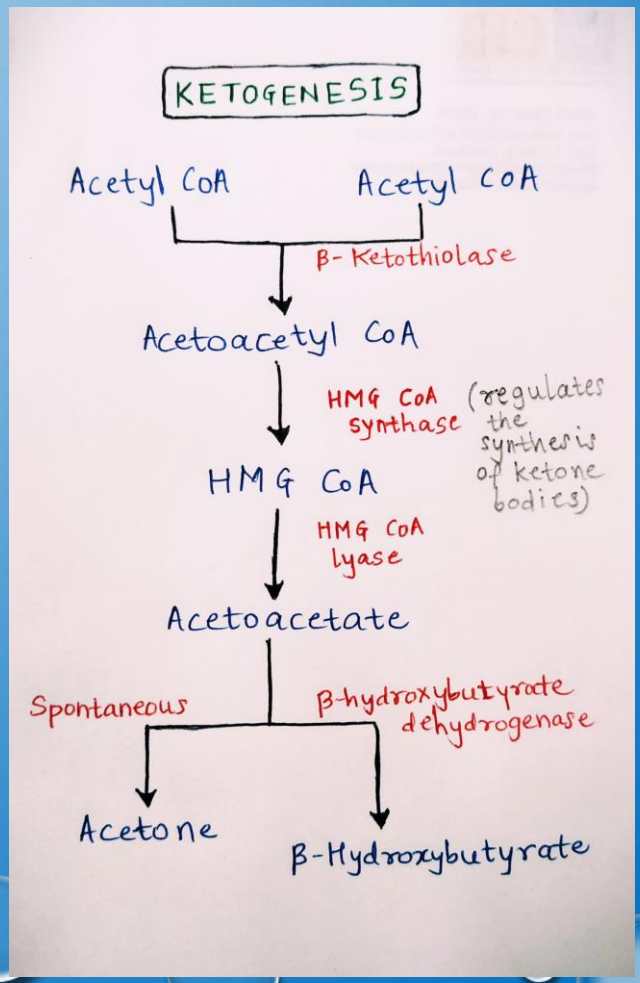
SCFAS IN ELDERLY:
DECREASE IN SCFAS PRODUCERS AND „BUTYRATE GEN PRODUCING GENE“ IN ELDERLY





MICROBIOTA REGULATE NOT ONLY SCFAS BUT ALSO KETONE BODIES IN CALORIC RESTRICTION, BETA HYDROXY BUTYRATE , BHB



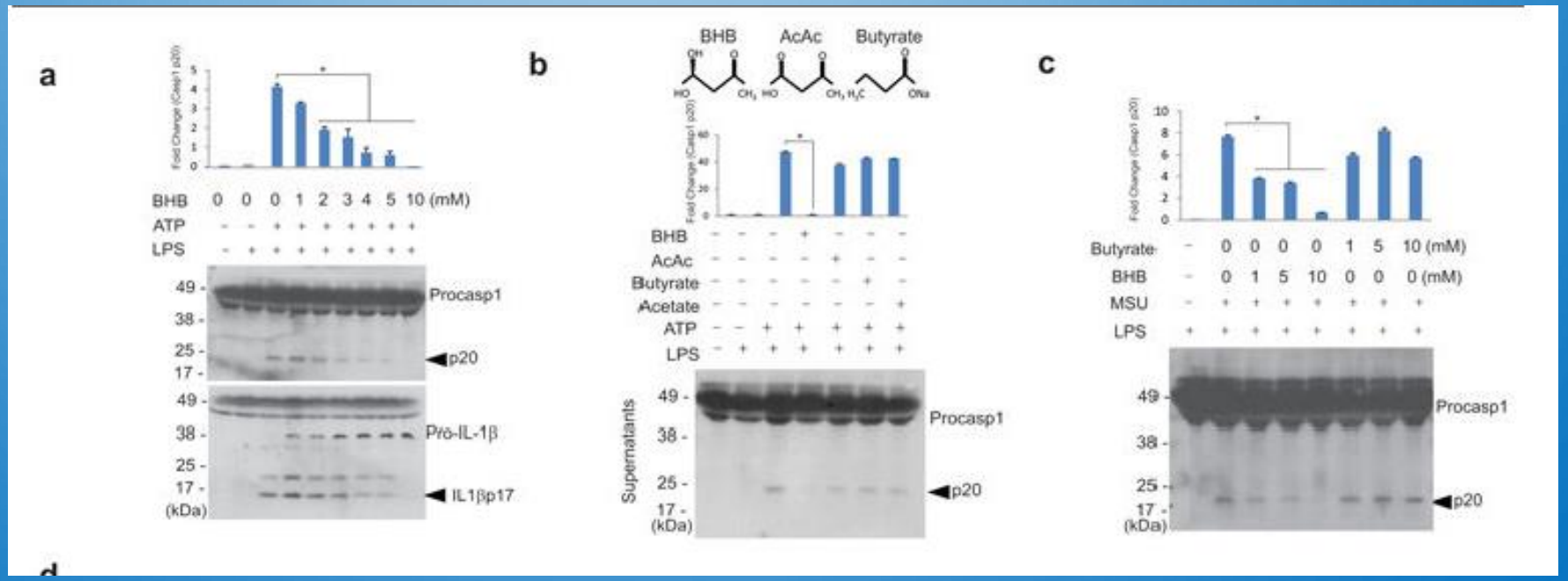


Crawford PA et al, 2009). Regulation of myocardial ketone body metabolism by the gut microbiota during nutrient deprivation. *Proceedings of the National Academy of*

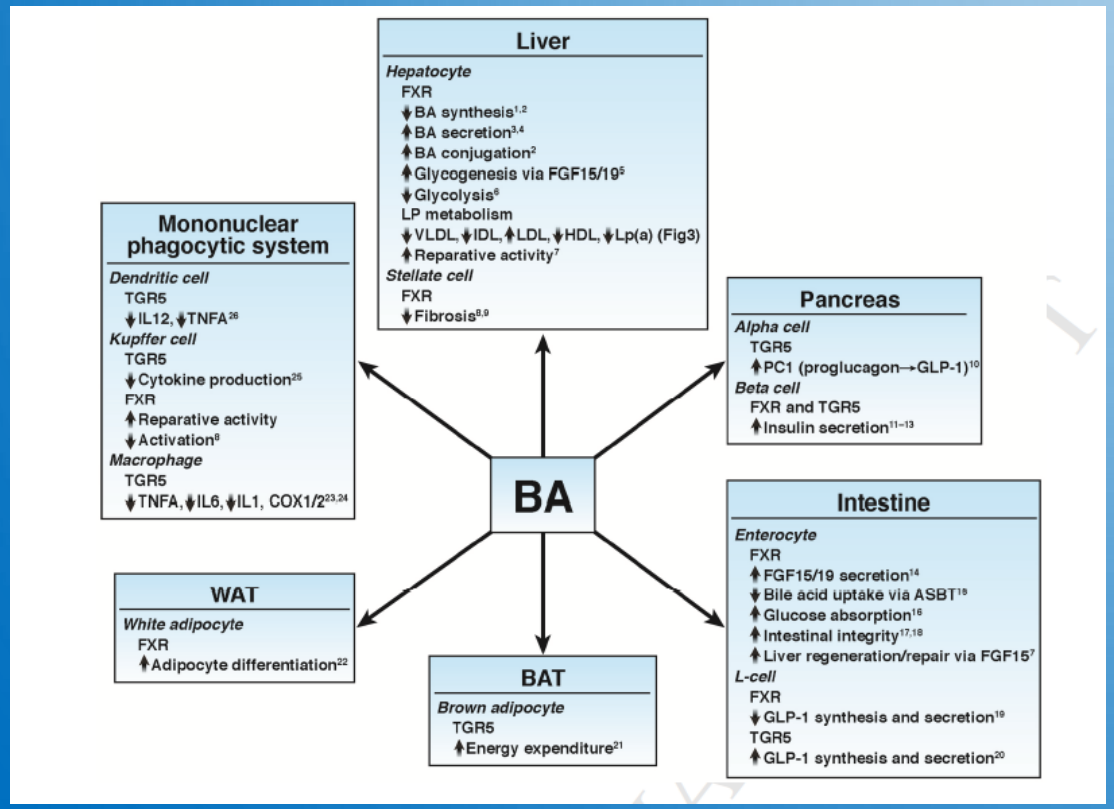
KETONE BODY B-HYDROXYBUTYRATE BLOCKS THE NLRP3 INFLAMMASOME-MEDIATED INFLAMMATORY DISEASE(CASPASE SUBUNIT)

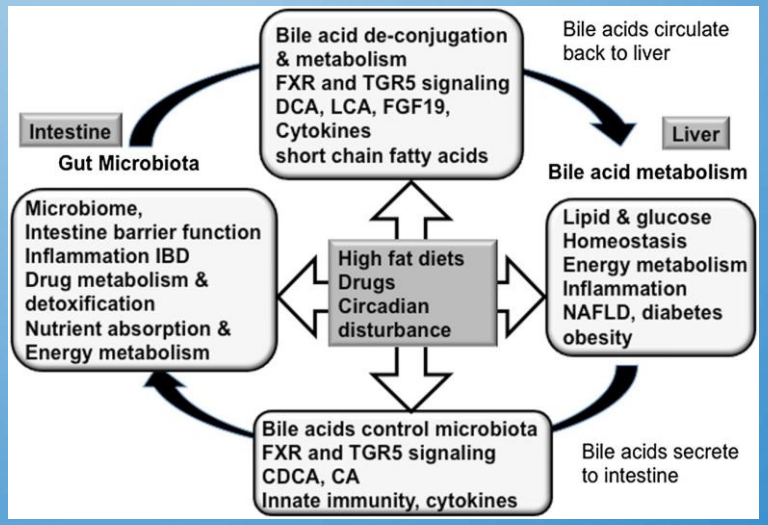
Ketogeneic diet may improve inflammation via epigenetics, but can also lead to an overload of LPS thru high SFA and low vegtable intake

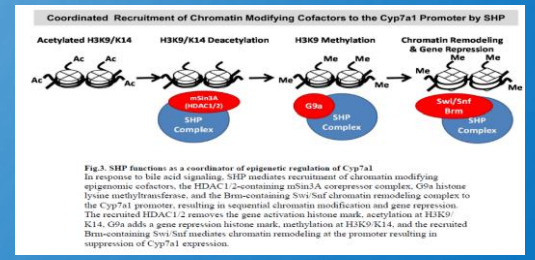
Yun-Hee Youm et al.
Nat med. 2015



MICROBIOTA MODULATED BILE ACIDS ARE EPIGENETICALLY ACTIVE AND VIA FXR REGULATE INFLAMMATION



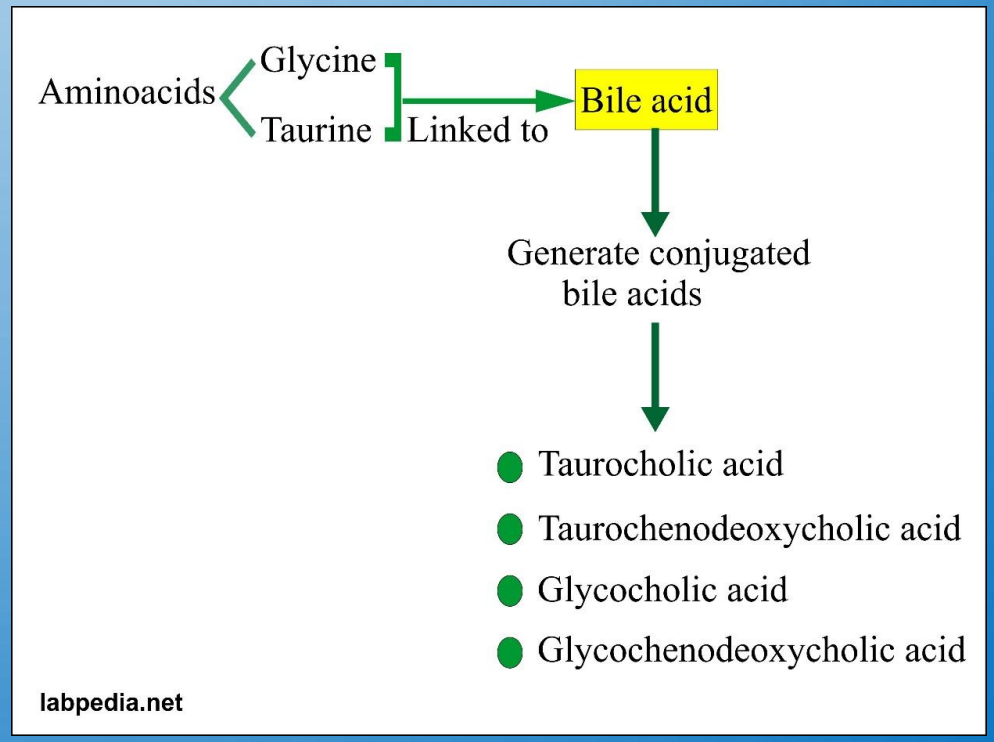




Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia and NAFLD
Oscar Chávez-Talavera, et al, 2017

BILE ACIDS

Primary bile acids are synthesized by the liver. Secondary bile acids result from bacterial actions in the colon. In humans, taurocholic acid and glycocholic acid (derivatives of cholic acid) and taurochenodeoxycholic acid and glycochenodeoxycholic acid (derivatives of chenodeoxycholic acid) are the major bile salts in bile and are roughly equal in concentration



GUT BRAIN / IMMUNE- AXIS

Effects of intestinal microbiota on anxiety-like behavior

Karen-Anne M. Neufeld,[1,4] Nancy Kang,[1,2] John Bienenstock[1,3] and Jane A. Foster[1,2,*]
[1]Brain-Body Institute; St. Joseph's Healthcare; [2]Department of Psychiatry and Behavioral Neurosciences; [3]Department of Pathology and Molecular Medicine; [4]Medical Sciences Graduate Program; McMaster University; Hamilton, ON Canada

The acquisition of intestinal microbiota in the immediate postnatal period has a defining impact on the development and function of many immune and metabolic systems integral to health and well-being. Recent research has shown that the presence of gut microbiota regulates the set point for hypothalamic-pituitary-adrenal (HPA) axis activity.[1] Accordingly, we sought to investigate if there were other changes of brain function such as behavioral alterations in germ free (GF) mice, and if so, to compare these to behavior of mice with normal gut microbiota. Our recent paper showed reduced anxiety-like behavior in the elevated plus maze (EPM) in adult GF mice when compared to conventionally reared specific pathogen-free (SPF) mice.[2] Here, we present data collected when we next colonized the adult GF mice with SPF feces thereby introducing normal gut microbiota, and then reassessed anxiety-like behavior. Interestingly, the anxiolytic behavioral phenotype observed in GF mice persisted after colonization with SPF intestinal microbiota. These data show that gut-brain interactions are important to CNS development of stress systems and that a critical window may exist after which reconstitution of microbiota and the immune system does not normalize the behavioral phenotype.

Key words: germ free, microbiota, anxiety-like behavior, gut-brain, elevated plus maze
Submitted: 04/06/11
Accepted: 04/07/11

comorbidity found between mood and anxiety disorders and both inflammatory bowel disease and the functional bowel disorders.[6-8] Indeed the focus of Rome III, a diagnostic instrument designed to aid clinicians in the diagnosis of functional bowel disorders such as irritable bowel syndrome (IBS), is on gut, brain and spinal cord interactions and their involvement in the generation of symptoms of pain and intestinal dysfunction.[9] Luminal contents have also become a focus of study in the etiology of functional bowel disorders, with a number of studies pointing to variations in the composition of gut microbiota in patients suffering from IBS compared to controls.[10] A recent report found that compared to specific pathogen-free (SPF) mice, adult germ free mice showed an exaggerated stress response, as evidenced by increased plasma corticosterone (CORT) and adrenocorticotrophic hormone (ACTH) levels in response to restraint stress.[1] Clearly the study of the impact of gut microbiota on the development of HPA dysfunction and potentially anxiety-like behavior has important clinical applications in the study of both gastrointestinal and psychiatric health and disease, as they are essentially involved in the communication between the gut and the brain.

We propose that the intestinal microbiota housed within the gastrointestinal

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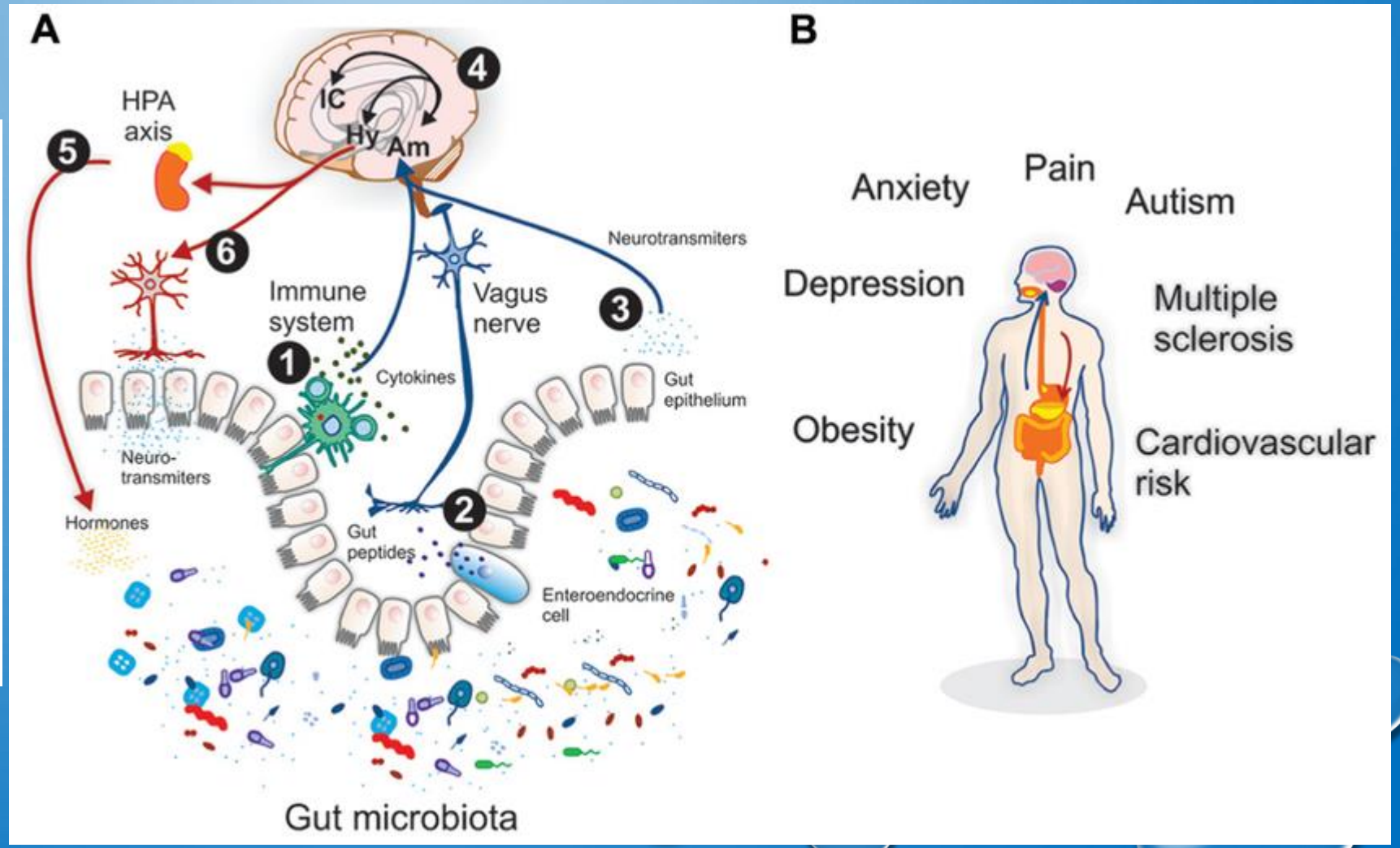
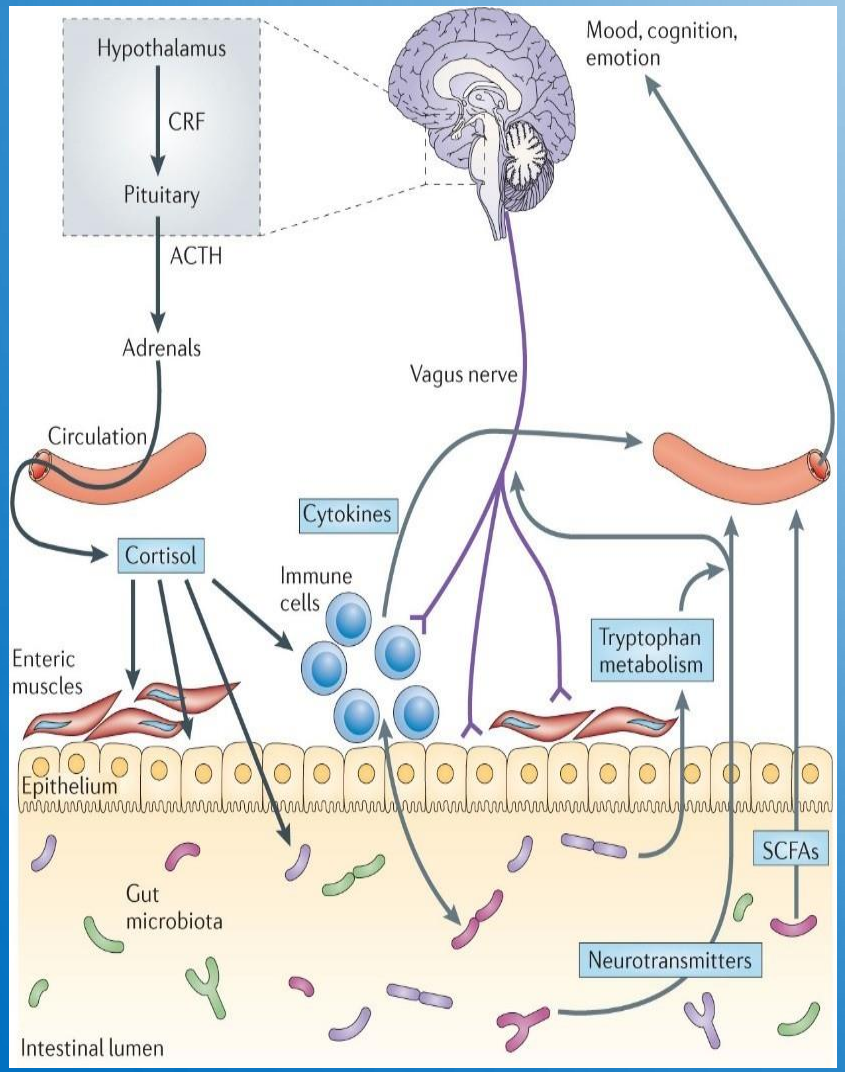
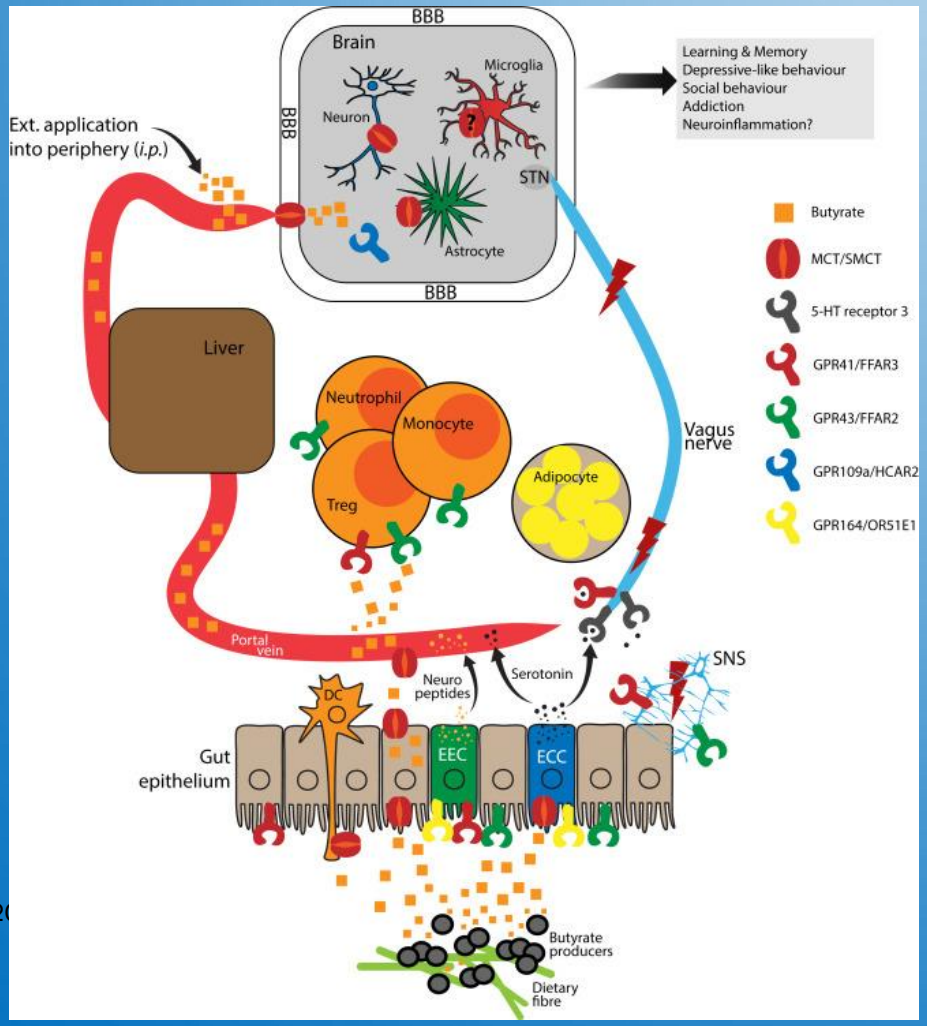


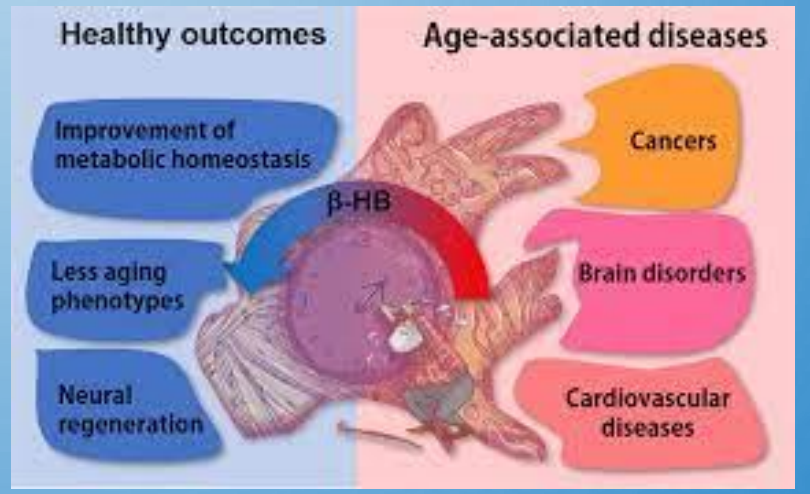
Gut-Microbiota-Brain Communication

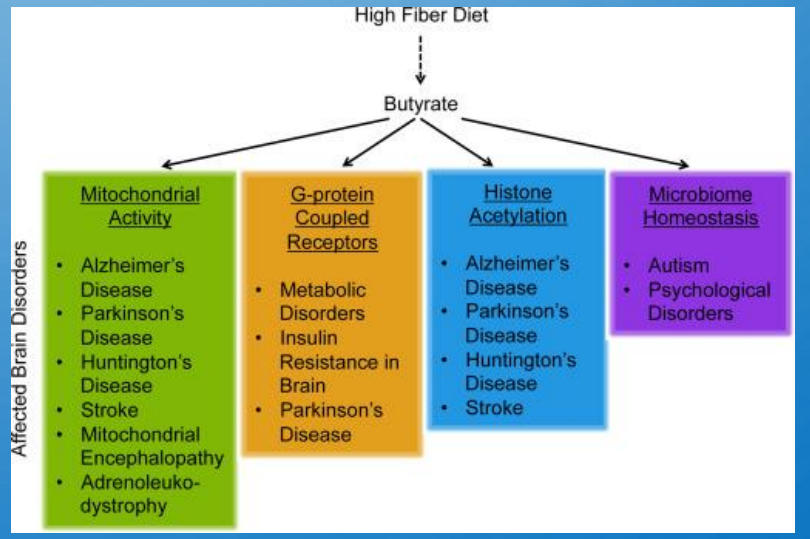


- Bidirectional communication
  - Central nervous system (brain and spinal cord)
  - Autonomic nervous system (sympathetic and parasympathetic)
  - Enteric nervous system (intrinsic nervous system of GI tract)
  - Hypothalamic pituitary adrenal axis (HPA)
  - Microbiome (collection of microorganisms and their genomes in the gut)

BUTYRATE, BETA-HYDROXYBUTYRATE AND THE BRAIN







VAGUS NERVE

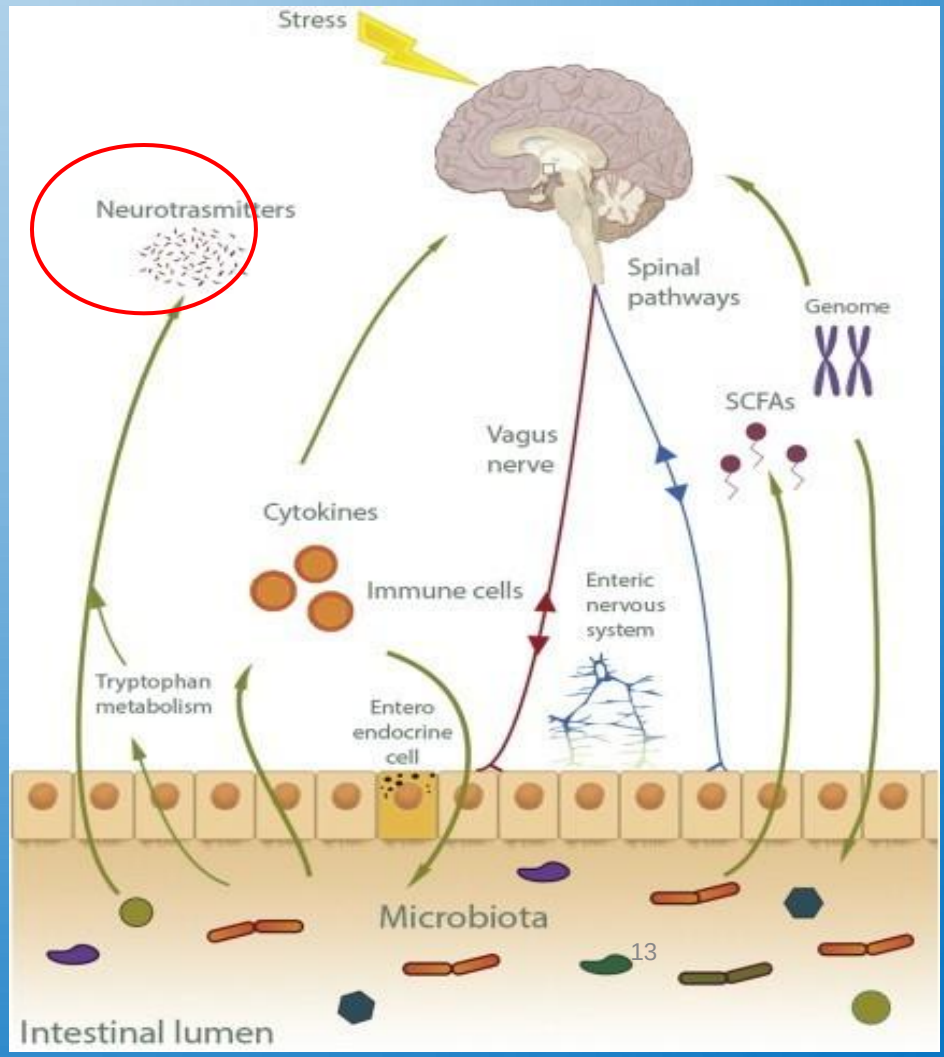
- Major nerve of the parasympathetic division of the autonomic nervous system
- Important pathway for bidirectional communication between the gut microbes and the brain
- Preclinical/animal studies demonstrate that probiotic effects on brain are dependent on vagal afferent signals
  - *Lactobacillus rhamnosus* directly activates vagal neurons
  - Induces region-dependent alterations in GABA receptor expression in the brain and reduced stress-induced corticosterone and anxiety- and depression-like symptoms via vagus nerve signaling in mice
- Vagotomized mice do not exhibit this effect

Bravo, Javier A., et al. *Proceedings of the National Academy of Sciences* 108.38 (2011): 16050-16055.

12

Neurotransmitter and the gut

- Acetylcholine
- Noradrenaline
- Adrenaline
- Gamma-amino butyric acid (GABA)
- Serotonin



Burokas et al., Advances in Applied Microbiology. 91 (2015): 1-62

Bacteria & Neurotransmitters

Neurotransmitter	Genus
GABA	*Lactobacillus, Bifidobacterium*
Norepinephrine	*Escherichia, Bacillus, Saccharomyces*
Acetylcholine	*Lactobacillus*
Serotonin	*Candida, Streptococccus, Escherichia, Enterococcus*

Lyte, Mark. *Bioessays* 33.8 (2011): 574-581.

SEROTONIN

- Biogenic amine that functions as a neurotransmitter
  - Tryptophan is precursor
  - Involved in GI secretion
  - Gut motility
  - Pain perception
  - Maintenance of mood and cognition
- 95% of serotonin is contained in the gut in the mucosa and nerve terminals of the enteric nervous system
- Alterations in serotonin transmission may underlie pathological symptoms
  - Selective serotonin reuptake inhibitors are known to modulate psychiatric and GI disorders (e.g., IBS)

O'Mahony, S. M., et al. Behavioural brain research 277 (2015): 32-48.

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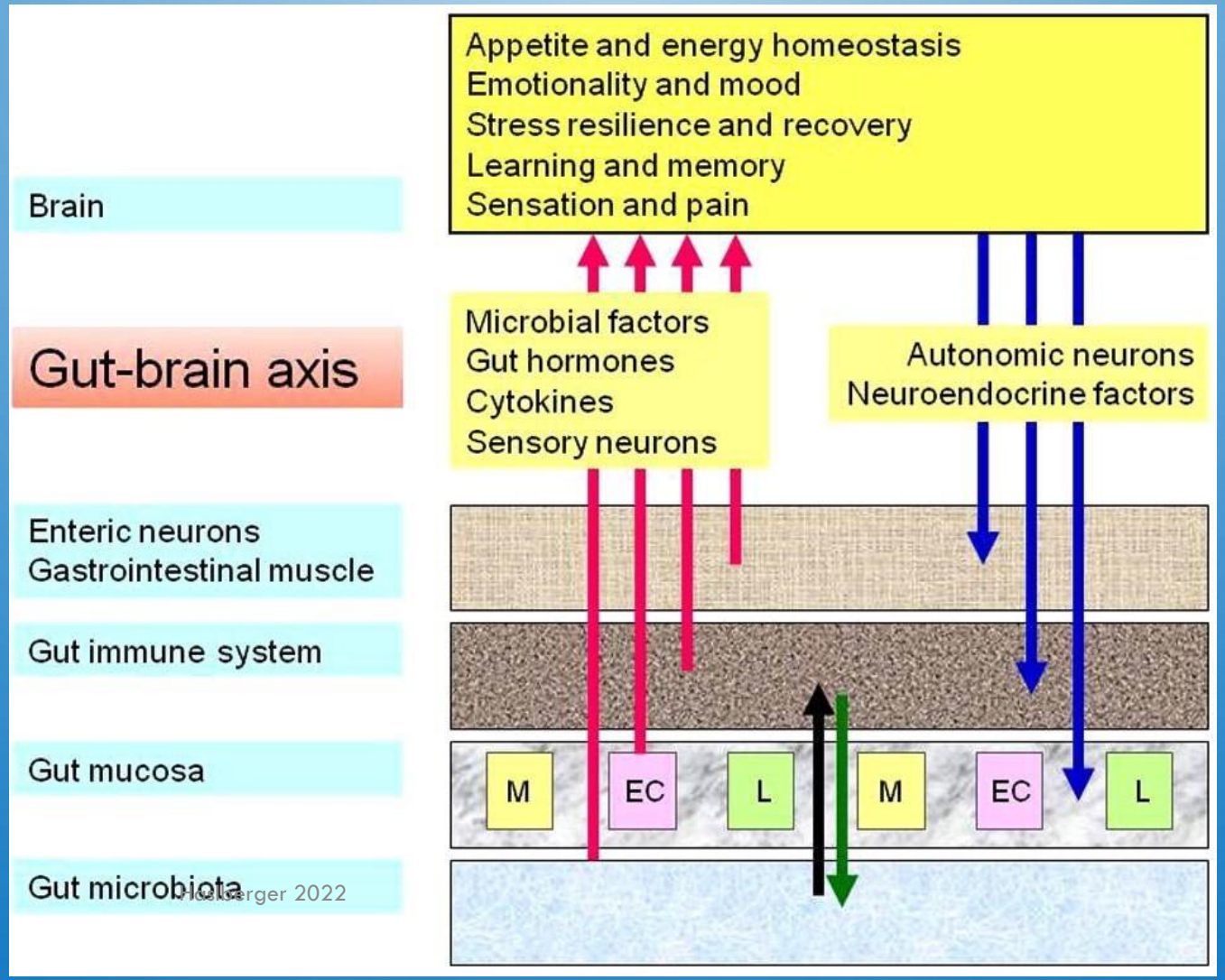
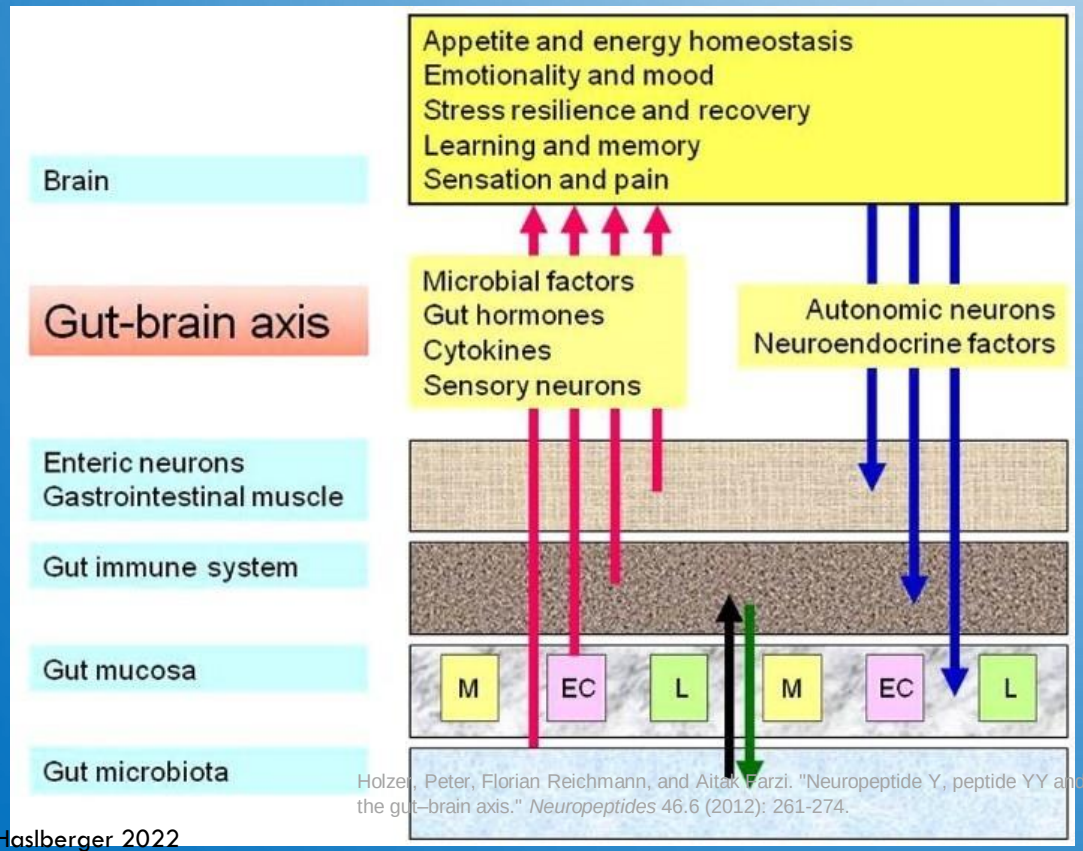
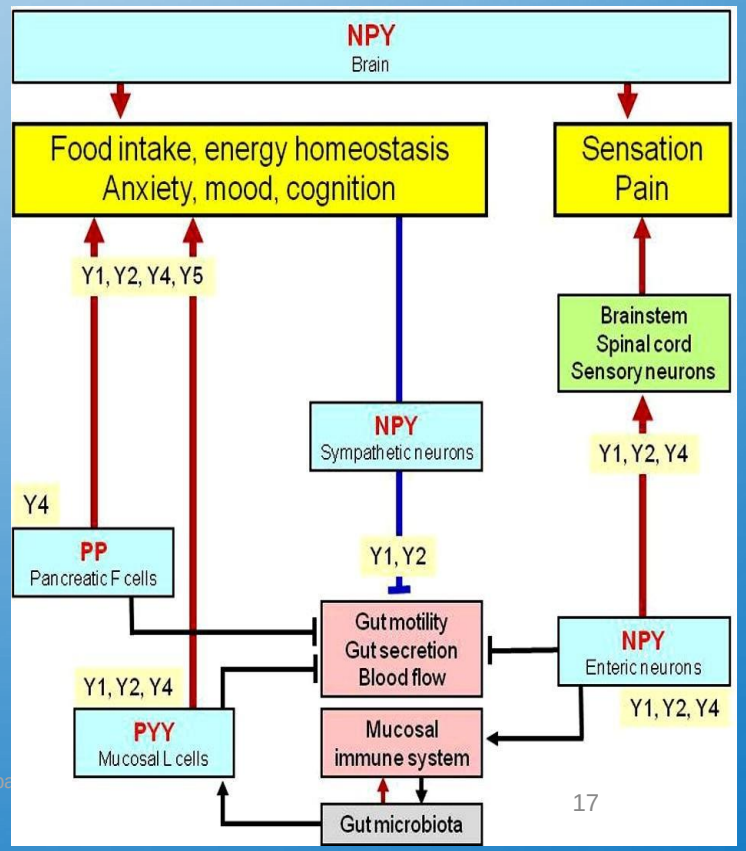
FUNCTIONS OF GUT BRAIN AXIS, APPETITE



Gut Hormones and Neuropeptides

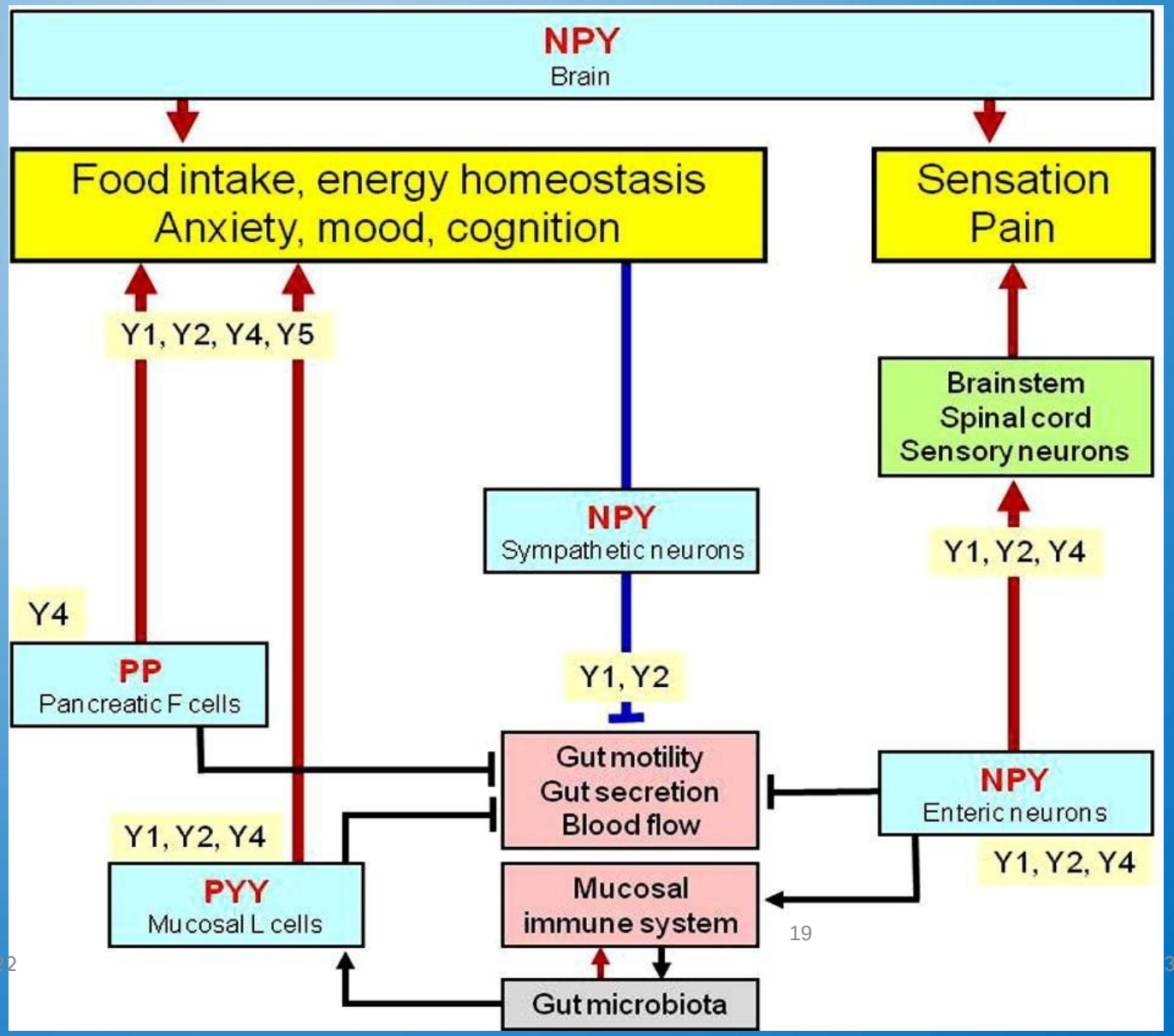




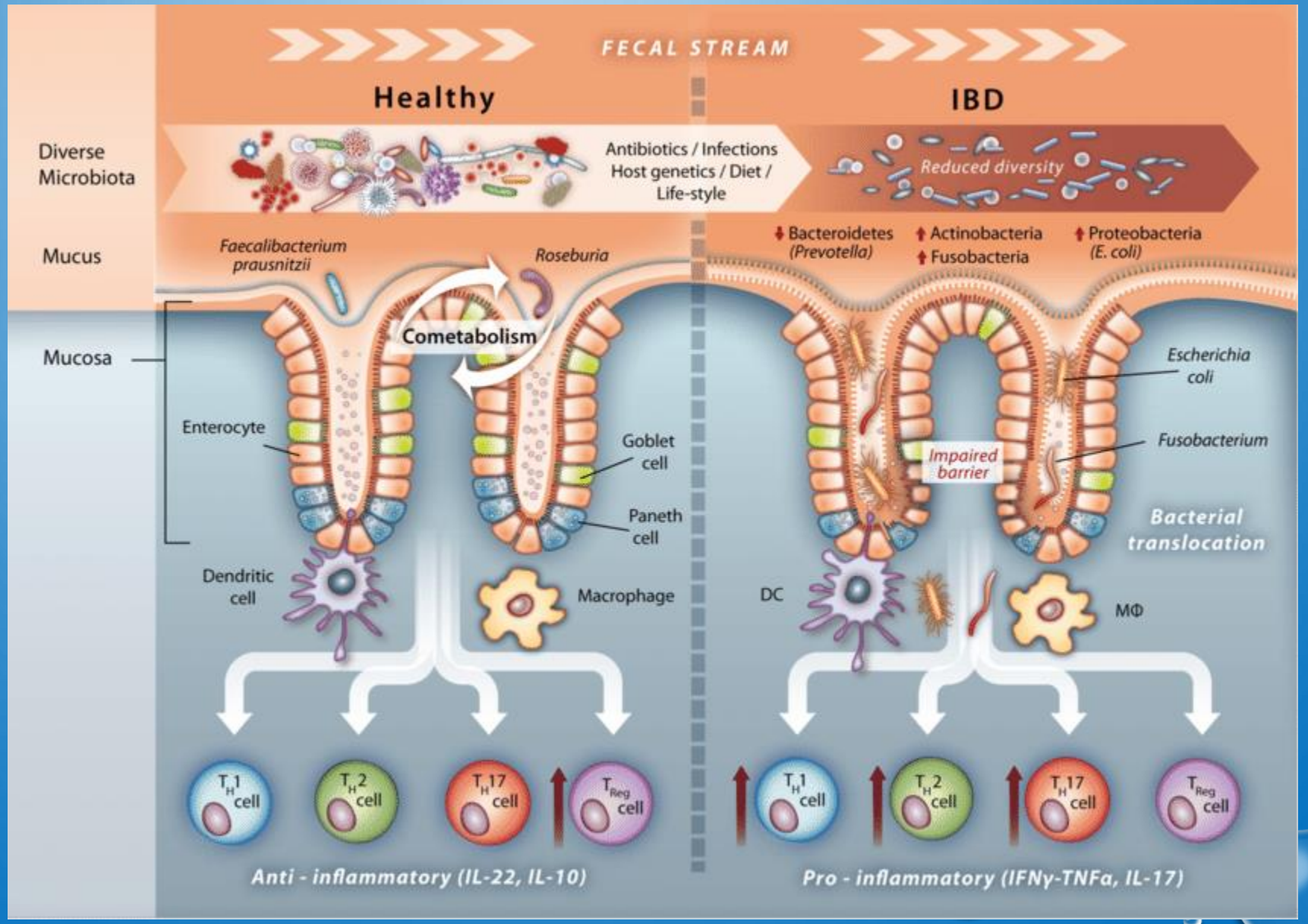
Holzer, Peter, Florian Reichmann, and Aitak Farzi. "Neuropeptide Y, peptide YY and pa
the gut–brain axis." *Neuropeptides* 46.6 (2012): 261-274.

17

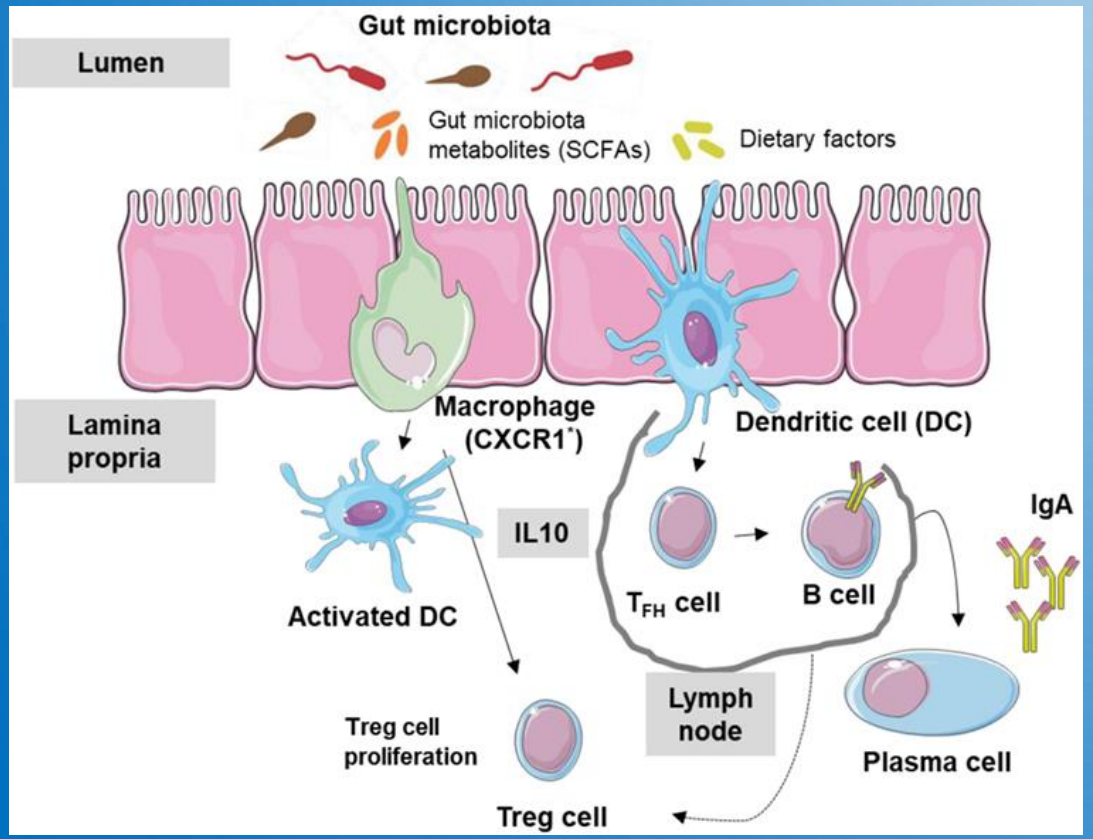
Neuro-peptide Y and the gut

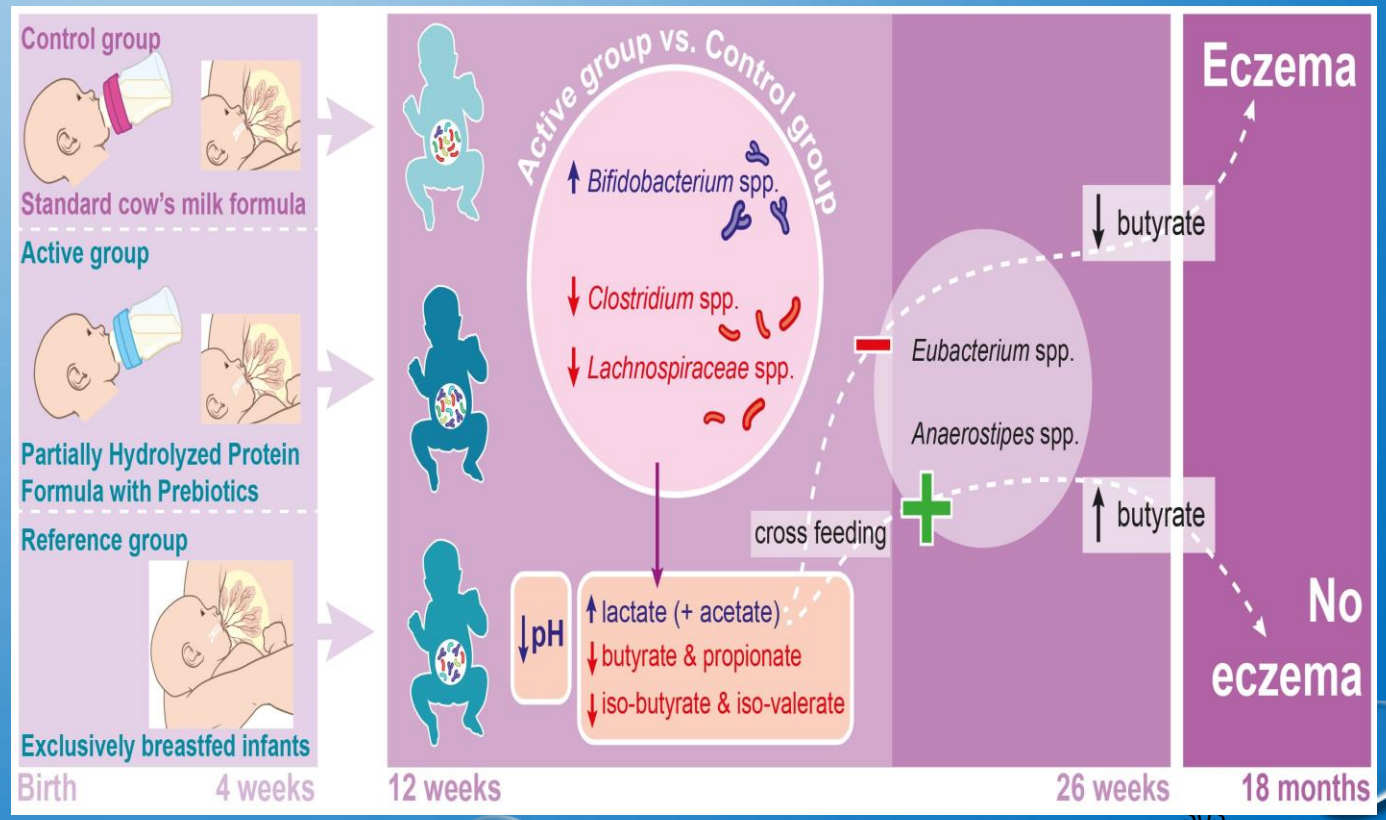


IBD


FECAL STREAM
Healthy
IBD
Diverse Microbiota
Antibiotics / Infections
Host genetics / Diet /
Life-style
Reduced diversity
Mucus
Bacteroidetes (Prevotella)
Actinobacteria
Fusobacteria
Proteobacteria (E. coli)
Faecalibacterium prausnitzii
Roseburia
Cometabolism
Mucosa
Escherichia coli
Enterocyte
Goblet cell
Fusobacterium
Impaired barrier
Paneth cell
Bacterial translocation
Dendritic cell
Macrophage
DC
MΦ
TH1 cell
TH2 cell
TH17 cell
TReg cell
Anti - inflammatory (IL-22, IL-10)
Pro - inflammatory (IFNγ-TNFa, IL-17)

ALLERGY, MICROBIOTA, BIFIDOB., BUTYRATE





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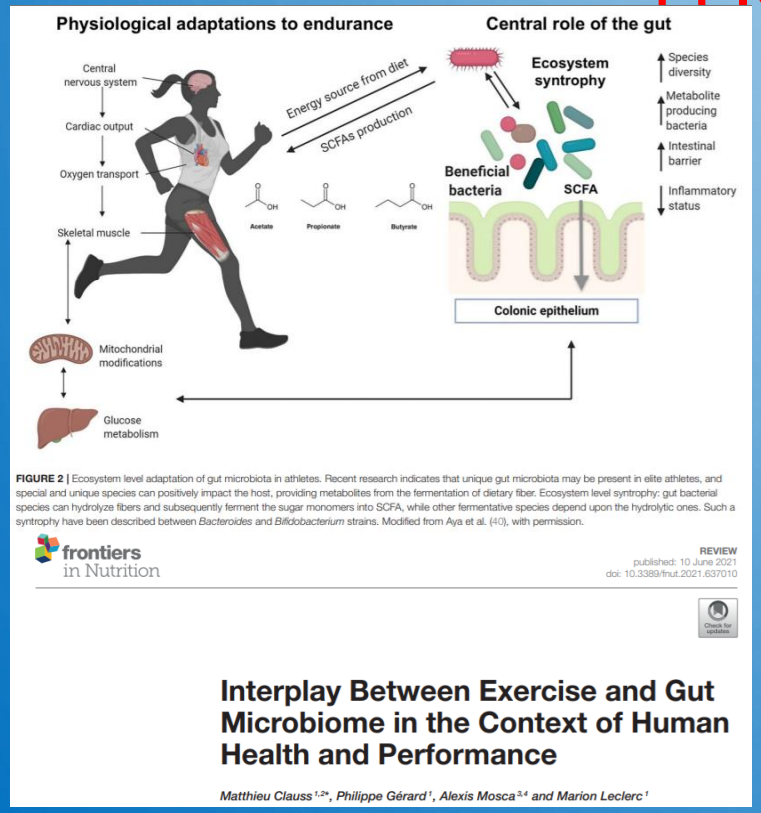
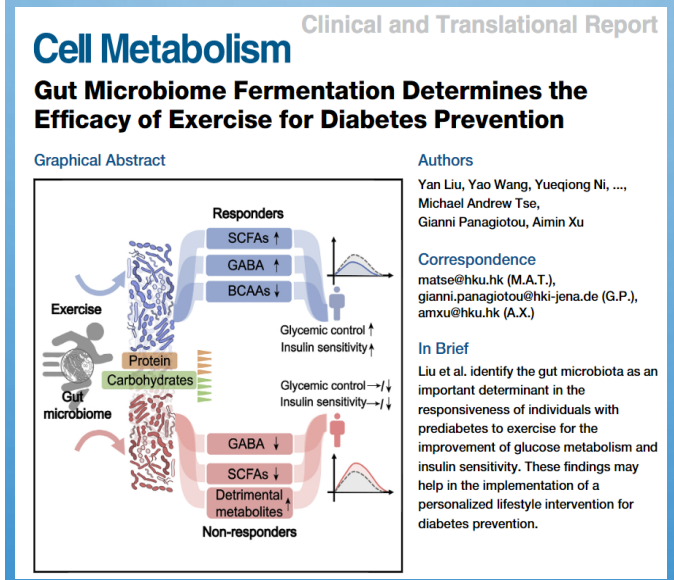
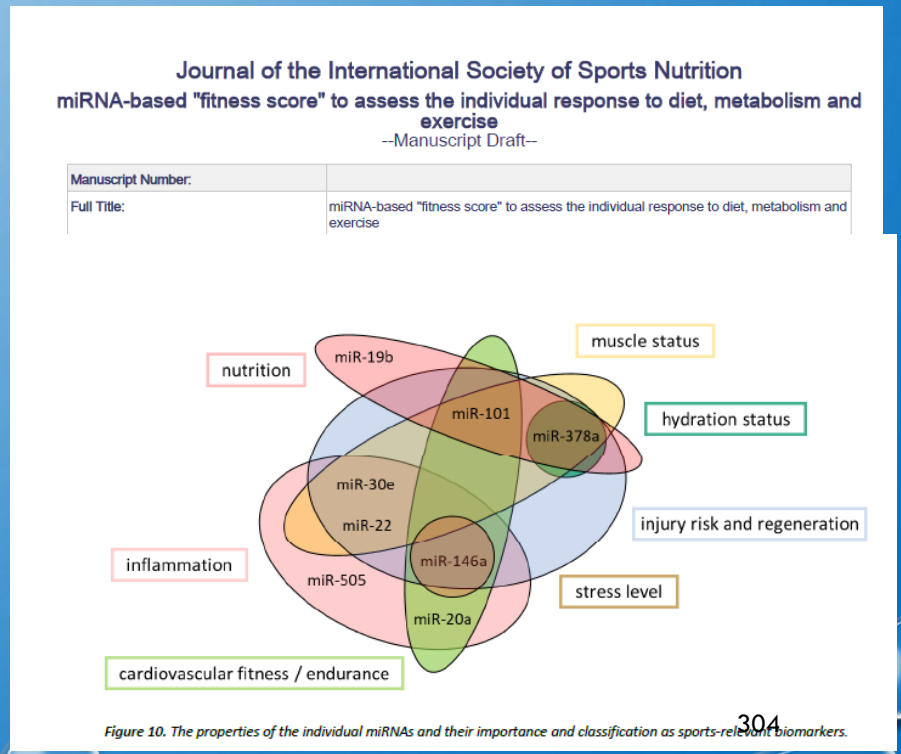
LIFESTYLE: EXERCISE MODULATES MICROBIOTA, METABOLITES AND EPIGENETICS (MIRNAS)



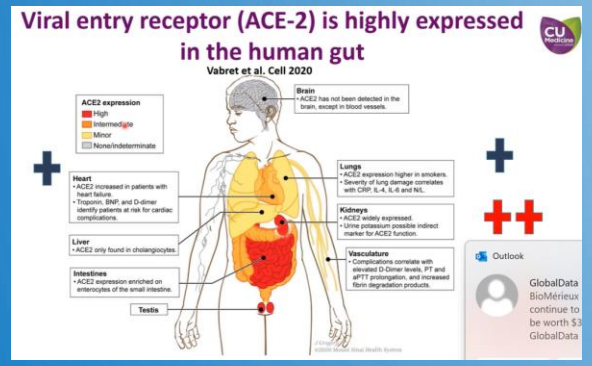


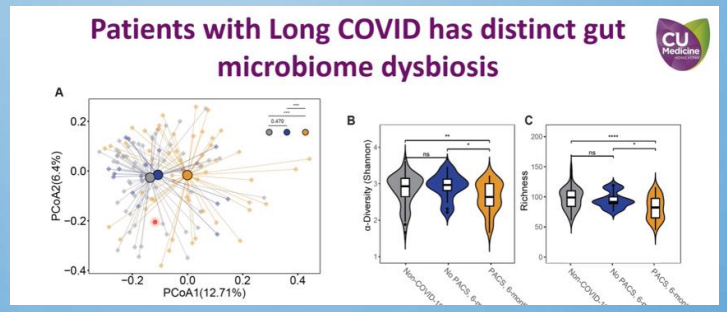


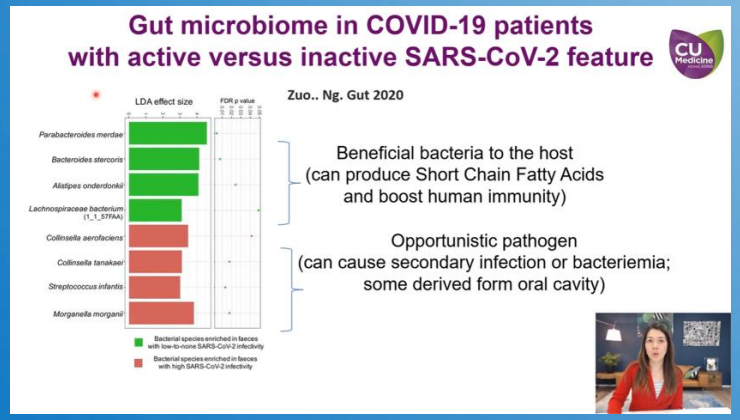
Enhanced amount of SCFA producers by exercise ?
Production of metabolites decides effectivity of exercise against diabetes

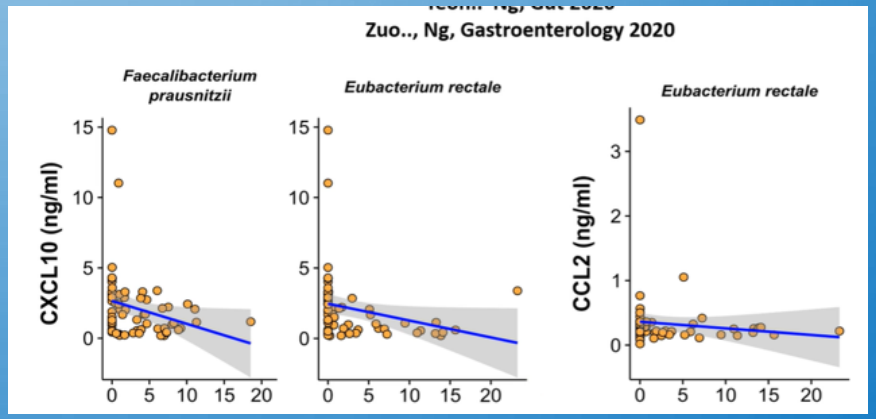
Haslberger 2022

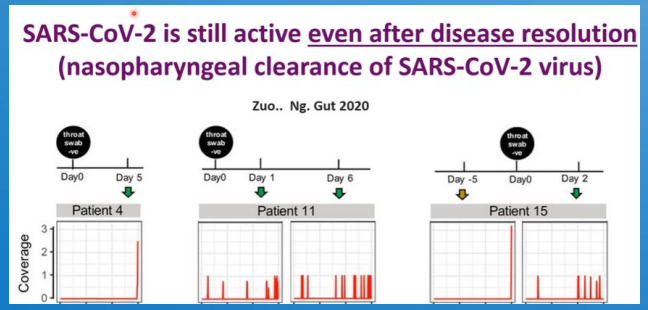
COVID, LONG COVID, MICROBIOTA AND EPIGENETICS











The Promise of Microbiota Modulation during COVID-19 Pandemic

Siew C Ng, University of Hong Kong, Hong Kong

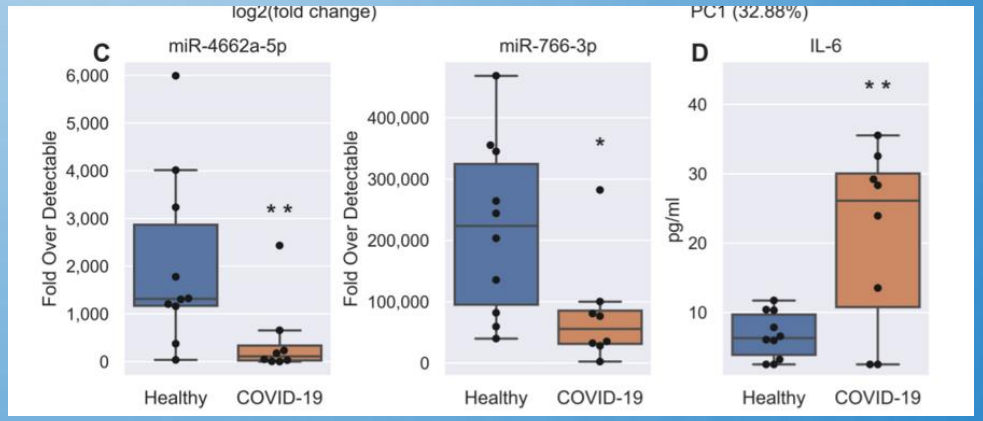
3 MIRNAS MONITOR SARS-COV-2 INFECTION, MIRNAS MONITOR ANTI-VIRAL IMMUNE- RESPONSES

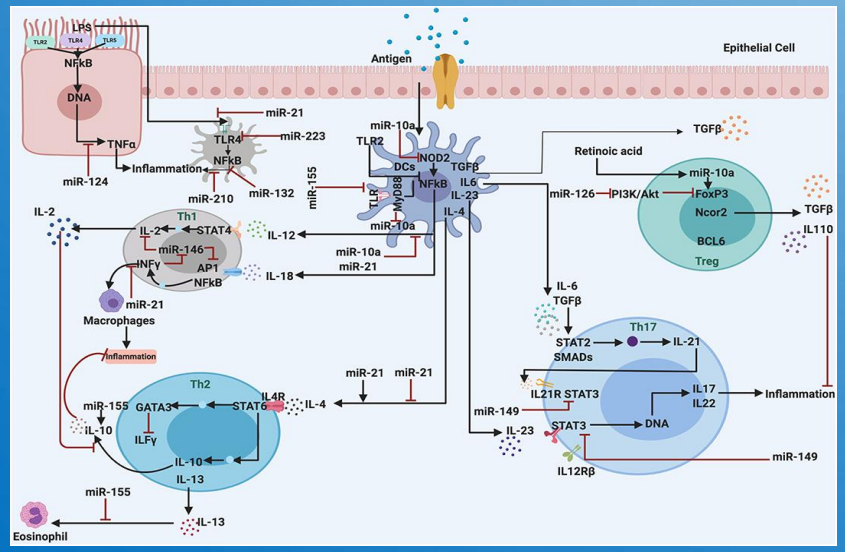
RESEARCH ARTICLE

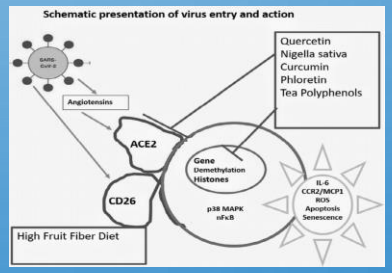
Altered microRNA expression in COVID-19 patients enables identification of SARS-CoV-2 infection

Ryan J. Farr[1], Christina L. Rootes[1], Louise C. Rowntree[2], Thi H. O. Nguyen[2], Luca Hensen[2], Lukasz Kedzierski[2,3], Allen C. Cheng[4,5], Katherine Kedzierska[2,6], Gough G. Au[1], Glenn A. Marsh[1], Seshadri S. Vasan[1,7], Chwan Hong Foo[8], Christopher Cowled[1], Cameron R. Stewart[1]*

1 CSIRO Health & Biosecurity, Australian Centre for Disease Preparedness, Geelong, Victoria, Australia,

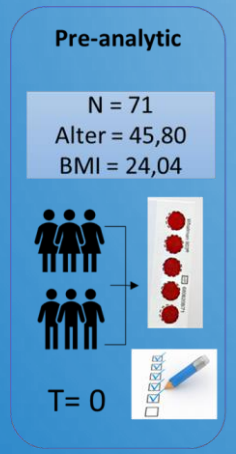






NÄHRWERTANGABEN *NUTRITIONAL INFORMATION*	1 KAPSEL *1 CAPSULE*	%NRV
Vitamin D3 (Cholecalciferol)	20 µg	400%
Vitamin B9 (Folate)	600 µg	400%
Zink / *Zinc*	14 mg	150%
Salbei-Extrakt / *Sage extract* (Polyphenole)	140 mg	
Grüntee-Extrakt / *Green tea extrakt* (EGCG)	125 mg	
Berberin / *Berberine*	4 mg	
Apfel-Extrakt / *Apple extract* (Phloretin)	40 mg	
Zwiebel-Extrakt / *Onion extract* (Quercetin)	140 mg	
Holunderbeeren-Extrakt / *Elderberry extract* (Anthocyanin)	110 mg	
Traubenhaut-Extrakt / *Grape skin extract* (Resveratrol)	140 mg	

MODULATION OF I.S. -, AND VIRAL INFECTION RELEVANT MIRNAS AND INFLAMMATION RELATED NFKB AFTER 2 M



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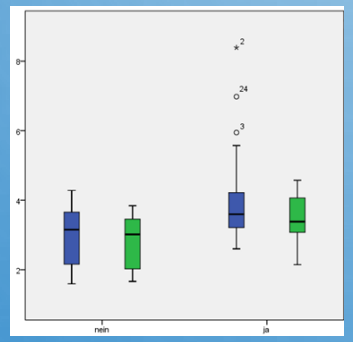
p= 0,01



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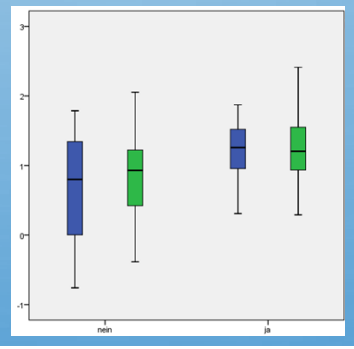
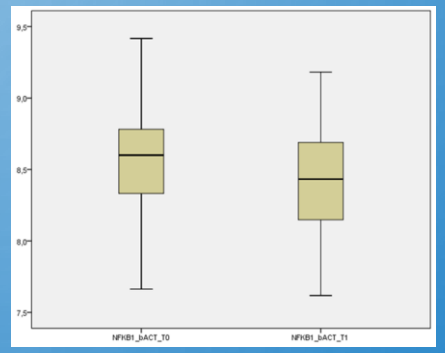


NFkb mRNA
p= ,050



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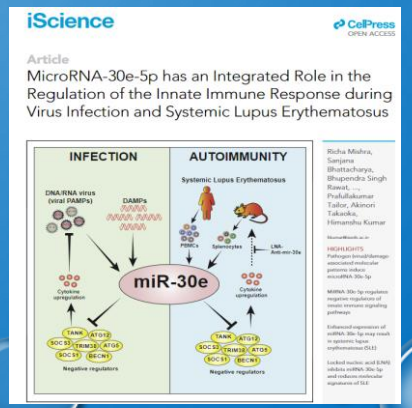
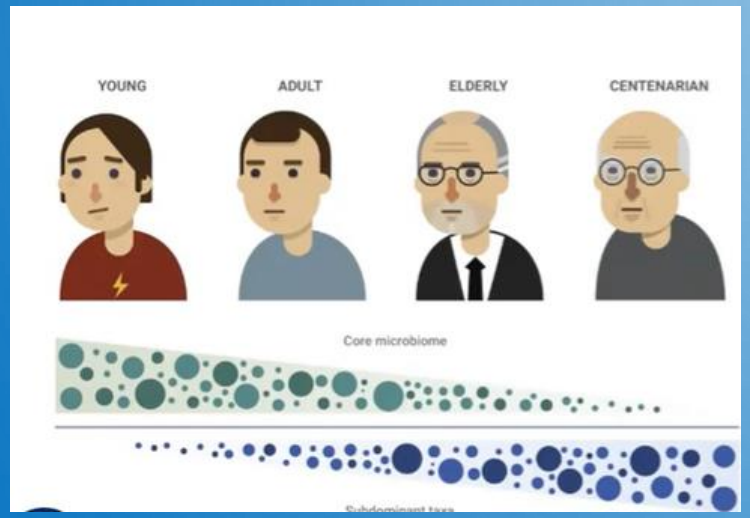
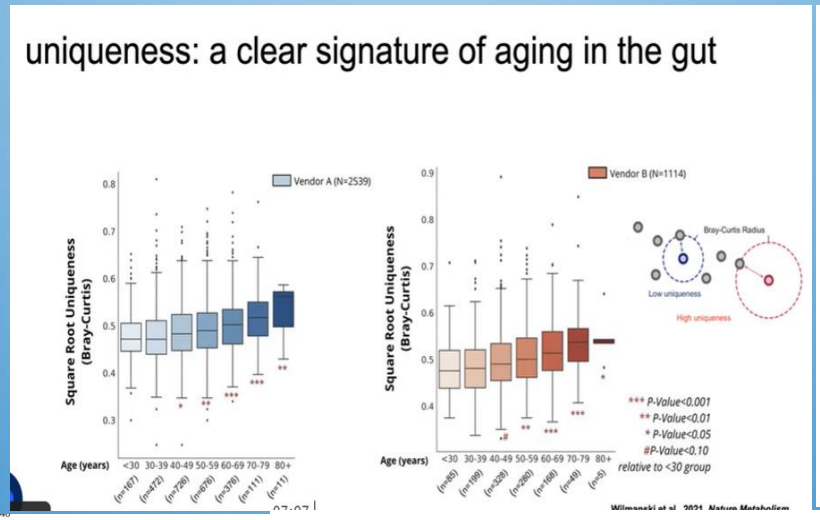
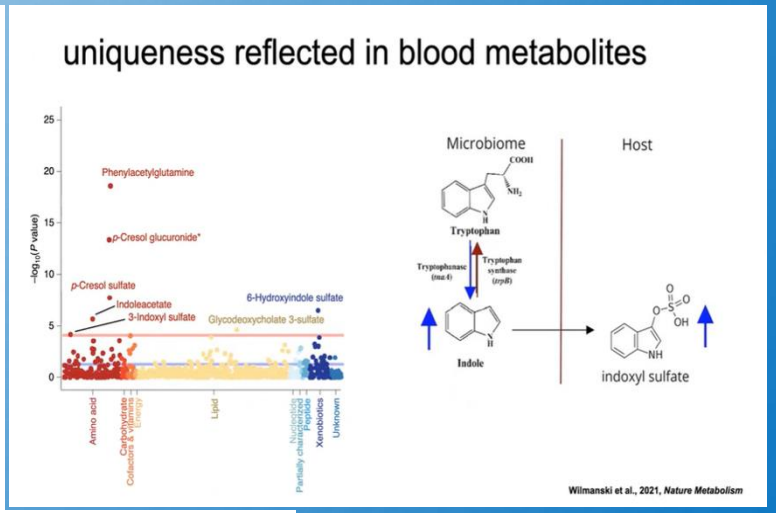
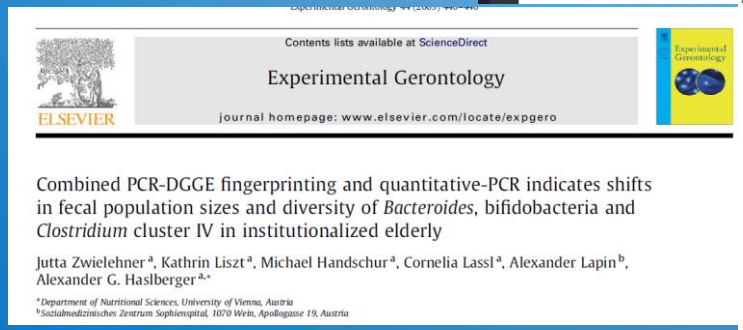


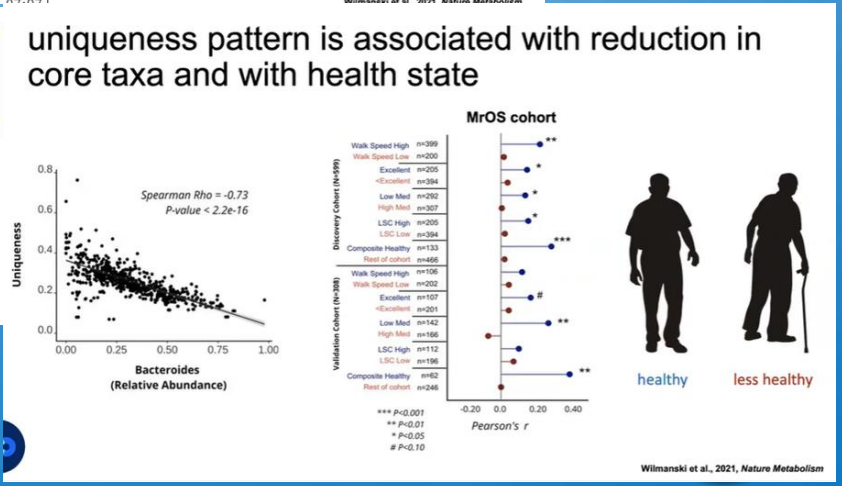
AGING, BACTERIAL DIVERSITY, UNIQUENESS AND HEALTH







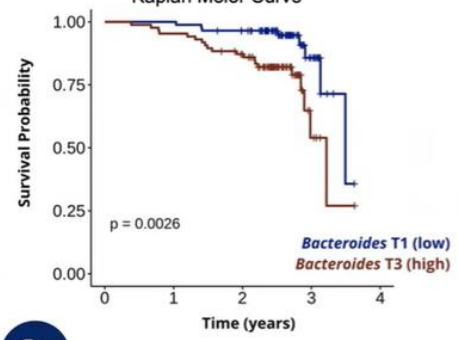




BACTEROIDETES DECIDE UPON HEALTHY AGING ?

Bacteroides abundance predicts survival in 4 year follow-up of MrOS subjects

Kaplan Meier Curve



Cox Proportional Hazards Regression models

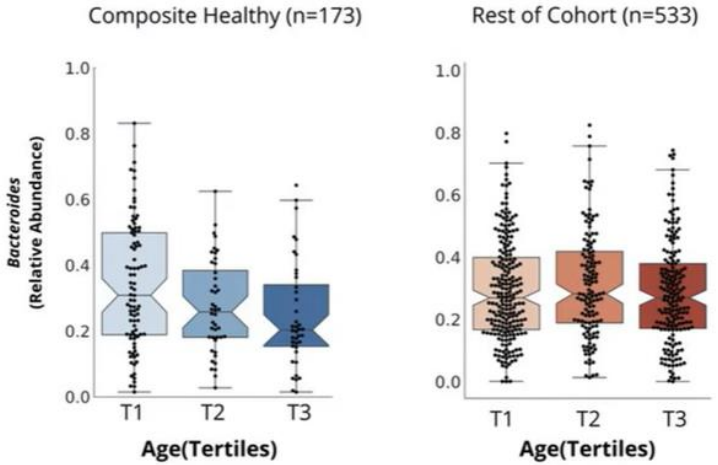
	Unadj. HR (95%CI)	Age, Clinical Site, & batch Adj. HR (95%CI)	Multivariable Adj. HR (95% CI)*	
Relative *Bacteroides* Abundance	1.21 (0.95-1.53)	1.30 (1.01-1.67)	1.28 (1.00-1.64)	Community dwelling participants all ages (N=706)
Uniqueness (Bray-Curtis)	1.17 (0.92-1.48)	1.1 (0.86-1.40)	1.11 (0.87-1.42)	
Relative *Bacteroides* Abundance	1.70 (1.25-2.31)	1.88 (1.35-2.62)	1.90 (1.37-2.64)	Community dwelling Participants 85+ years old only (N=257)
Uniqueness (Bray-Curtis)	0.76 (0.54-1.07)	0.69 (0.49-0.99)	0.70 (0.50-0.99)	

Wilmanski et al., 2021, *Nature Metabolism*

Bacteroides declines with extreme age in healthiest subjects, but not in the less healthy subjects

MrOS cohort

78-98 years old



Wilmanski et al., 2021, *Nature Metabolism*

Article | Published: 18 February 2021

Gut microbiome pattern reflects healthy ageing and predicts survival in humans

Tomasz Wilmanski, Christian Diener, Noa Rappaport, Sushmita Patwardhan, Jack Wiedrick, Jodi Lapidus, John C. Earls, Anat Zimmer, Gustavo Glusman, Max Robinson, James T. Yurkovich, Deborah M. Kado, Jane A. Cauley, Joseph Zmuda, Nancy E. Lane, Andrew T. Magis, Jennifer C. Lovejoy, Leroy Hood, Sean M. Gibbons, Eric S. Orwoll & Nathan D. Price

Nature Metabolism 3, 274–286 (2021) | Cite this article

The New York Times

A Changing Gut Microbiome May Predict How Well You Age

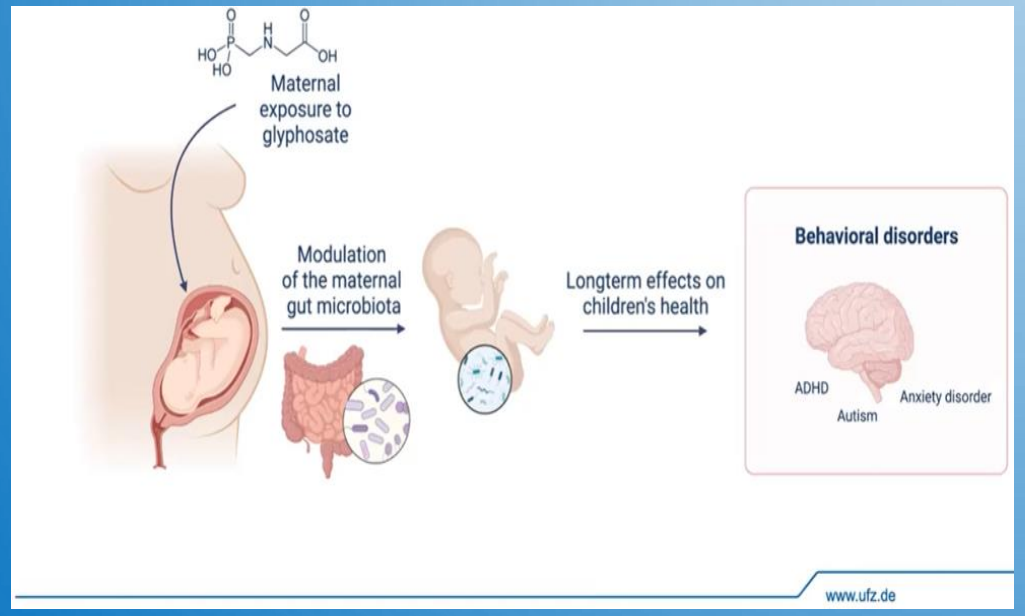
People whose gut bacteria transformed over the decades tended to be healthier and live longer.

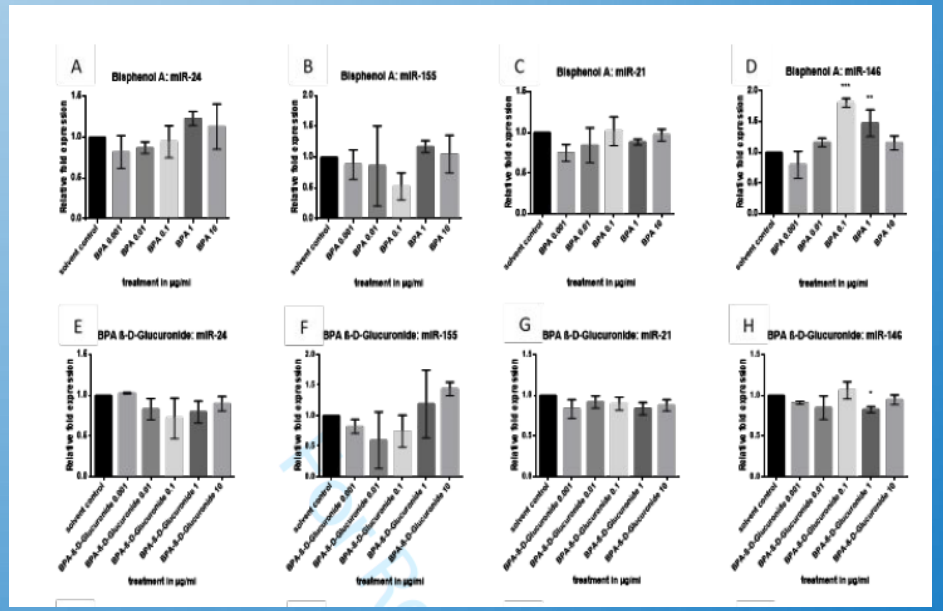
By Anahad O'Connor

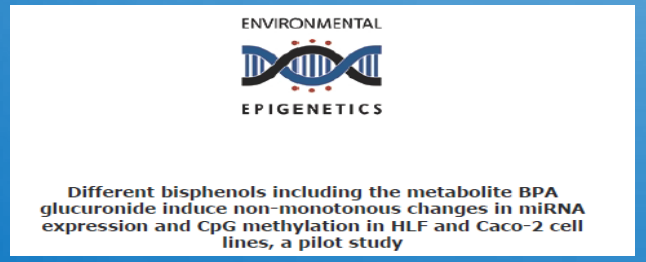
March 18, 2021

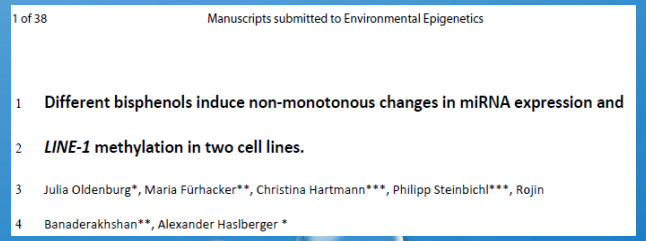
The identified microbiome pattern of healthy ageing is characterized by a **depletion of core** genera found across most humans, primarily Bacteroides. Retaining a high Bacteroides dominance into older age, or having a low gut microbiome uniqueness measure, predicts decreased survival in a 4-year follow-up

TOXINS: GLYPHOSATE, BISPHENOLS, MICROBIOTA AND EPIGENETICS



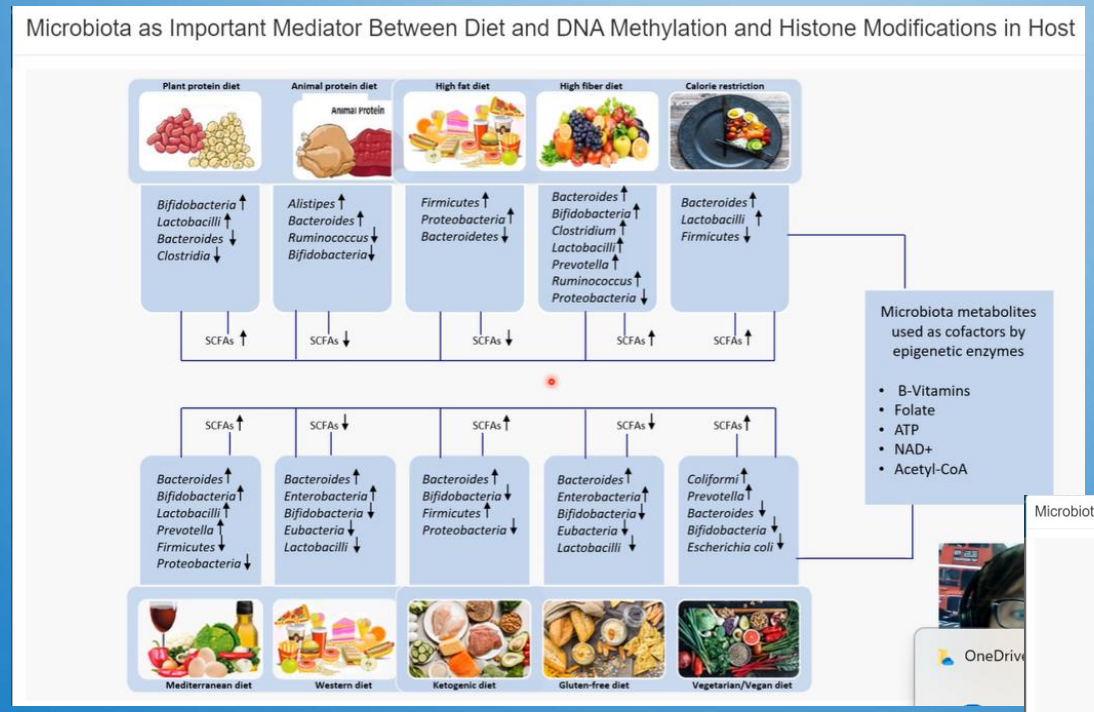




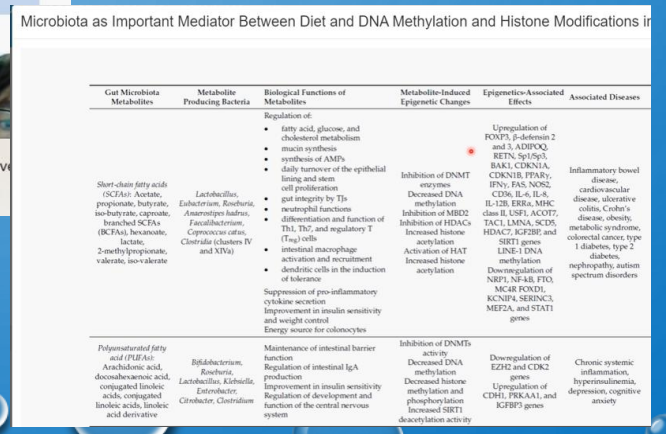


Lisa Buchenauer, Helmholtz Centre for Environmental Research Leipzig, Germany

INTERACTIONS DIET MICROBIOTA AND EPIGENETICS, EXPERIENCE

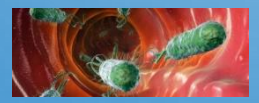


Dina Bellizzi, University of Calabria, Italy , Annalisa Terranegra, Sidra Medical and Research Center, Qatar

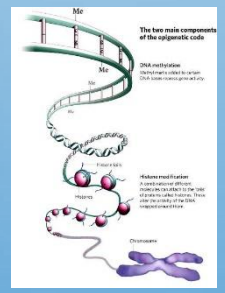


CONCEPT: DIETS AFFECT EPIGENETIC REGULATION (ALSO) VIA GI-MICROBIOTA- METABOLITES ?

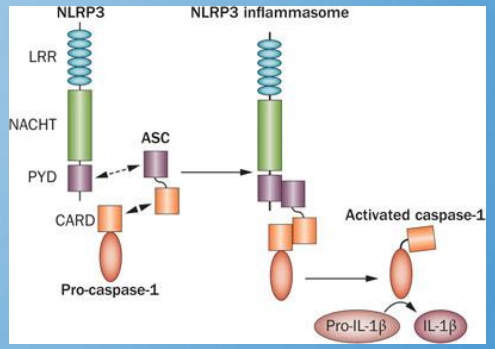
Nutrition
Feremnted milk products

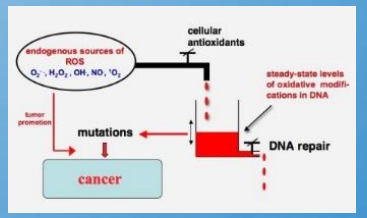


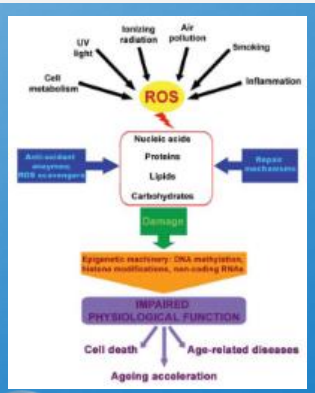
GI microbiota, metabolites, e.g.SCFAs



Epigenetic regulation

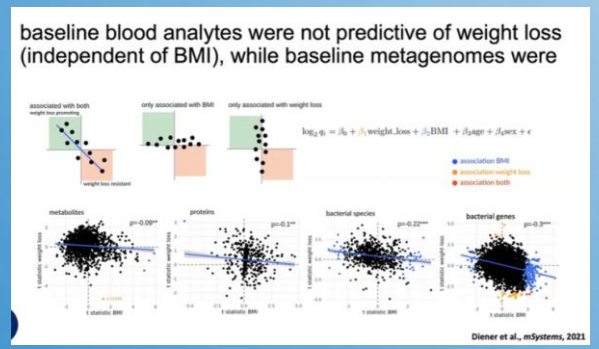


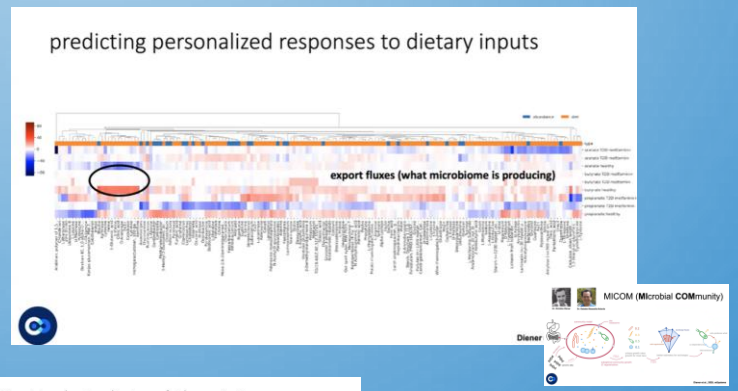


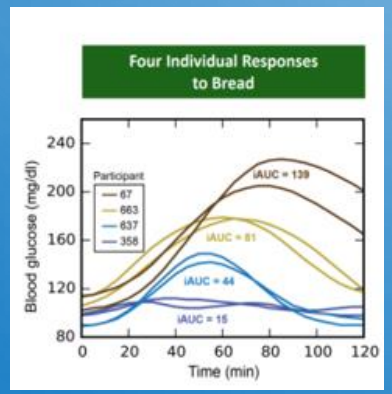


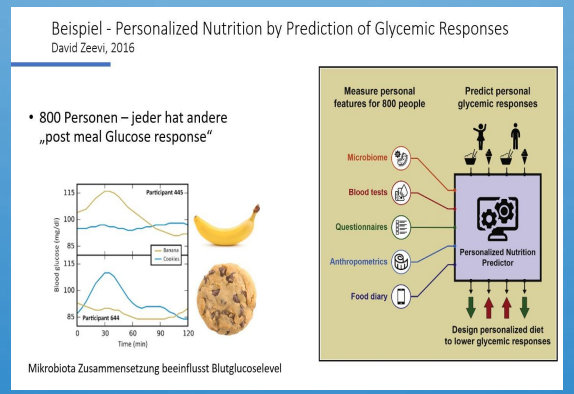
Inflammation, DNA damage, ageing

MICROBIOTA PREDICT PERSONAL RESPONSES TO DIETS









Eran Elinav and Eran Segal, Weizmann Institute of monitoring the blood sugar, diets, and other traits of 800 people, then built an algorithm that can accurately predict how a person's blood-sugar levels will spike after eating any given meal.
They also used these personalized predictions to develop tailored dietary plans for keeping blood sugar in check.

PROBIOTIC

- POSITIVE EFFECTS ON HEALTH ALREADY 100 YEARS AGO SUGGESTED BY NOBEL PRIZE WINNER ELIE METCHNIKOFF [METCHNIKOFF, 2004]
- DEFINITION: "LIVE MICROORGANISMS THAT, WHEN ADMINISTERED IN ADEQUATE AMOUNTS, CONFER A HEALTH BENEFIT ON THE HOST" [FAO/WHO, 2002]
- OVER 8000 RESEARCH ARTICLES PUBLISHED SINCE 2002 → SEVERAL PROBIOTIC PRODUCTS ON THE MARKET [HILL ET AL., 2014]
- CELL COMPONENTS OF PROBIOTICS ABLE TO INDUCE EFFECTS IN HOST [DOTAN AND RACHMILEWITZ, 2005] BUT REQUIREMENT FOR SURVIVABLE CELLS REMAINS A CRUCIAL FACTOR FOR EFFICACY [MA ET AL., 2004]

ANTIMICROBIAL SUBSTANCES

- PROBIOTICS PRODUCE VARIOUS ANTIMICROBIAL ACTING SUBSTANCES
- EXAMPLES: LACTIC ACID, HYDROGEN PEROXIDE, MICROCINES, DECONJUGATED BILE ACIDS [OELSCHLAEGER, 2010], BACTERIOCINS [MAQUEDA ET AL., 2008]
- ANTIBIOTICS ALSO PRODUCED BY PROBIOTICS → REUTERIN:
  - BROAD-SPECTRUM ANTIBIOTIC
  - ACTIVE AGAINST YEAST, GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA, FUNGI, VIRUSES, PROTOZOA
  - PRODUCED BY STRAIN ATCC55730 FROM L. REUTERI [CLEUSIX ET AL., 2007]

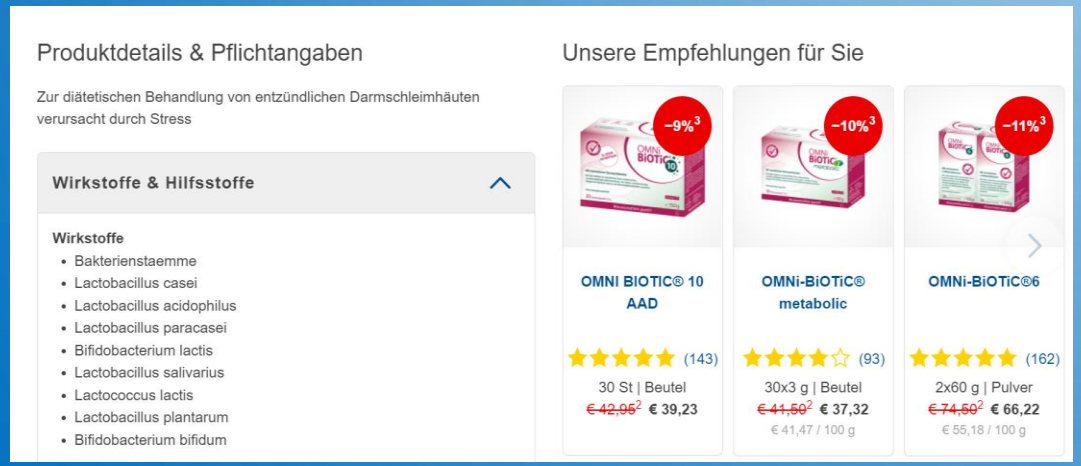
SPECIES

- LACTOBACILLI:
  - PRESENT IN GIT, ORAL CAVITY AND VAGINA OF HUMANS [WALTER, 2008]
  - WIDESPREAD USE IN PRODUCTION AND FERMENTATION OF FOODS → ABILITY TO CONVERT HEXOSE SUGARS TO LACTIC ACID → PRESERVATION [FIJAN, 2014]
  - EXCELLENT FOR USE AS PROBIOTICS: HIGH TOLERANCE TO ACID AND BILE, CAPABILITY TO ADHERE TO INTESTINAL SURFACES [TULUMOGLU ET AL., 2013]
- BIFIDOBACTERIA:
  - FIRST COLONIZERS OF THE HUMAN GUT TOGETHER WITH LACTOBACILLI [TURRONI ET AL., 2012]
  - WELL KNOWN FOR RESISTANCE AGAINST BILE SALTS [FIJAN, 2014]

SPECIES

- BACILLUS SPECIES:
  - EITHER SPORE-FORMING AEROBIC OR FACULTATIVE AEROBIC, GRAM POSITIVE BACTERIA
  - B. SUBTILIS, B. CEREUS, B. COAGULANS ARE MEMBERS WITH PROBIOTIC CHARACTERISTICS [FIJAN, 2014]
- ESCHERICHA COLI NISSLE 1917:
  - ABLE TO COLONIZE THE GUT AND COMPETE WITH RESIDENT AND PATHOGENIC BACTERIA THROUGH MULTIPLE FITNESS FACTORS [BEHNSEN ET AL., 2013]
  - STIMULATION OF EPITHELIAL DEFENSIN PRODUCTION → RESTORATION OF DISTURBED GUT BARRIER
  - „SEALING EFFECT“ ON TIGHT JUNCTIONS OF ENTEROCYTES [SONNENBORN AND SCHULZE, 2009]

PROBIOTIC : SPECIES : STRAIN SPECIFICITY



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Beispiele stammspezifischer Wirkungen von Probiotika	
Abkürzungen: L: Lactobacillus; B: Bifidobacterium; Ssp: subspecies. Stammbezeichnung zwischen Klammern.	
L. acidophilus (LA1):	▪ wirkt bei der Milchzuckerverdauung mit. ▪ besitzt die Fähigkeit, wichtige Vitamine wie Folsäure, Vitamin B3 und B6 herzustellen, um sie dann dem Organismus zuzuführen.
L. bulgaricus (LB2):	▪ ist in der Lage, Milchzucker in Milchsäure umzusetzen. ▪ besitzt die Fähigkeit, den pH-Wert in einem günstigen Bereich zu halten, somit wird schädliches Bakterienwachstum eingedämmt.
L. casei (LC03):	▪ spielt bei der Abwehr von Salmonellen oder ähnlichen schädlichen Bakterien eine sehr wichtige Rolle ▪ trägt dazu bei, gravierende Infektionen zu verhindern.
L. salviarius (LS04):	▪ wirkt generell positiv auf den Zustand der Haut. ▪ stärkt die Mundschleimhaut und hilft, Zahnfleischbluten vorzubeugen bzw. zu verhindern.
L. paracasei (101/37):	▪ wirkt bereits im Mund und beugt der Entstehung von Karies vor. ▪ verbessert die Immunabwehr gegen eine Vielzahl von Krankheitserregern.
L. rhamnosus (LR1):	▪ sehr widerstandsfähig gegenüber Magensäure und Gallensäften im Dünndarm. Es schützt dadurch andere Milchsäurebakterien auf ihrem Weg durch den Dickdarm.
L. plantarum (14D):	▪ wirkt bei der Verdauung von Milch mit und hat eine positive Wirkung auf den Cholesterinspiegel.
B. longum ssp. infantis (Bi-26):	▪ ist ein wichtiger Vitaminproduzent (Folsäure, Vitamin B1, Niacin, B6 und Biotin). ▪ kann Durchfall entgegenwirken, indem es die auslösenden Bakterien verdrängt.
B. animalis ssp. lactis (Bi1):	▪ bildet keine Gase und wirkt somit Blähungen entgegen. ▪ heftet sich an die Darmschleimhaut an und steuert dort die Durchlässigkeit. ▪ stimuliert die Immunabwehr.
B. longum (BL21):	▪ hat eine hohe Bedeutung für die Immunabwehr und die Bildung von Vitaminen. ▪ unterstützt die Aufnahme von Calcium (Anzahl verringert sich im Alter).
B. breve (Bbr8):	▪ verarbeitet viele schwerverdauliche Substanzen und verbessert somit die Darmtätigkeit. ▪ verringert sowohl das Auftreten von Durchfall, als auch von Verstopfung. ▪ verringert Allergien (Überreaktion von Immunzellen wird gehemmt – Anzahl verringert sich im Alter).
B. bifidum (BB04):	▪ kann verschiedene Säuren produzieren und hat einen positiven Einfluss auf die Immunabwehr.
Streptococus thermophilus (Z57):	▪ lindert Antibiotika-assoziierten Durchfall.

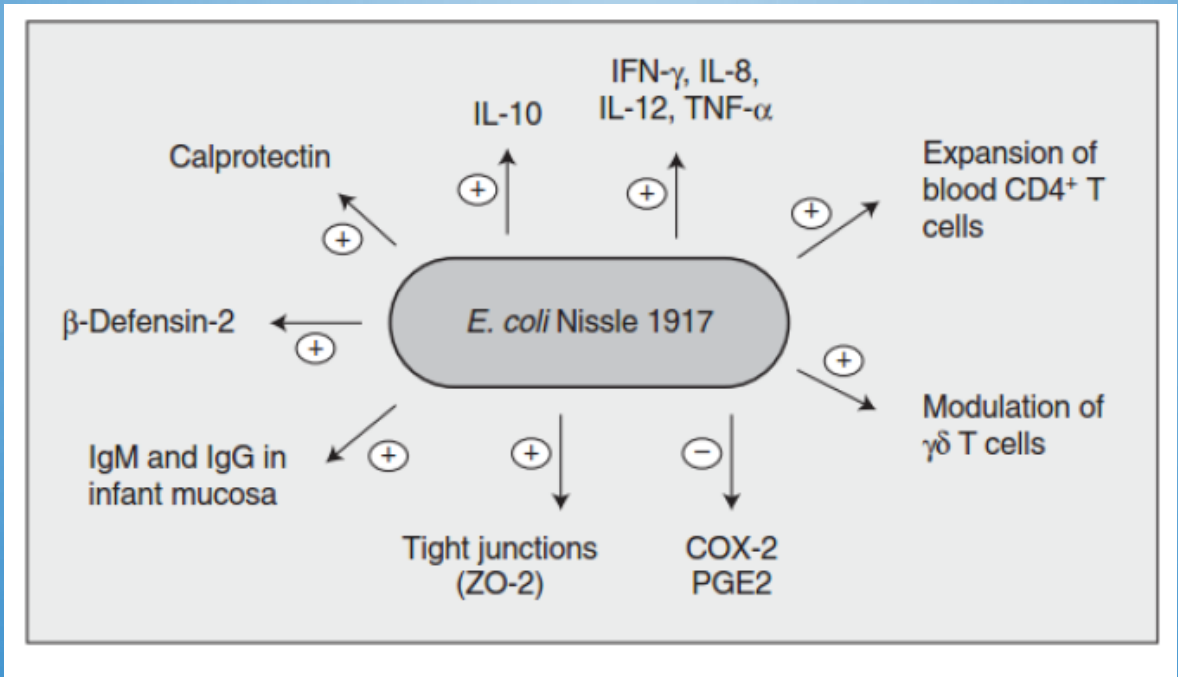


FIGURE 2. VARIOUS WAYS OF IMMUNE MODULATION BY E. COLI NISSLE 1917 (SUMMARY OF DATA FROM IN VITRO AND IN VIVO EXPERIMENTS) [BEHNSEN ET AL., 2013]

TREATMENT OF ANTIBIOTIC ASSOCIATED DIARRHEA WITH PROBIOTICS - META-ANALYSES

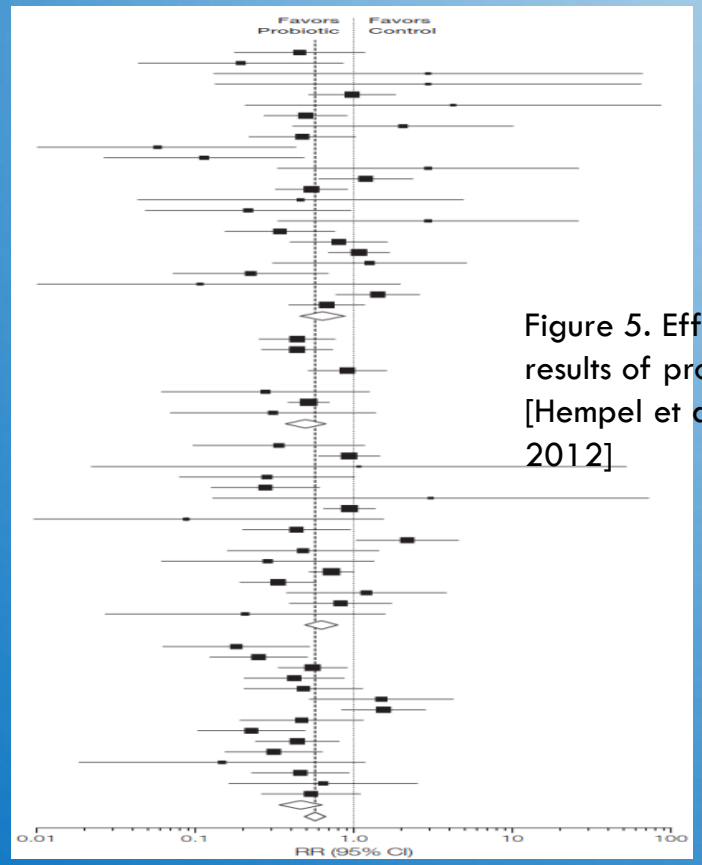


Figure 5. Efficacy results of probiotics [Hempel et al., 2012]

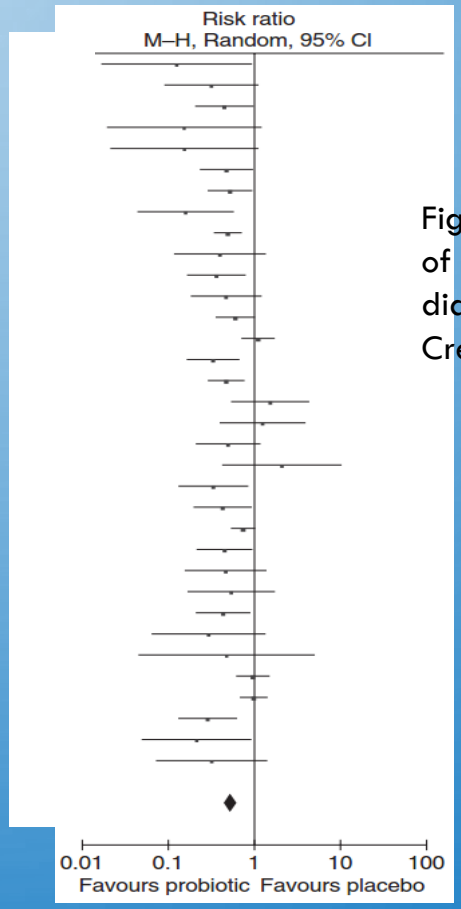


Figure 6. Developement of antibiotic associated diarrhea [Videlock and Cremonini, 2012]

TREATMENT OF ACUTE DIARRHEA WITH PROBIOTICS – META-ANALYSES

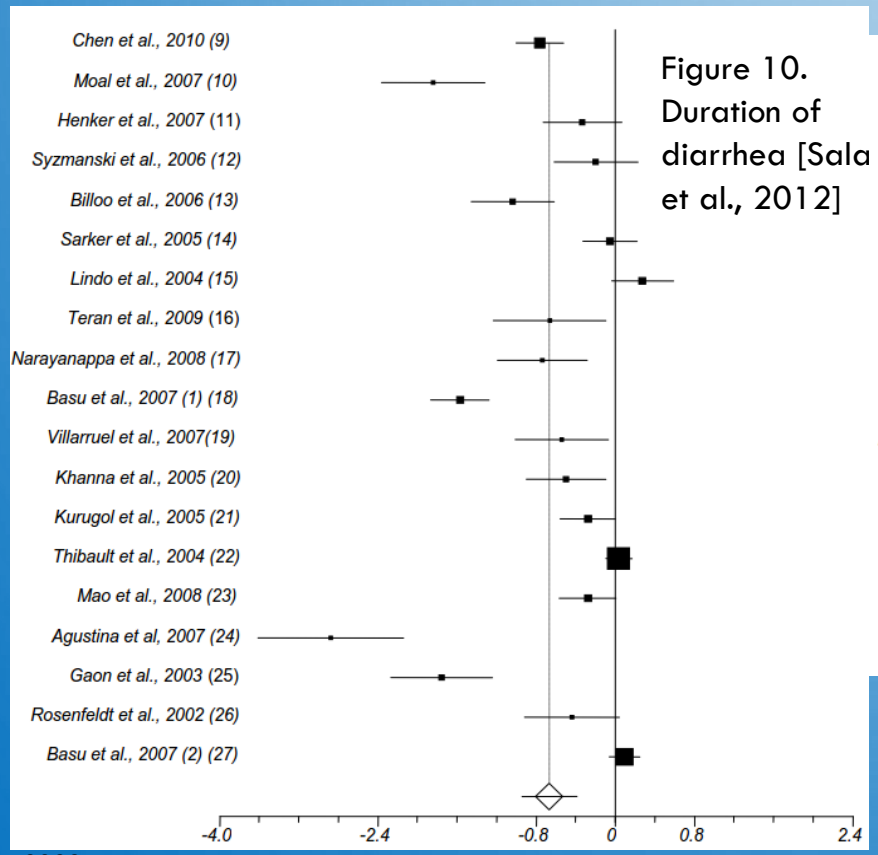


Figure 10. Duration of diarrhea [Sala et al., 2012]

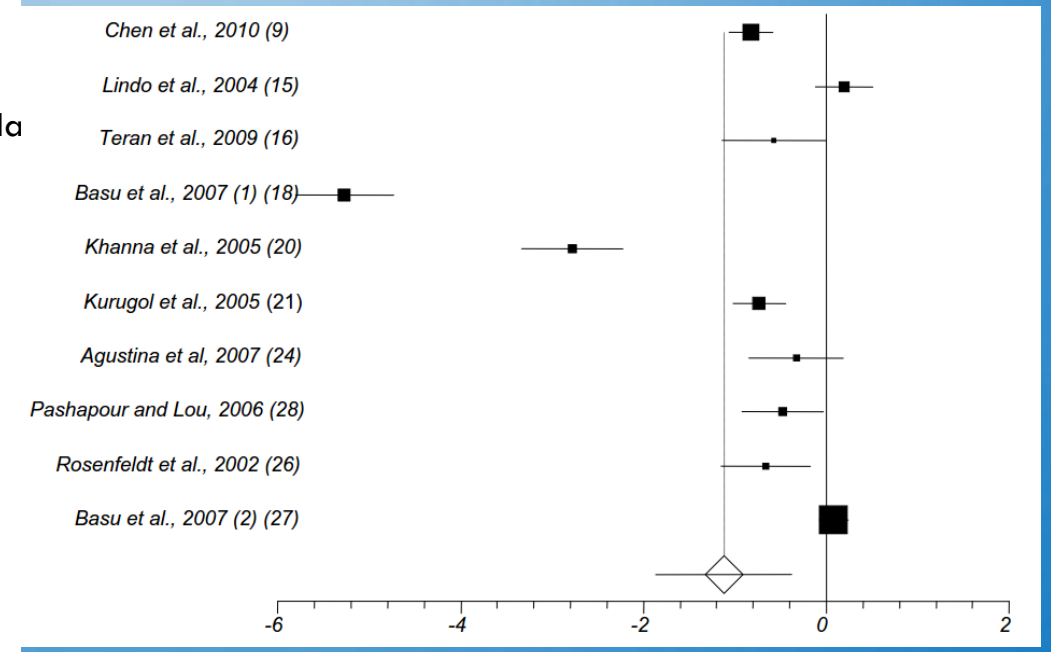


Figure 11. Duration of hospitalization [Salari et al., 2012]

PROBIOTIC NEW WAYS

nature › nature medicine › letters › article

Letter | Published: 01 July 2019

Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study

Clara Depommier, Amandine Everard, Céline Druart, Hubert Plovier, Matthias Van Hul, Sara Vieira-Silva, Gwen Falony, Jeroen Raes, Dominique Maiter, Nathalie M. Delzenne, Marie de Barsy, Audrey Loumaye, Michel P. Hermans, Jean-Paul Thissen, Willem M. de Vos & Patrice D. Cani

Nature Medicine **25**, 1096–1103 (2019) | Cite this article

Probiotika: Sind tote Bakterien wirksamer als lebende?

Das Prinzip von Probiotika kennt jeder – egal ob als Joghurt oder Supplement: Dem Körper werden mit der Nahrung Bakterien zugeführt, die sich im Darm vermehren und gesundheitsförderlich sein sollen. Soweit die Theorie. Doch eine aktuelle Studie wirft Fragen auf.

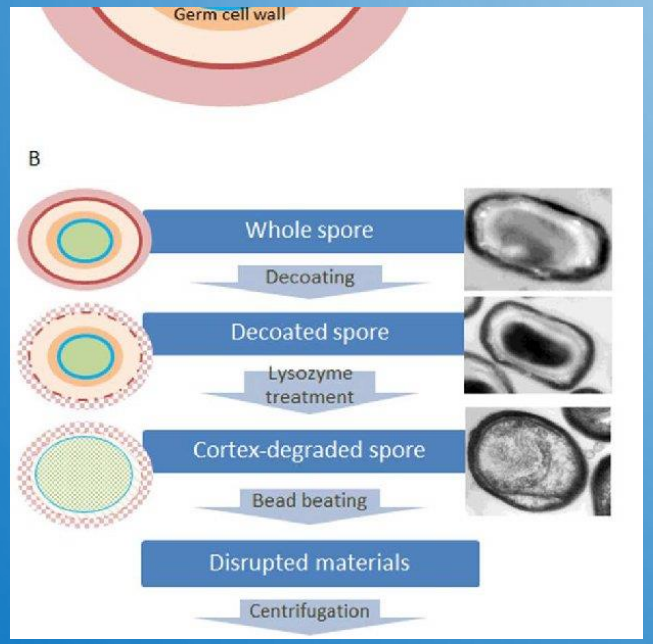
Commensal Obligate Anaerobic Bacteria and Health: Production, Storage, and Delivery Strategies

José Carlos Andrade[1†], Diana Almeida[2†], Melany Domingos[2], Catarina Leal Seabra[2‡], Daniela Machado[2], Ana Cristina Freitas[2*] and Ana Maria Gomes[2]

[1]CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Gandra, Portugal
[2]CBQF - Centro de Biotecnologia e Química Fina - Laboratório Associado, Escola Superior de Biotecnologia, Universidade Católica Portuguesa, Porto, Portugal

In the last years several human commensals have emerged from the gut microbiota studies as potential probiotics or therapeutic agents. Strains of human gut inhabitants such as *Akkermansia*, *Bacteroides*, or *Faecalibacterium* have shown several interesting bioactivities and are thus currently being considered as food supplements or as live biotherapeutics, as is already the case with other human commensals such as bifidobacteria. The large-scale use of

SPORES

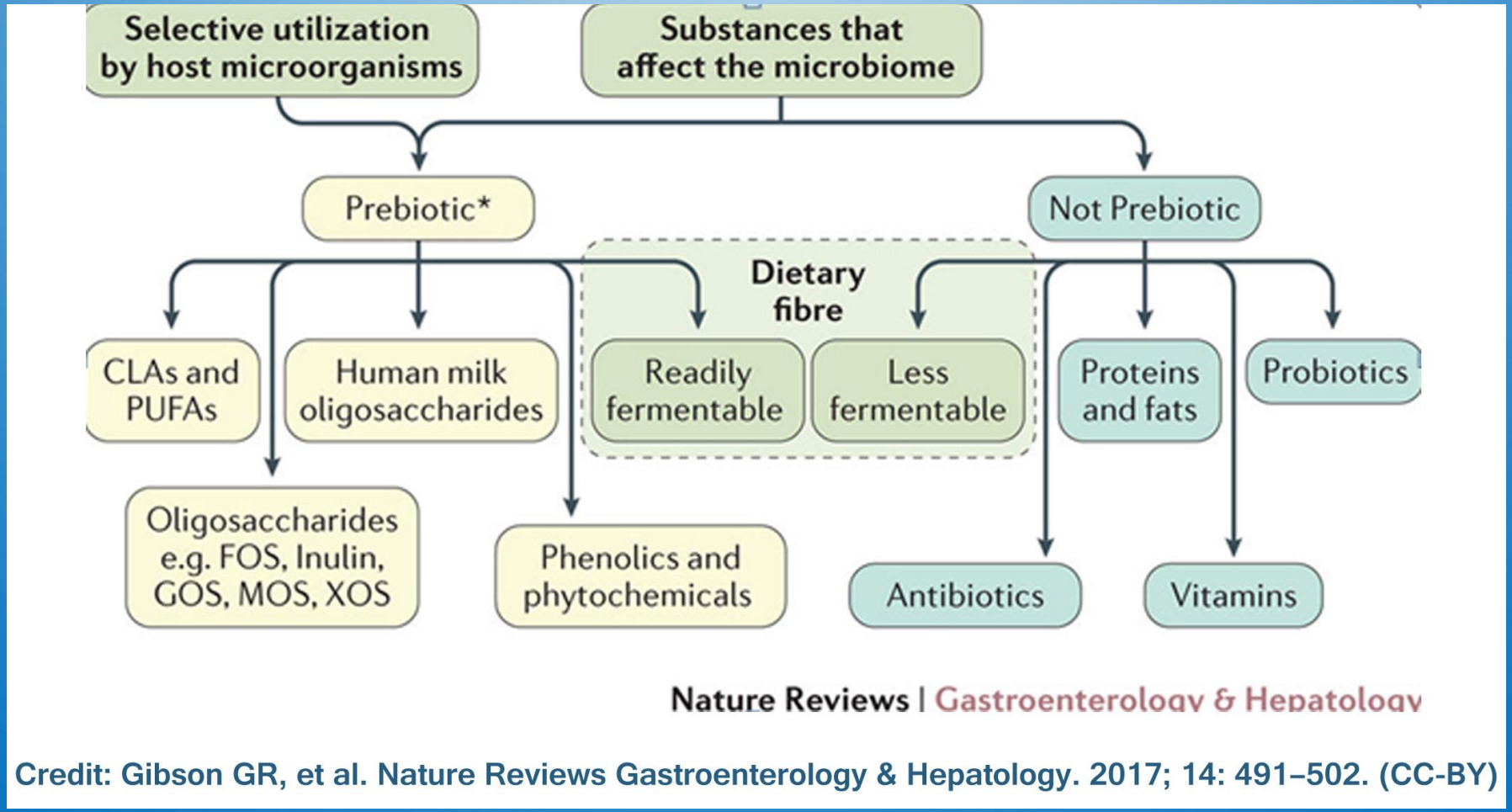


The ingredient

According to Deerland, DE111 is a genome sequenced strain of *Bacillus subtilis*. The genome sequencing confirmed the strain contained no plasmids, antibiotic resistant or deleterious genes; the human clinical studies showed the strain's ability to control microbial populations, aid in digestion and maintain general health. Because the strain is a spore former it remains viable under a wide temperature and pH range, making it ideal for use in supplements as well as food and beverages.

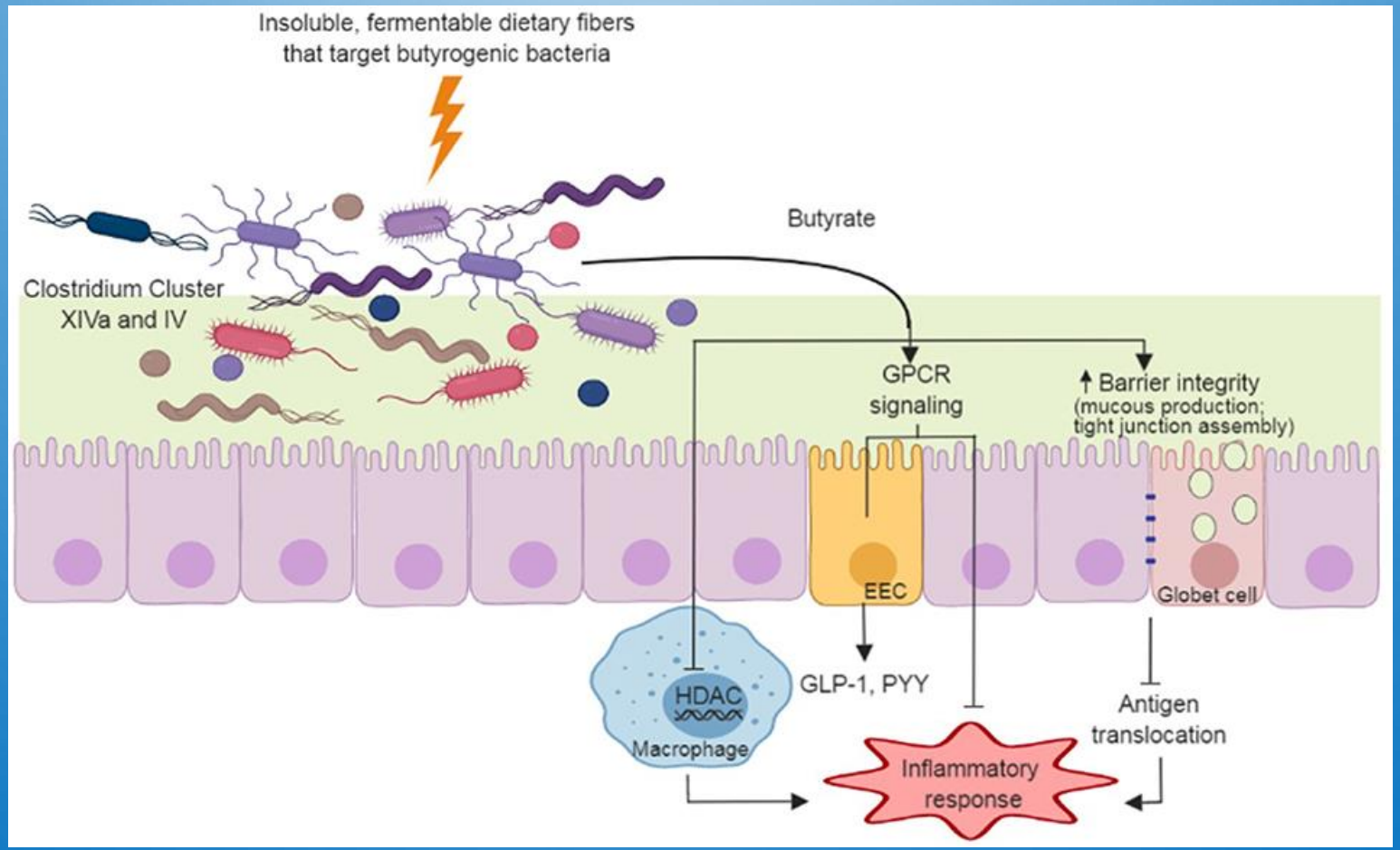
Source: *Journal of Probiotics & Health*
2017, 5:4, doi: 10.4172/2329-8901.1000189
"The Effect of Bacillus subtilis *DE111 on the Daily Bowel Movement Profile for People with Occasional Gastrointestinal Irregularity"*
Authors: A.M. Cuentas et al.

PREBIOTICS WHAT IS IT?

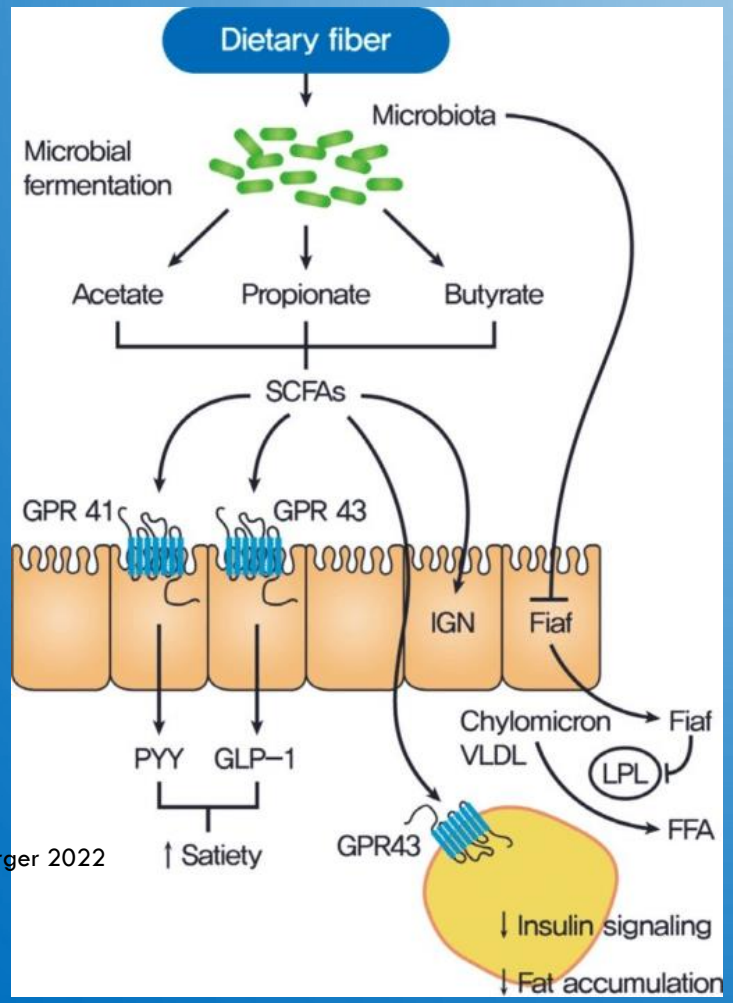


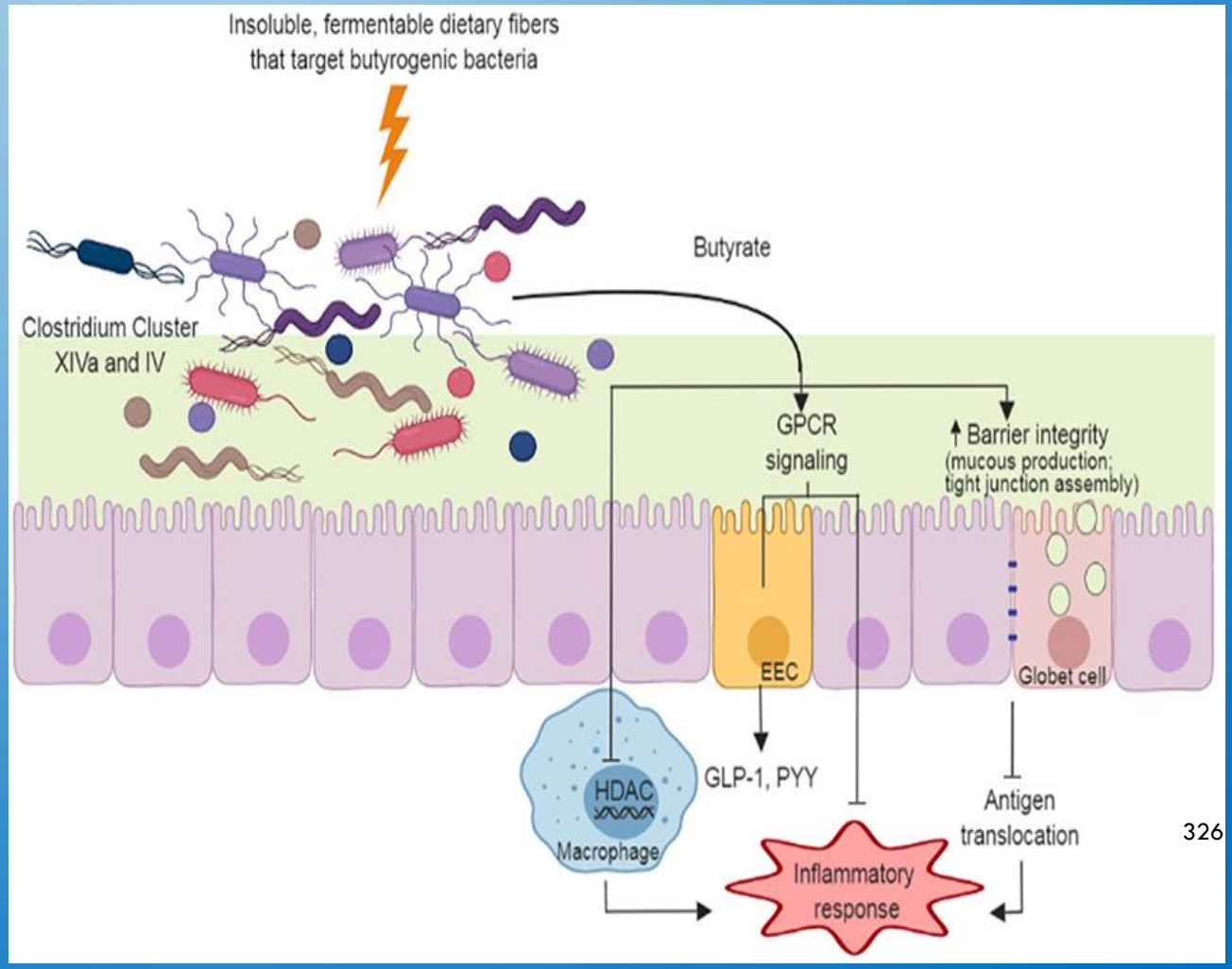
Credit: Gibson GR, et al. Nature Reviews Gastroenterology & Hepatology. 2017; 14: 491–502. (CC-BY)

FIBERS AND SCFA



FIBERS AND OBESITY, BUTYROGENIC





Pharmacokinetic study of butyric acid administered in vivo as sodium and arginine butyrate salts

Philippe Daniel [1,*], Michel Brazier [2], Italina Cerutti [3], François Pieri [1], Isabelle Tardivel [3], Gérard Desmet [2], Jean Baillet [4] and Charles Chany [3]

[1] Laboratoire Central de Virologie and [2] Laboratoire d'Hormonologie, C.H.R.U. d'Amiens, Hôpital Sud, Amiens, [3] INSERM Unité 43, Hôpital Saint Vincent de Paul, Paris and [4] Service de Médecine E, C.H.R.U. d'AMIENS, Hôpital Nord, Amiens (France)

(Received 10 April 1988; revision received 6 January 1989; accepted 18 January 1989)

Key words: Pharmacokinetics; Butyrate; Experimental animal; Man

Summary

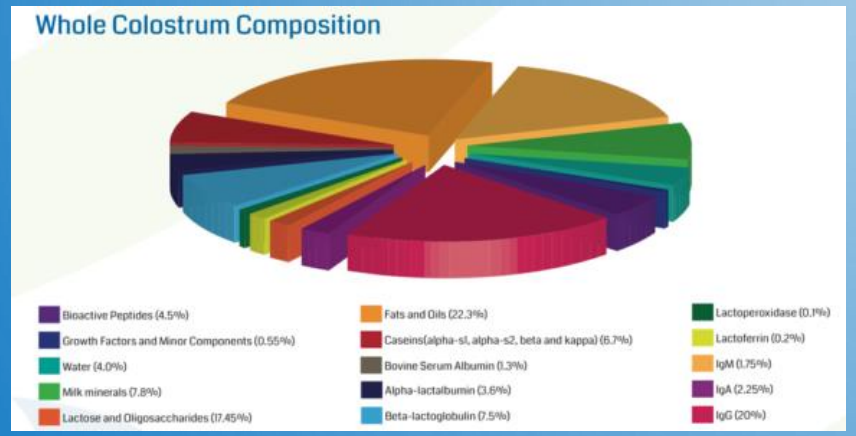
Considering that butyrate-treated malignant cells can recover in a transitory fashion a non-cancerous phenotype, the authors carried out a pharmacokinetics study of butyric acid injected as sodium or arginine salts for possible antitumor therapies.

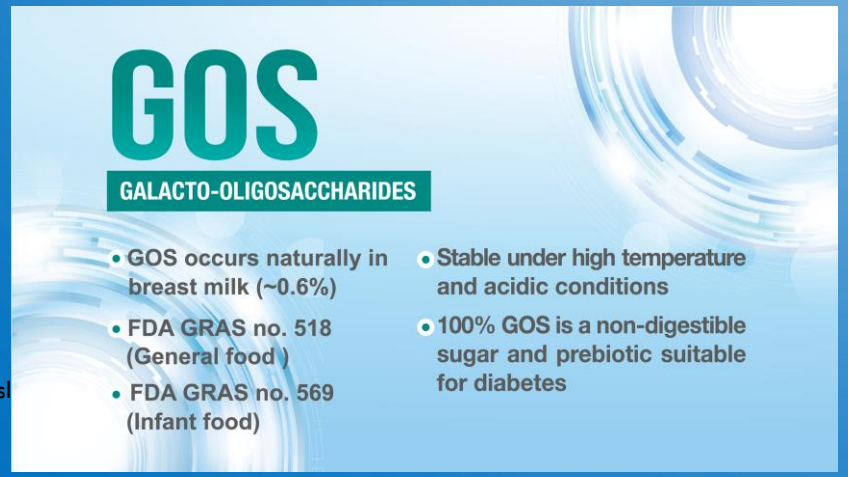
In the case of 1-^{14}C-labelled butyrate, the appearance of radioactivity in the blood of injected mice is rapid and some of it is maintained for relatively long periods in different organs, mainly the liver. However, no precision can be given about the structure of radioactive compounds in blood and tissues.

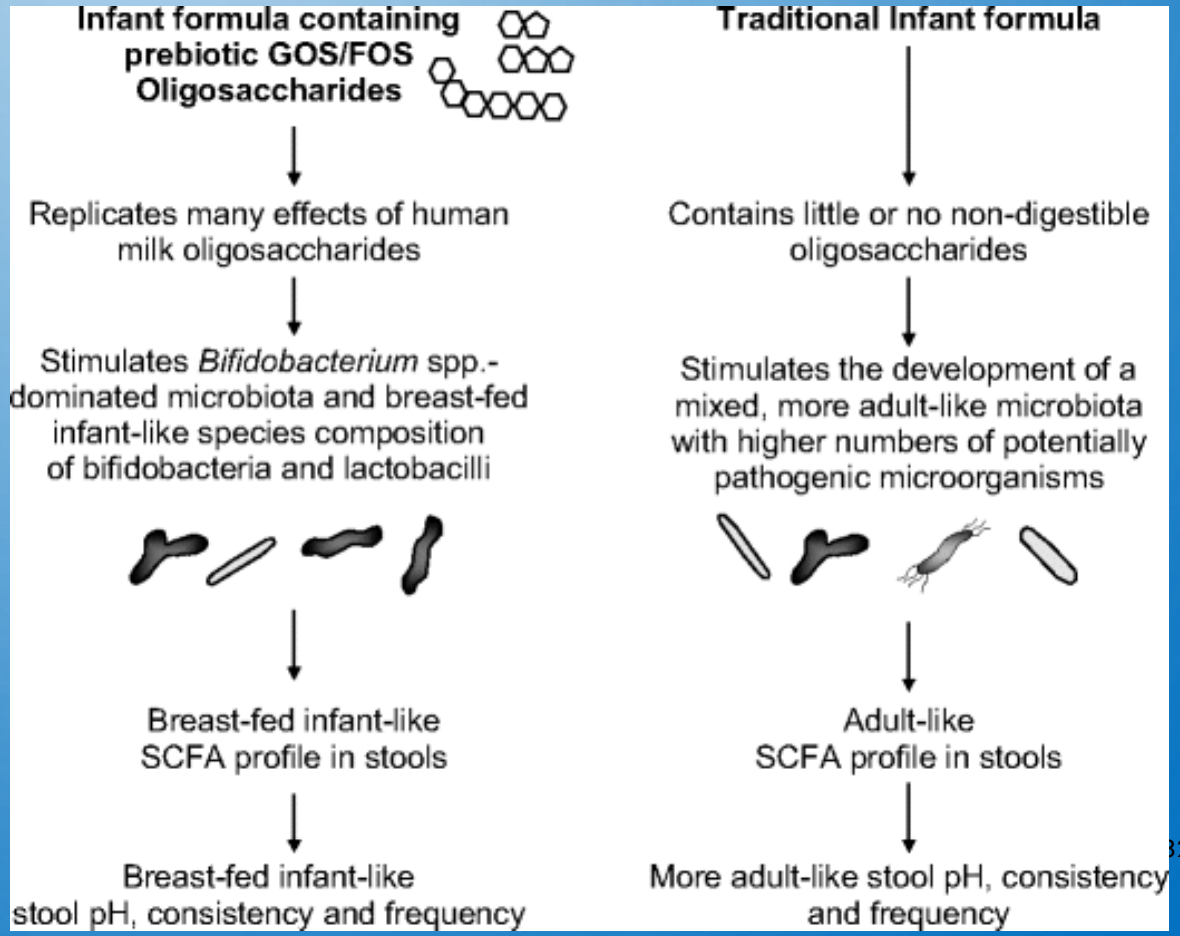
Using gas–liquid chromatography, the authors studied the metabolism of butyrate in both animals and man. In mice and rabbits, the half-life is < 5 min. In man, the butyric acid elimination curve can be divided into two parts corresponding to two half-lives: for the first (0.5 min), the slope suggests an accelerated excretion, while for the following (13.7 min), a slow plateau is observed.

The rapid elimination of butyrate is a limiting factor for practical applications. However, the lack of toxicity supports its use in human therapy.

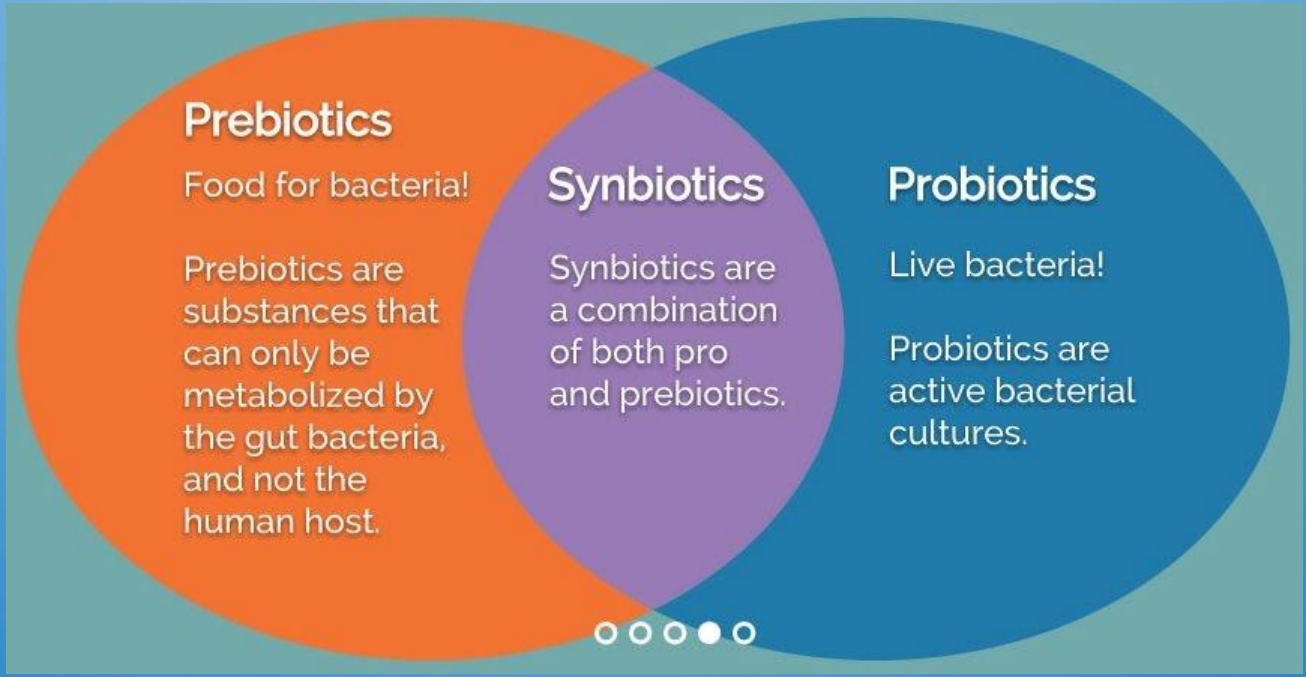
FORUMLA DIETS, THE WAY TO MIMIC BREAT MILK



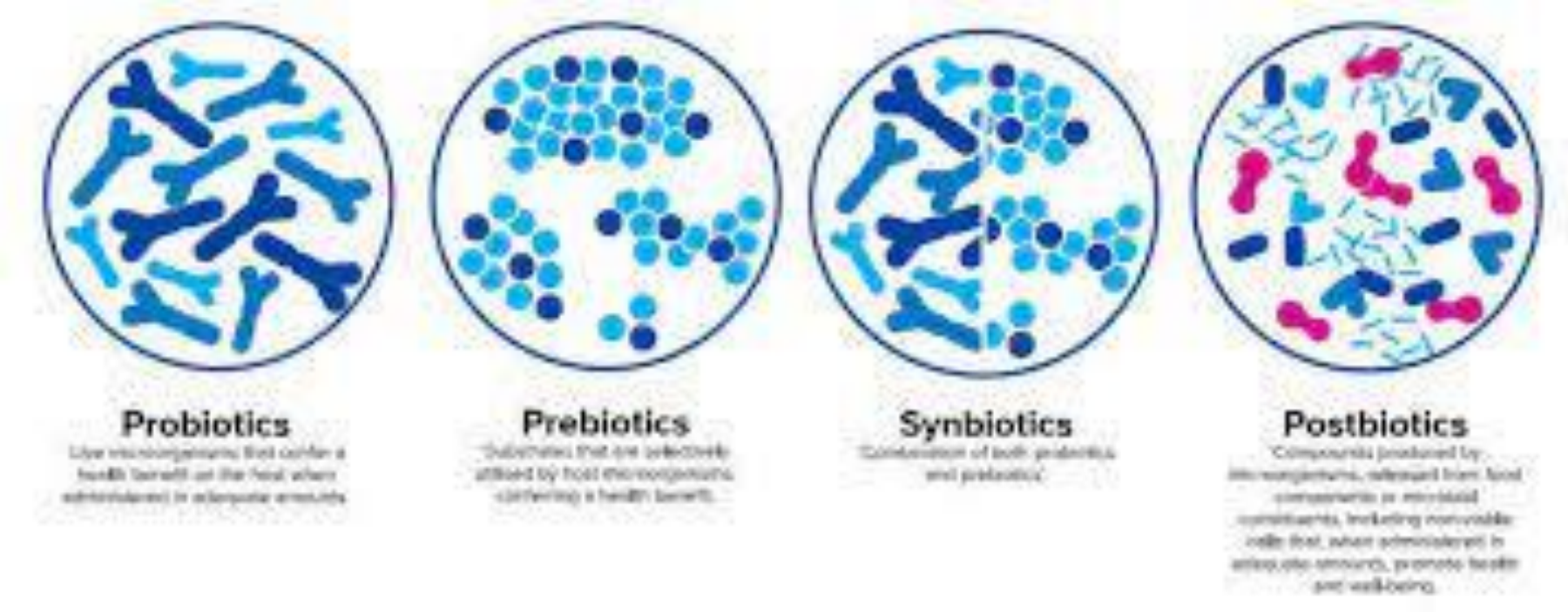




SYNBIOTICS


Prebiotics
Food for bacteria!
Prebiotics are substances that can only be metabolized by the gut bacteria, and not the human host.
Synbiotics
Synbiotics are a combination of both pro and prebiotics.
Probiotics
Live bacteria!
Probiotics are active bacterial cultures.

POSTBIOTICS



POSTBIOTICS

- **Bacteriocins** *(protective compounds that make life hard for the bad guys)**
- **Enzymes** *(help to digest food, get rid of toxins and assist other metabolic processes)**
- **Vitamins** *(like the B's and vitamin K)**
- **Amino acids** *(building blocks of protein)**
- **Neurotransmitters** *(carry messages between the nerves and brain and can even affect appetite)**
- **Immune-signaling compounds** *(they support the body's immune cells)**
- **Short-chain fatty acids** *(created from fiber, they keep the intestinal lining strong and healthy)**
- **Nitric oxide** *(crucial for cardiovascular health)**
- **Organic acids** *(such as Fulvic and Humic acid. They combine with minerals, making them easier to absorb and help maintain the correct pH in the GI tract)**

AGING, AGEOTYPES AND PREVENTION

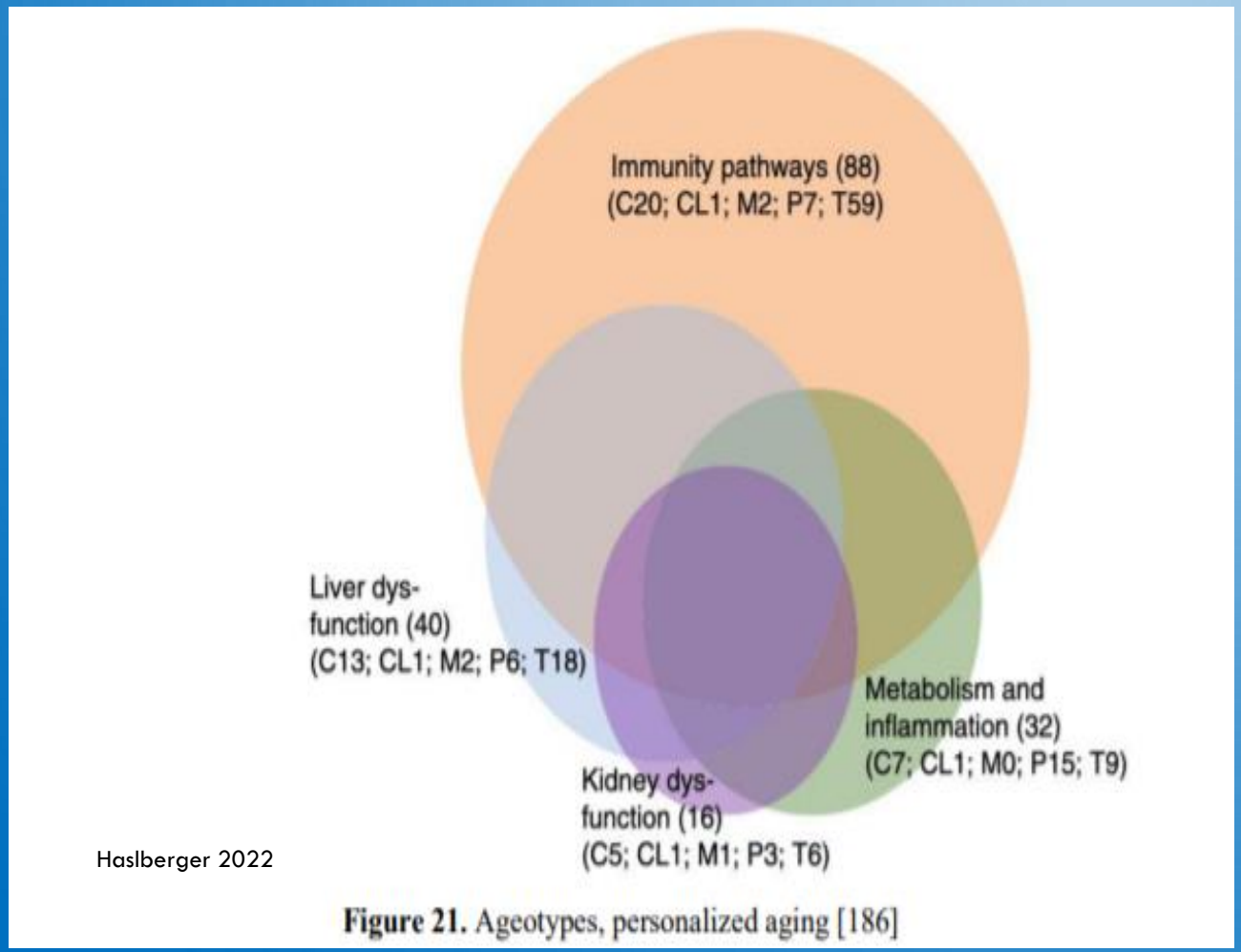
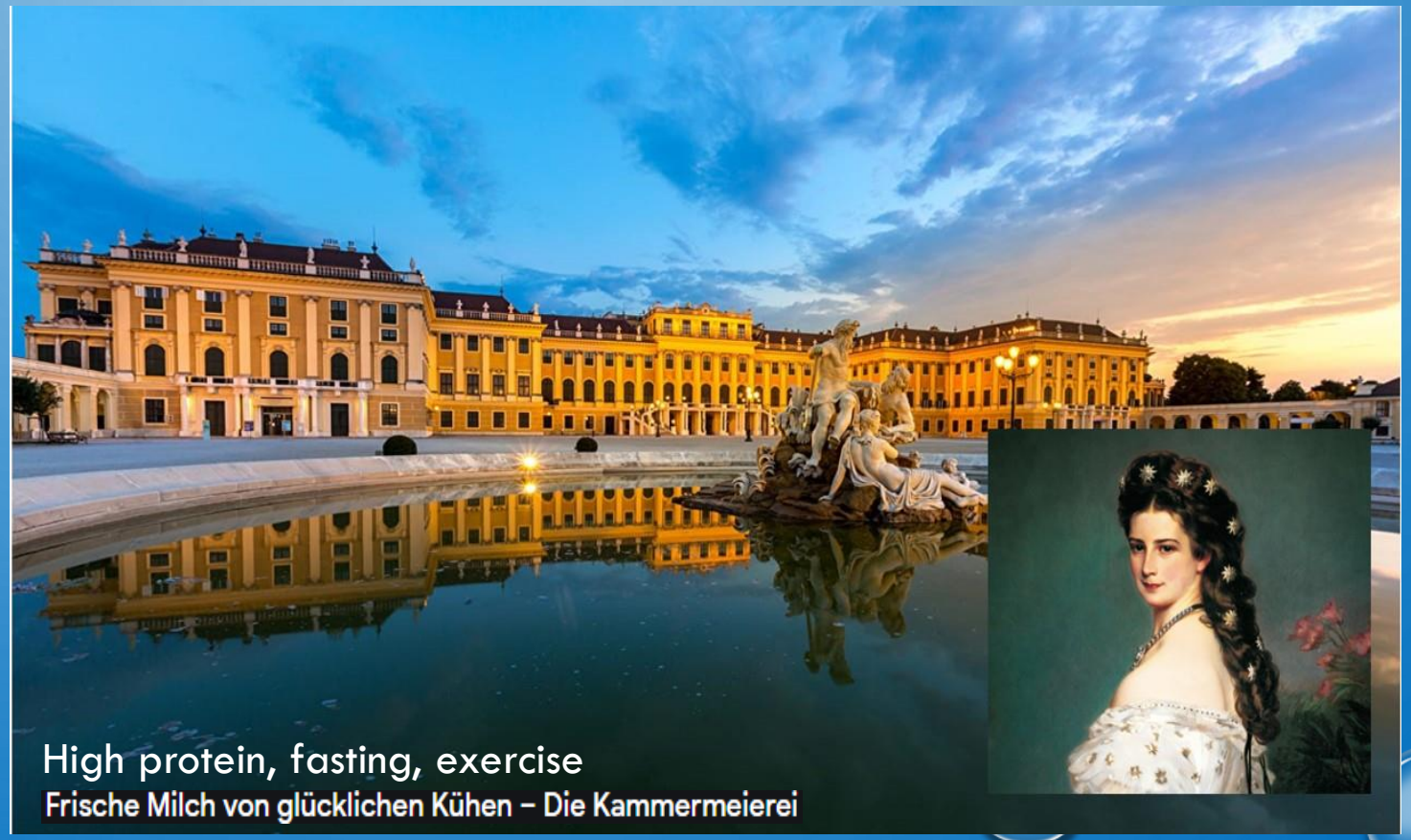
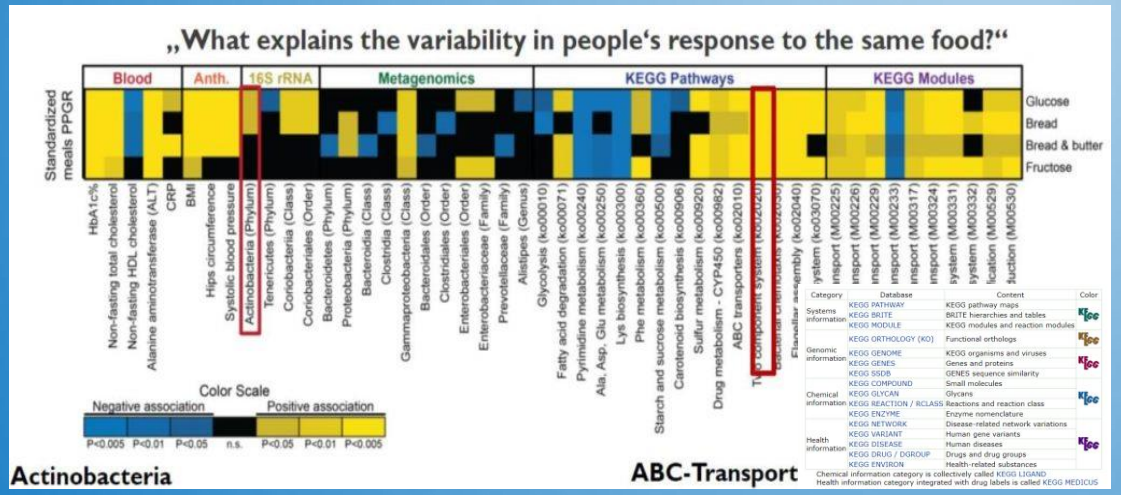


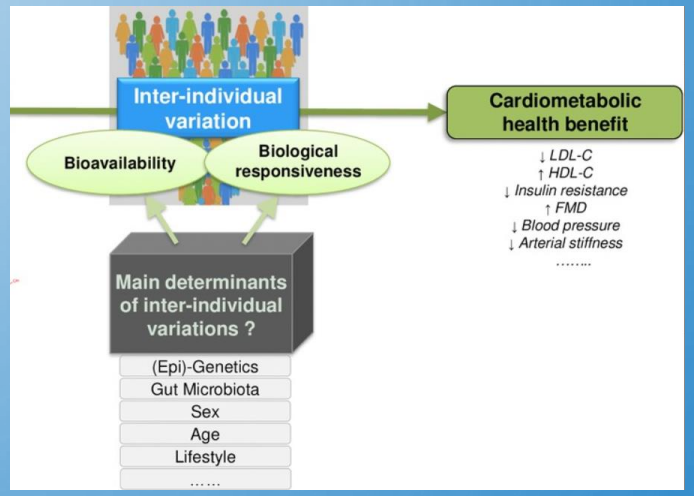
Figure 21. Ageotypes, personalized aging [186]

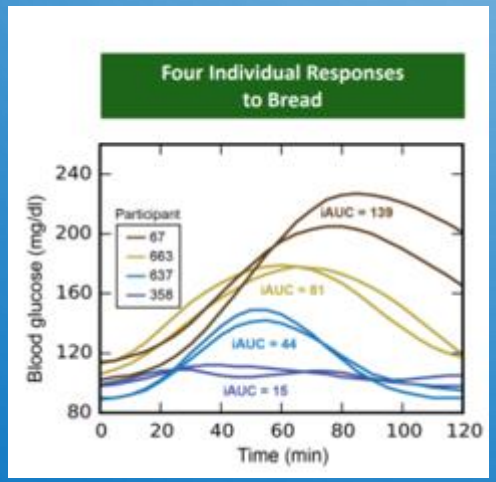
Special diets



SCIENCE: HIGHLY DIFFERENT PERSONAL RESPONSES TO DIETS, EG POST- PRANDIAL GLYCEMIC RESPONSES, EXPLANATIONS ?







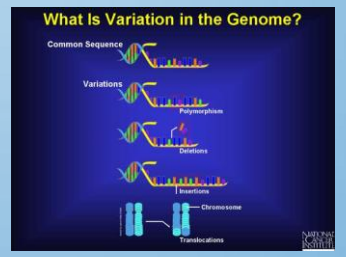
Different people have different, opposite responses to standardized meal, bread, Zeevi et al., 2015, Cell

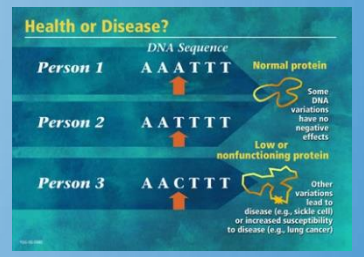

Review

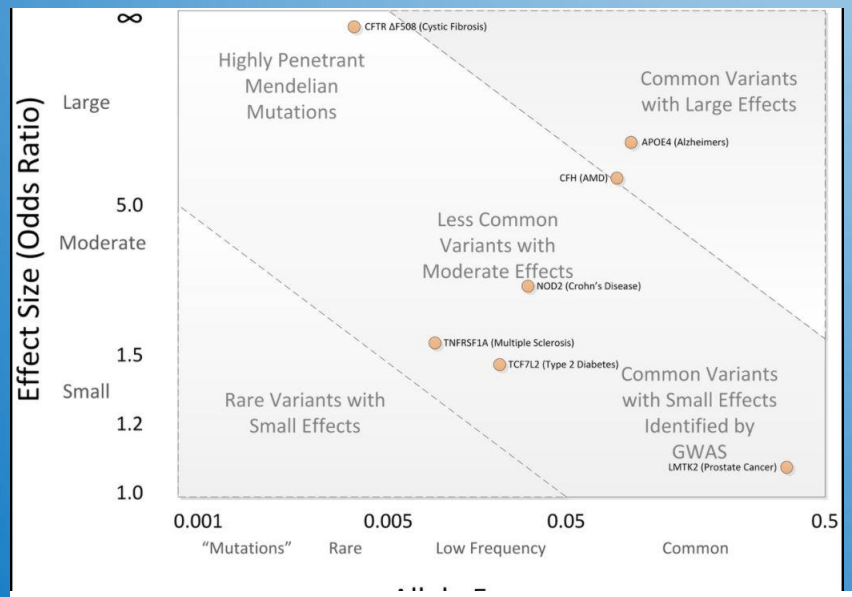
Addressing the inter-individual variation in response to consumption of plant food bioactives: Towards a better understanding of their role in healthy aging and cardiometabolic risk reduction

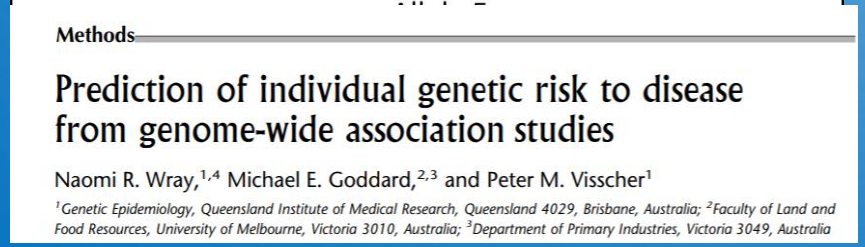
Claudine Manach[1], Dragan Milenkovic[1], Tom Van de Wiele[2], Ana Rodriguez-Mateos[3], Baukje de Roos[4], Maria Teresa Garcia-Conesa[5], Rikard Landberg[6,7], Eileen R. Gibney[8], Marina Heinonen[9], Francisco Tomás-Barberán[5] and Christine Morand[1]

GWAS : SNPS, COMMON VARIANTS HAVE OFTEN ONLY MODERATE EFFECTS; IN DIFFERENT METABOLIC AREAS





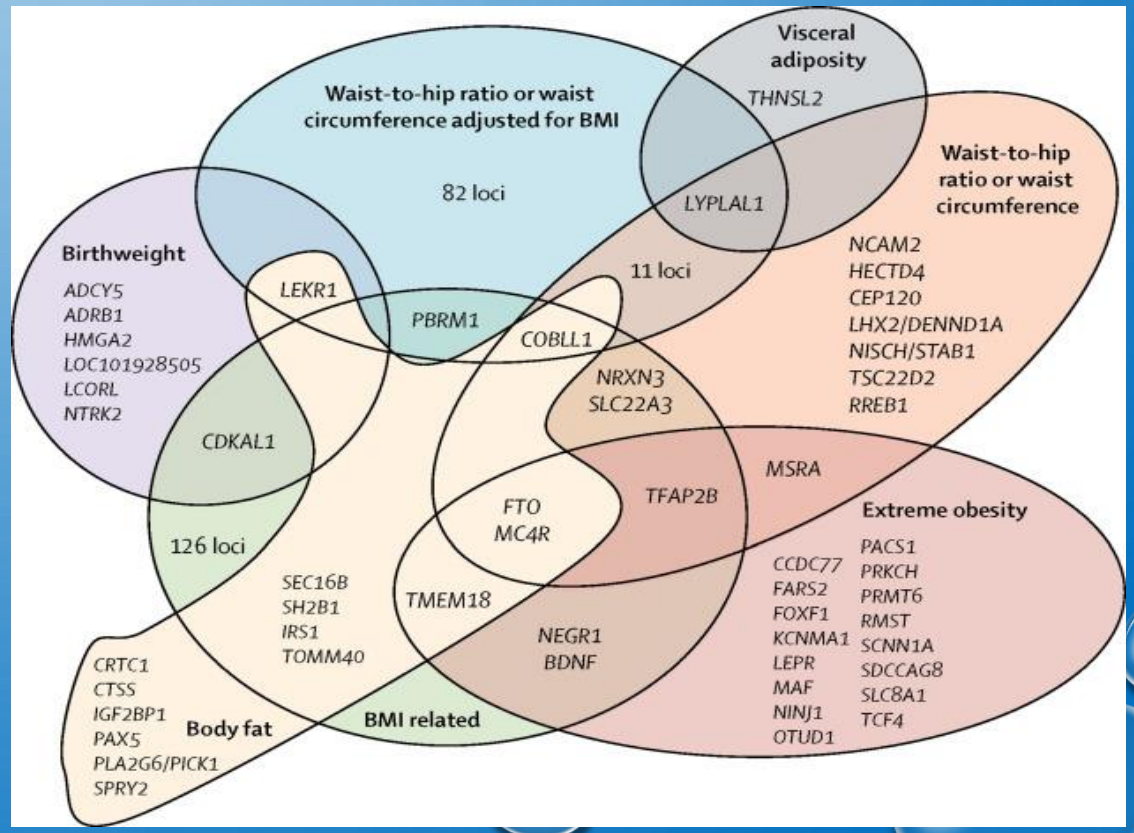



Methods

Prediction of individual genetic risk to disease from genome-wide association studies

Naomi R. Wray,[1,4] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

[1]Genetic Epidemiology, Queensland Institute of Medical Research, Queensland 4029, Brisbane, Australia; [2]Faculty of Land and Food Resources, University of Melbourne, Victoria 3010, Australia; [3]Department of Primary Industries, Victoria 3049, Australia



Haslberger 2022

DESPITE LOW PENETRANCE OF SNPS, D-T-C GENETIC TESTING FOR NUTRITIONAL ADVICE

Computational and Structural Biotechnology Journal 19 (2021) 3747–3754

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

A survey of direct-to-consumer genotype data, and quality control tool (*GenomePrep*) for research

Chang Lu [a,*], Bastian Greshake Tzovaras [b], Julian Gough [a]

[a] MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, UK
[b] Center for Research and Interdisciplinarity (CRI), Université de Paris, INSERM U1284, Paris, France

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Open genome
Personal genome
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ABSTRACT

Two major forces have contributed to the fast growth of human genetic data. One from medical research supported by governments and academic institutes; the other from direct-to-consumer (DTC) sequencing companies. While the former benefits from meticulously designed sequencing standards and quality control procedures, the latter comes in various formats and sequencing methods which are subject to changes over time and the particular needs of different companies. Thanks to the general public who shared their DNA data without constraint, here we provide a review for over 7000 genomes made public between 2011 and 2020, and produced by over six DTC sequencing companies. An open source tool-kit to systematically parse, quality check and filter genome files and statistically problematic alleles is provided to prepare consumer DNA datasets for research. The *GenomePrep* output is available in two common DNA datafile formats to enable further analysis with other tools. We also provide for download the combined output for all OpenSNP array genomes processed in this paper in a single data freeze file.

For diseases controlled by 1000 loci of mean relative risk of only 1.04, a case-control study with 10,000 cases and controls can lead to selection of ~75 loci that explain >50% of the genetic variance. The 5% of people with the highest predicted risk are three to seven times more likely to suffer the disease than the population average, depending on heritability and disease prevalence. Whether an individual with known genetic risk develops the disease depends on known and unknown environmental factors.

But:
FTO+MC4R : 1.7 % increase in fat mass

J Mol Med (Berl). 2009 May; 87(5): 537–46. doi: 10.1007/s00109-009-0451-0. Epub 2009 Mar 3.

Combined effects of MC4R and FTO common genetic variants on obesity in European general populations.

Cauchi S[1], Stutzmann F, Cavalcanti-Proença C, Durand E, Pouta A, Hartikainen AL, Marre M, Vol S, Tammelin T, Laitinen J, Gonzalez-Izquierdo A, Blakemore AI, Elliott P, Meyre D, Balkau B, Järvelin MR, Froguel P.

Author information

Abstract

Genome-wide association scans recently identified common polymorphisms, in intron 1 of FTO and 188 kb downstream MC4R, that modulate body mass index (BMI) and associate with increased risk of obesity. Although their individual contribution to obesity phenotype is modest, their combined effects and their interactions with environmental factors remained to be evaluated in large general populations from birth to adulthood. In the present study, we analyzed independent and combined effects of the FTO rs1421085 and MC4R rs17782313 risk alleles on BMI, fat mass, prevalence and incidence of obesity and subsequent type 2 diabetes (T2D) as well as their interactions with physical activity levels and gender in two European prospective population-based cohorts of 4,762 Finnish adolescents (NFBC 1966) and 3,167 French adults (D.E.S.I.R.). Compared to participants carrying neither FTC nor MC4R risk allele (20-24% of the populations), subjects with three or four risk alleles (7-10% of the populations) had a 3-fold increased susceptibility of developing obesity during childhood. In adults, their combined effects were more modest (approximately 1.8-fold increased risk) and associated with a 1.27% increase in fat mass (P = 0.001). Prospectively, we demonstrated that each FTO and MC4R risk allele increased obesity and T2D incidences by 24% (P = 0.02) and 21% (P = 0.02), respectively. However, the effect on T2D disappeared after adjustment for BMI. The Z-BMI and ponderal index of newborns homozygous for the rs1421085 C allele were 0.1 units (P = 0.02) and 0.27 g/cm(3) (P = 0.005) higher, respectively, than in those without FTO risk allele. The MC4R rs17782313 C allele was more associated with obesity and fat mass deposition in males than in females (P = 0.003 and P = 0.03, respectively) and low physical activity accentuated the effect of the FTO polymorphism on BMI increase and obesity prevalence (P = 0.008 and P = 0.01, respectively). In European general populations, the combined effects of common polymorphisms in FTO and MC4R are therefore additive, predictive of obesity and T2D, and may be influenced by interactions with physical activity levels and gender, respectively.

Science. 2007 May 11;316(5826):889-94. Epub 2007 Apr 12.

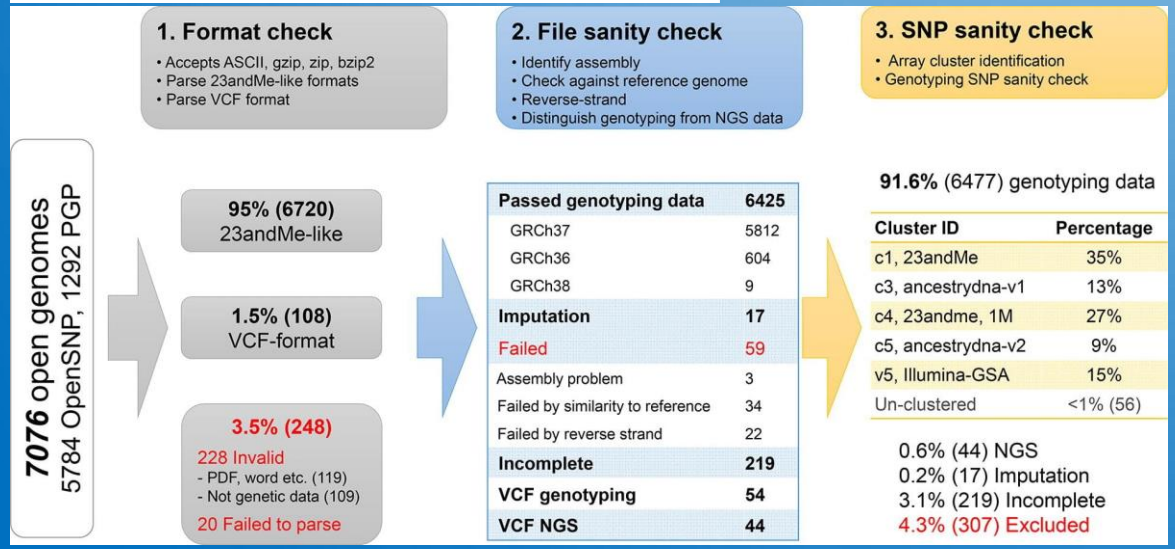
A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity.

Frayling TM[1], Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI.

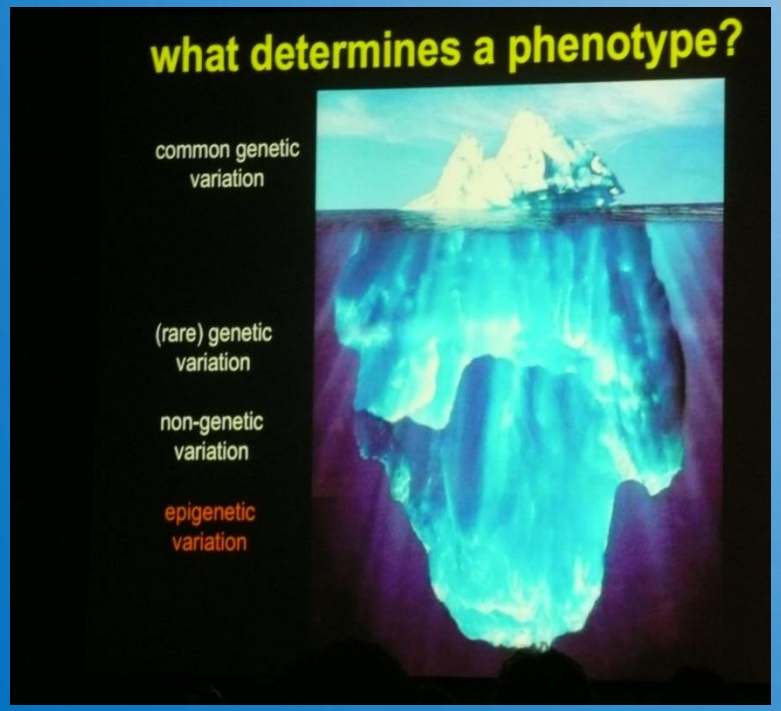
Author information

Abstract

Obesity is a serious international health problem that increases the risk of several common diseases. The genetic factors predisposing to obesity are poorly understood. A genome-wide search for type 2 diabetes-susceptibility genes identified a common variant in the FTO (fat mass and obesity associated) gene that predisposes to diabetes through an effect on body mass index (BMI). An additive association of the variant with BMI was replicated in 13 cohorts with 38,759 participants. The 16% of adults who are homozygous for the risk allele weighed about 3 kilograms more and had 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele. This association was observed from age 7 years upward and reflects a specific increase in fat mass.



MISSING HERITABILITY: WHAT IS MISSING TO UNDERSTAND A PHENOTYPE: GENE- ENVIRONMENT INTERACTIONS, EPIGENETICS, REVERSIBILITY



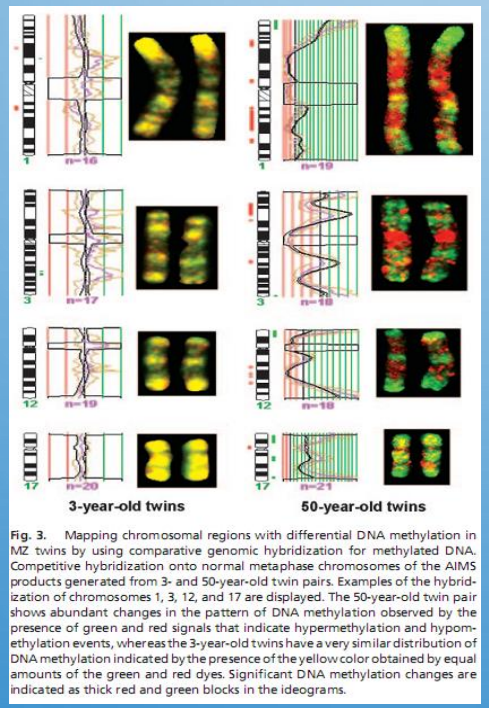
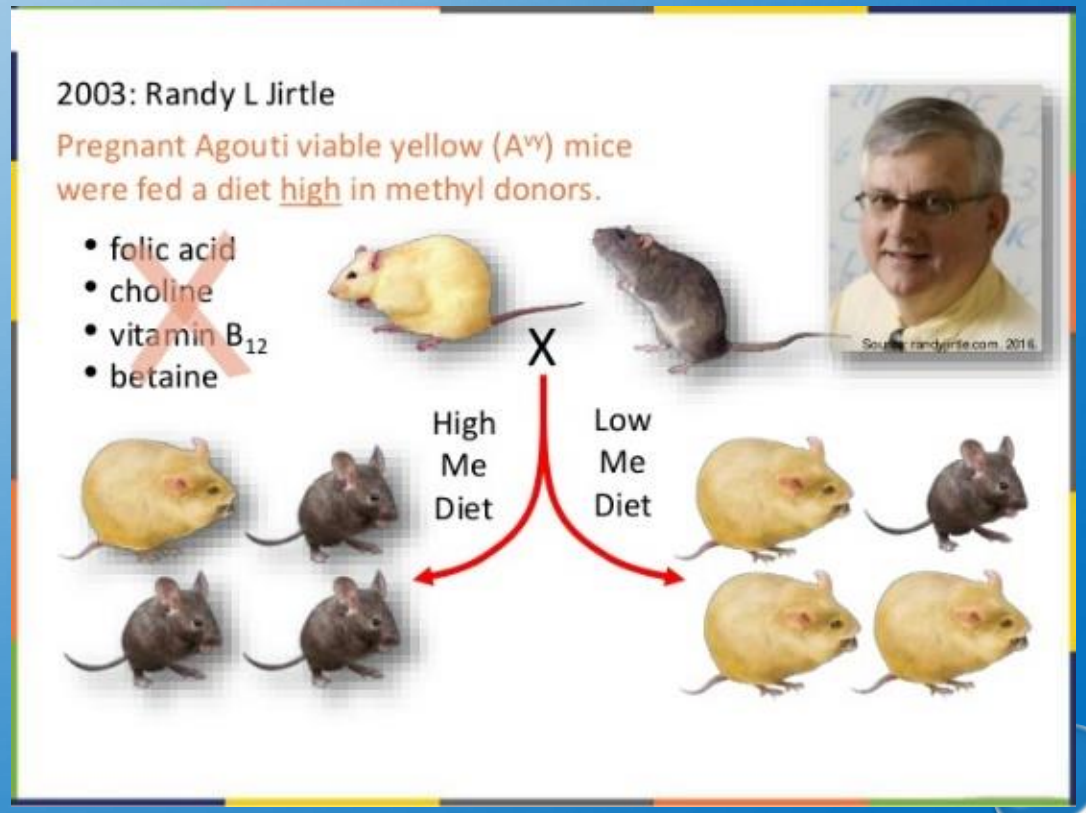
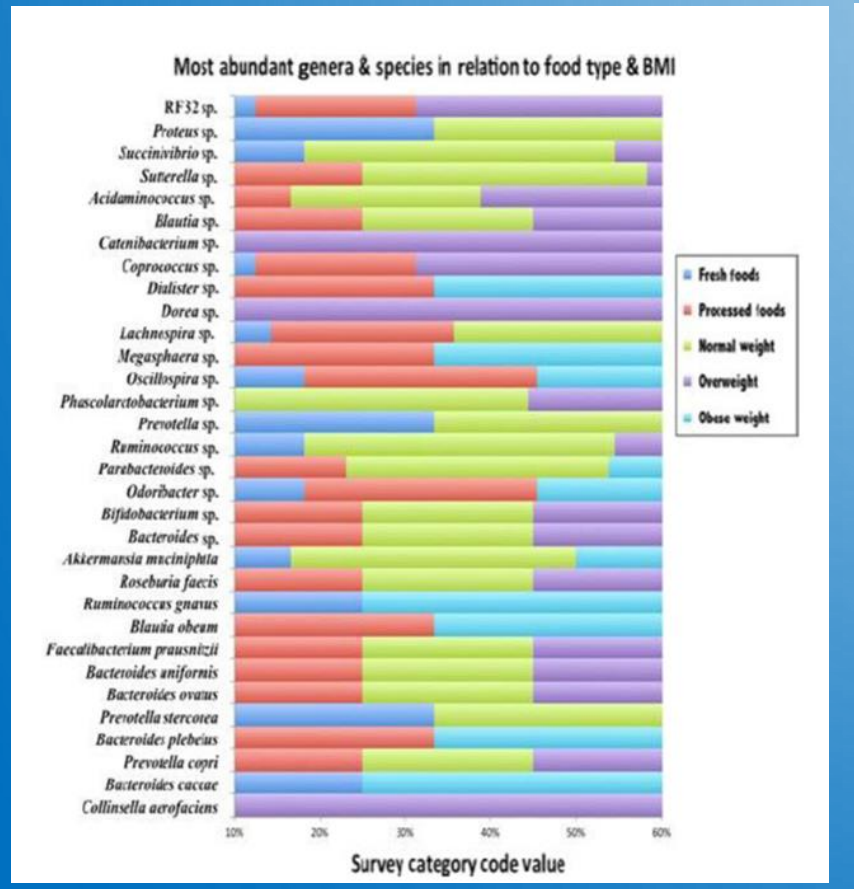
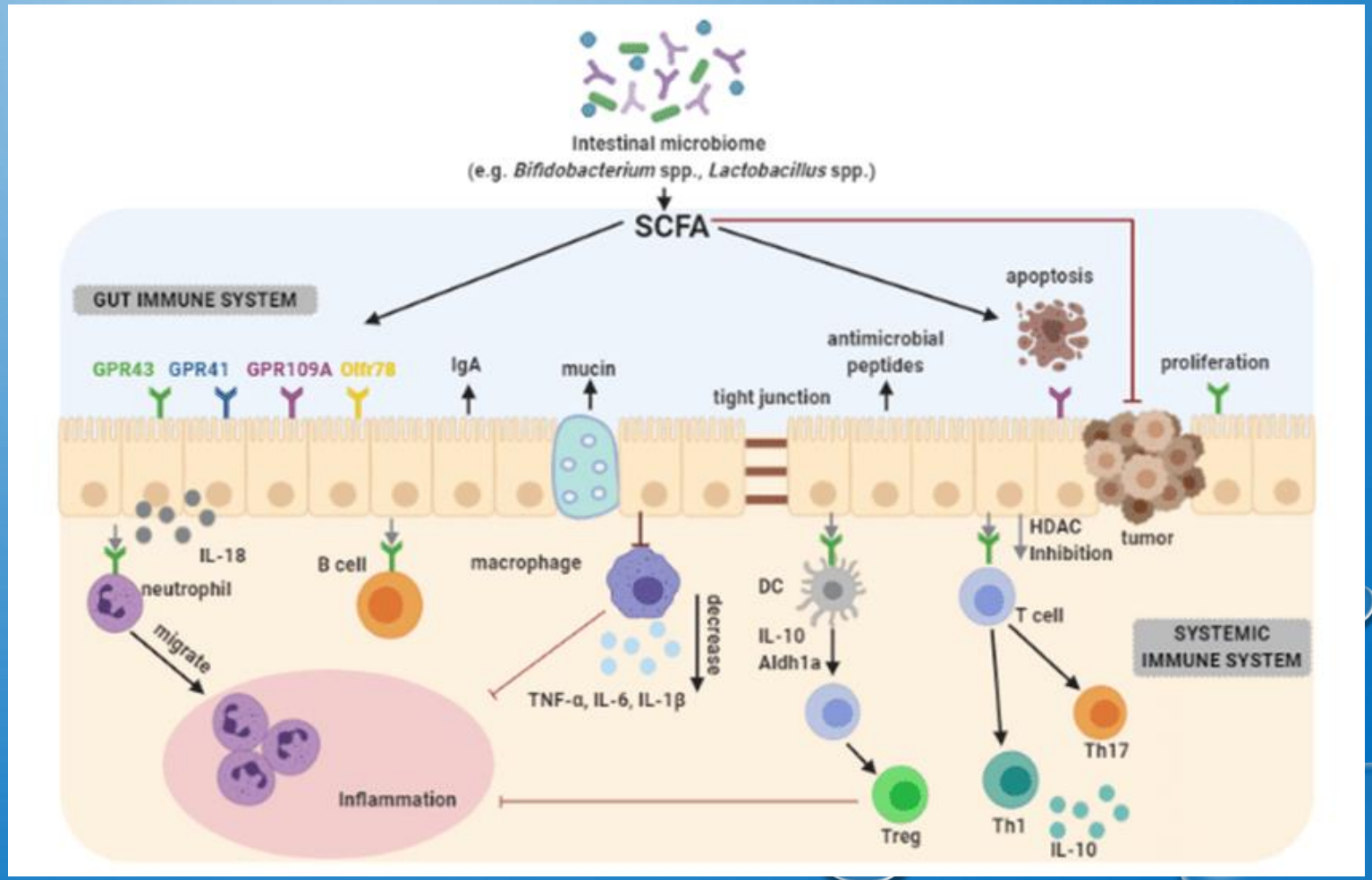


Fig. 3. Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA. Competitive hybridization onto normal metaphase chromosomes of the AIMS products generated from 3- and 50-year-old twin pairs. Examples of the hybridization of chromosomes 1, 3, 12, and 17 are displayed. The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation observed by the presence of green and red signals that indicate hypermethylation and hypomethylation events, whereas the 3-year-old twins have a very similar distribution of DNA methylation indicated by the presence of the yellow color obtained by equal amounts of the green and red dyes. Significant DNA methylation changes are indicated as thick red and green blocks in the ideograms.



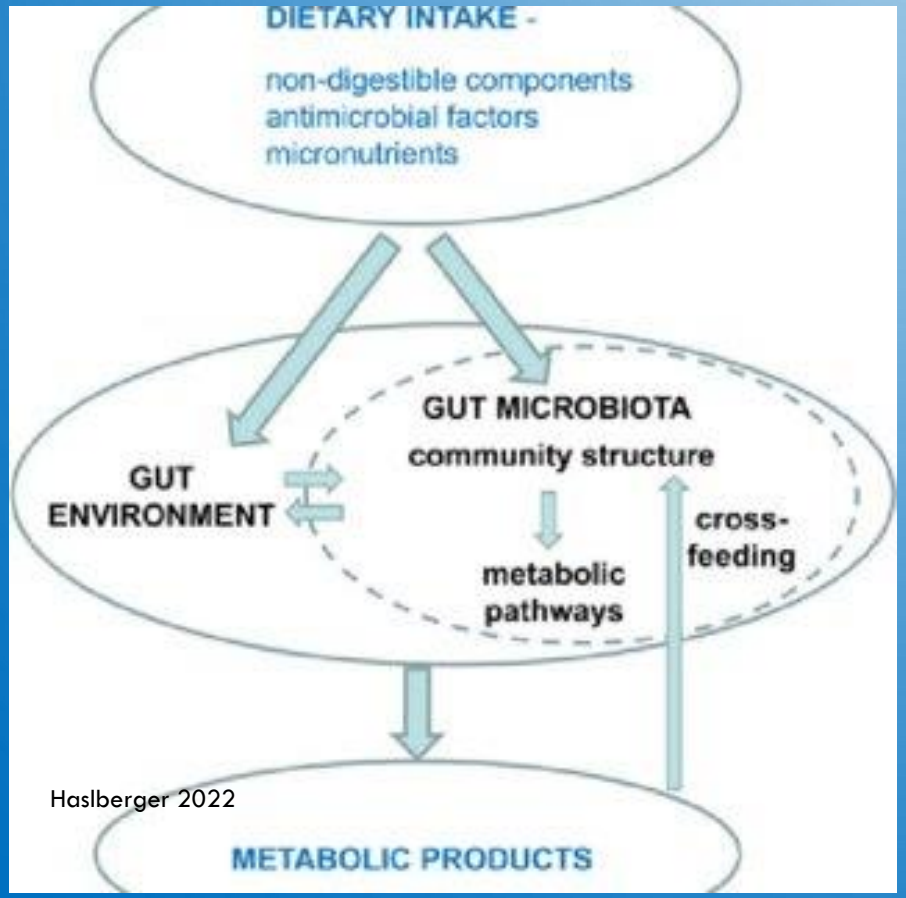
HIGH INDIVIDUAL DIVERSITY OF GUT MICROBIOTA REFLECTS NUTRITION AND LIFESTYLE , RESULTS IN DIFFERENT EXPRESSION OF METABOLITES ESP. SCFAS





Davis SC et al. / Microbiologyopen 2017

HIGHLY PERSONALDIFFERENT RESPONSES OF MICROBIOTA TO DIETS, (CROSSFEEDING) AND METABOLISATION OF FOODS



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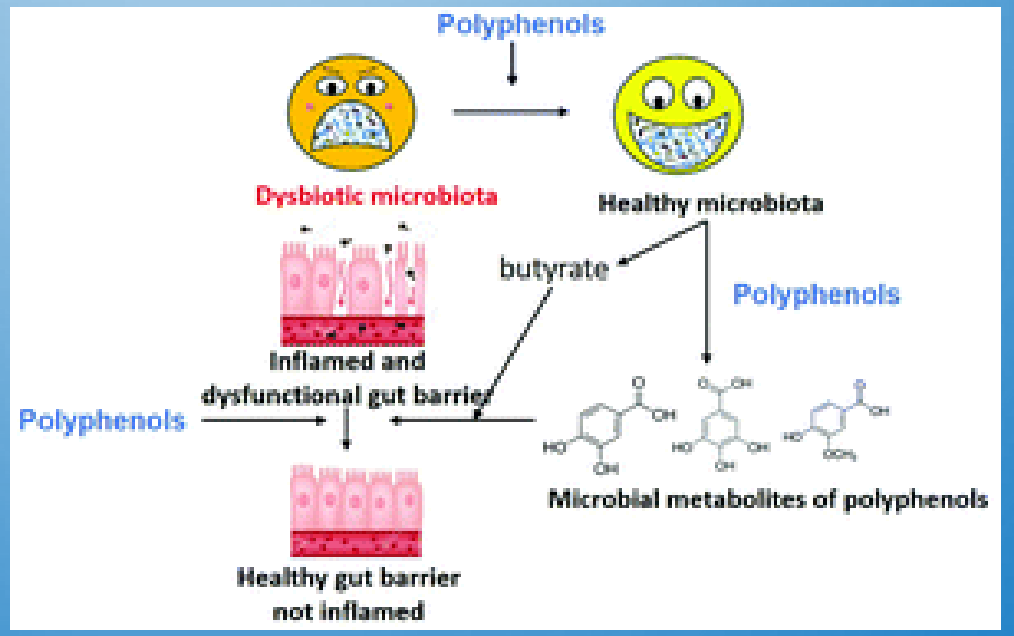
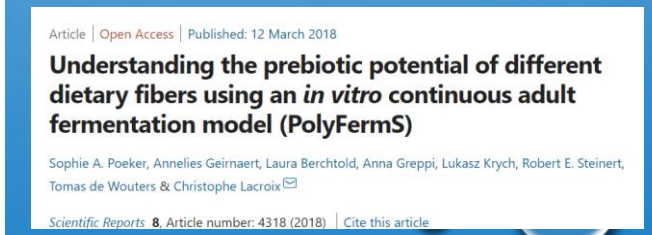




Article | Open Access | Published: 12 March 2018

Understanding the prebiotic potential of different dietary fibers using an *in vitro* continuous adult fermentation model (PolyFermS)

Sophie A. Poeker, Annelies Geirnaert, Laura Berchtold, Anna Greppi, Lukasz Krych, Robert E. Steinert, Tomas de Wouters & Christophe Lacroix

Scientific Reports 8, Article number: 4318 (2018) | Cite this article

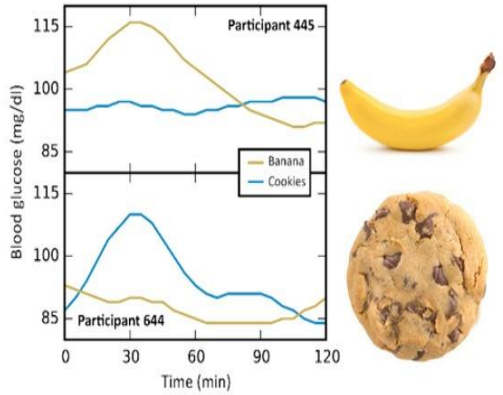
H. Flint

CORRELATION VON MICROBIOTA STRUCTURE WITH GLYCEMIC RESONSES USED FOR ALGORITHMS FOR DIETARY ADVICE

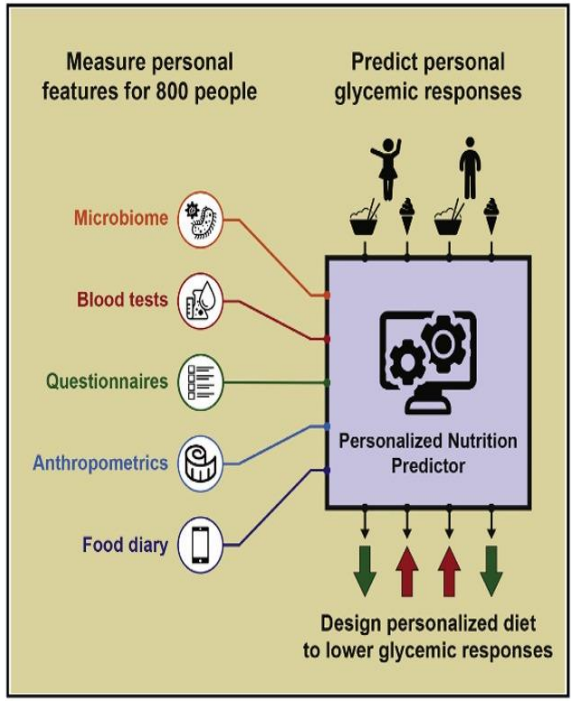
Beispiel - Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi, 2016

- 800 Personen – jeder hat andere „post meal Glucose response“

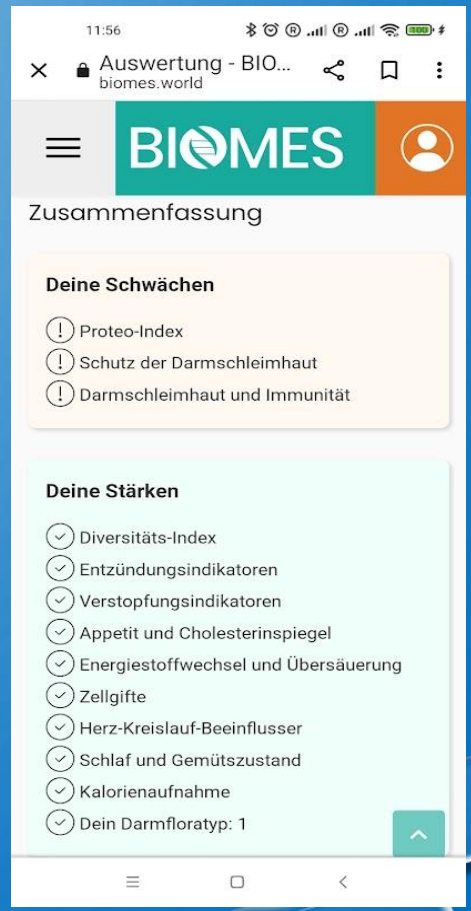


Mikrobiota Zusammensetzung beeinflusst Blutglucoselevel



Eran Elinav and Eran Segal, Weizmann Institute of monitoring the blood sugar, diets, and other traits of 800 people, they built an algorithm that can accurately predict how a person's blood-sugar levels will spike after eating any given meal.

They also used these personalized predictions to develop tailored dietary plans for keeping blood sugar in check.



PERSONAL DIFFERENT RESPONSES TO NUTRITON AFFECT AGING, E.G. CLOCK AND OTHER HALLMARKS OF AGING. STHIS RESULT IN PERSONAL TYPES OF AGING, AGEOTYPES ?

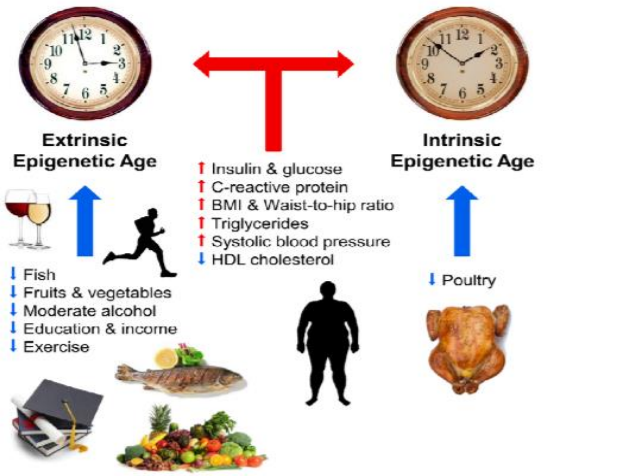


Figure 4. Pictorial summary of our main findings. The blue and red arrows depict anti-aging and pro-aging effects in blood respectively. The two clocks symbolize the extrinsic epigenetic clock (enhanced version of the Hannum estimate) and the intrinsic epigenetic clock (Horvath 2013) which are dependent and independent of blood cell counts, respectively.

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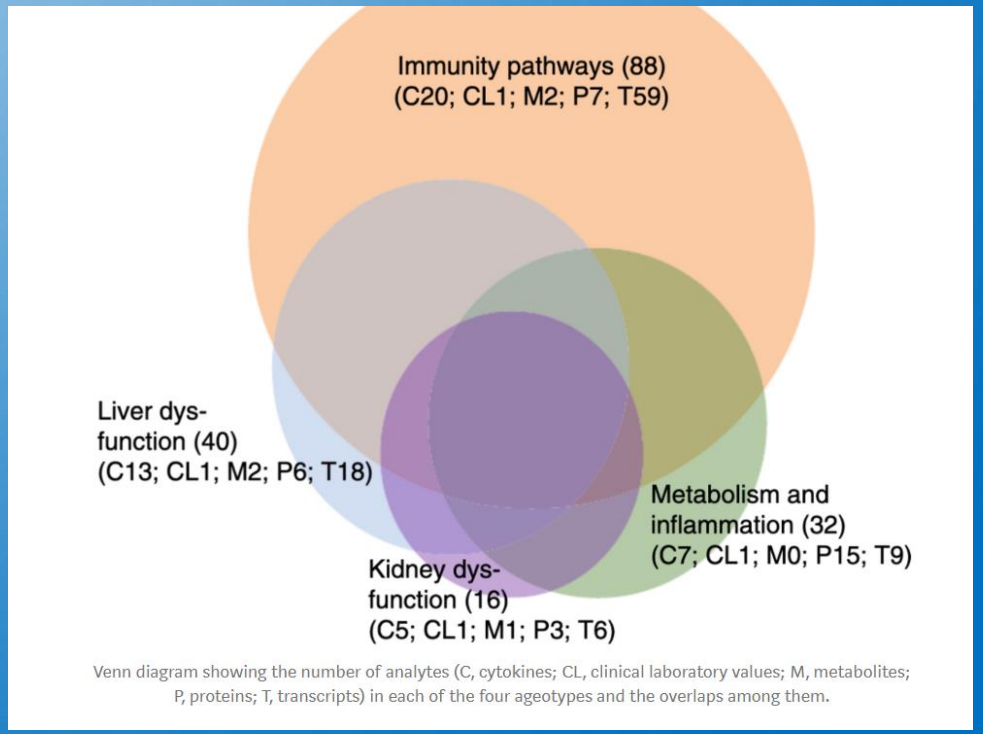
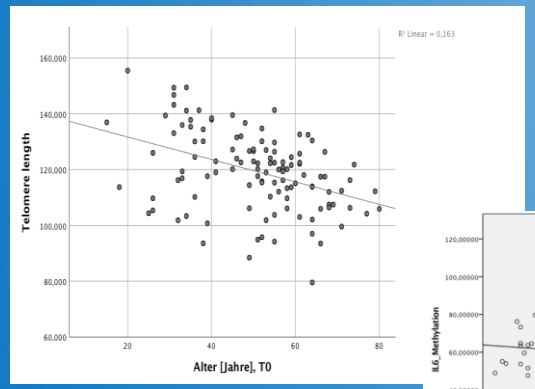
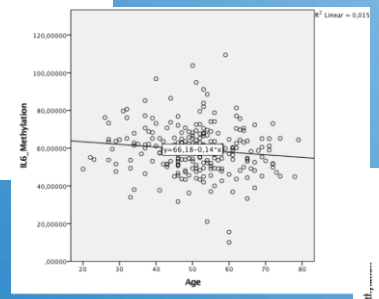


Venn diagram showing the number of analytes (C, cytokines; CL, clinical laboratory values; M, metabolites; P, proteins; T, transcripts) in each of the four ageotypes and the overlaps among them.

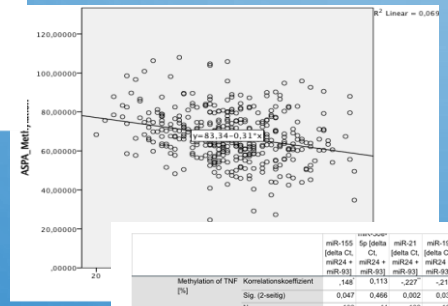
FACES OF PERSONAL AGING: CORRELATIONS OF AGE WITH TELOMERS, CPG-METHYLATION, INFLAMMATION, MIRNAS(N>500)



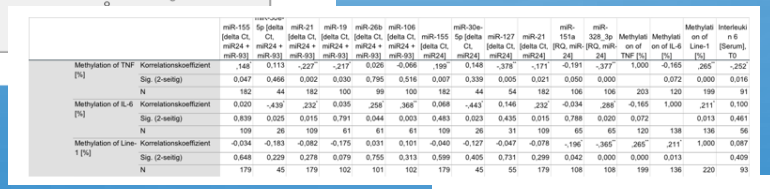
Correlation age with telomere-shortening



Correlation age with CPG methylation ASPA

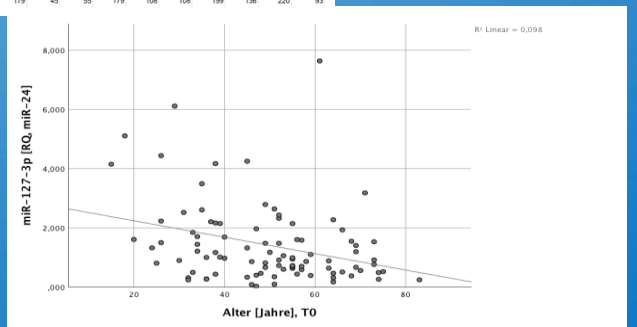


Correlation age with CPG methylation IL6



		miR-155 [delta Ct, miR24 + miR-93]	miR-5p [delta Ct, miR24 + miR-93]	miR-21 [delta Ct, miR24 + miR-93]	miR-19 [delta Ct, miR24 + miR-93]	miR-26b [delta Ct, miR24 + miR-93]	miR-106 [delta Ct, miR24 + miR-93]	miR-155 [delta Ct, miR24]	miR-30e-5p [delta Ct, miR24]	miR-127 [delta Ct, miR24]	miR-21 [delta Ct, miR24]	miR-151a [RQ, miR-24]	miR-328_3p [RQ, miR-24]	Methylation of TNF [%]	Methylation of IL-6 [%]	Methylation of Line-1 [%]	Interleukin 6 [Serum], T0
Methylation of TNF [%]	Korrelationskoeffizient	,148	0,113	-,227*	-,217	0,026	-0,066	,199	0,148	-,378*	-,171	-0,191	-,377*	1,000	-0,165	,265*	-,252
	Sig. (2-seitig)	0,047	0,466	0,002	0,030	0,795	0,516	0,007	0,339	0,005	0,021	0,050	0,000		0,072	0,000	0,016
	N	182	44	182	100	99	100	182	44	54	182	106	106	203	120	199	91
Methylation of IL-6 [%]	Korrelationskoeffizient	0,020	-,439*	,232*	0,035	,256*	,368**	0,069	-,443*	0,146	,232*	-0,034	,286*	-0,165	1,000	,211*	0,100
	Sig. (2-seitig)	0,839	0,025	0,015	0,791	0,044	0,003	0,483	0,023	0,435	0,015	0,788	0,020	0,072		0,013	0,461
	N	109	26	109	61	61	61	109	26	31	109	65	65	120	138	136	56
Methylation of Line-1 [%]	Korrelationskoeffizient	-0,034	-0,183	-0,082	-0,175	0,031	0,101	-0,040	-0,127	-0,047	-0,078	-,196*	-,365**	,265**	,211*	1,000	0,087
	Sig. (2-seitig)	0,648	0,229	0,278	0,079	0,755	0,313	0,599	0,405	0,731	0,299	0,042	0,000	0,000	0,013		0,409
	N	179	45	179	102	101	102	179	45	55	179	108	108	199	136	220	93

Correlation age with miRNA-127

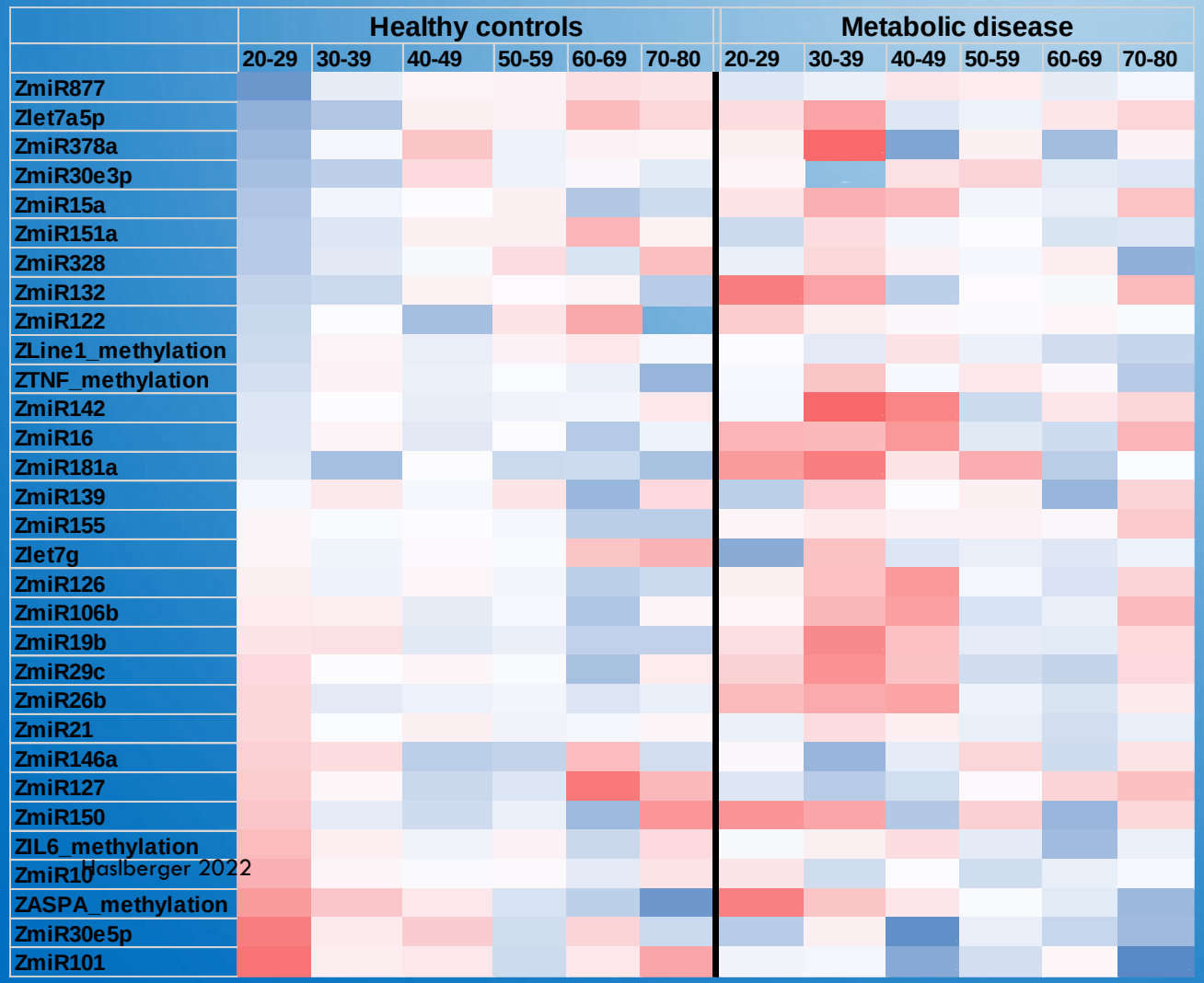


AGE DEPENDENT EPIGENETIC MARKERS: IN THE METABOLIC DISEASE GROUP (MD) CORRELATIONS ARE DISRUPTED, N>300

Marker	correlation analysis			age group comparison			direction
	All	HC	MD	all	HC	MD	
ASPA							--
IL6							--
TNF							--
miR-19b							--
miR-let-7a-5p							++
miR-877							++
miR-151a							++
miR-127							-+
miR-30e-5p							--
miR-150							
miR-21							
miR-101							

	correlation			Age Group			
	All	Healthy controls	Metabolic disorders	All	Healthy controls	Metabolic disorders	
ASPA	<0,001	<0,001	<0,001	p=0,000, korr. R2=0,185	0,001, korrR2 =0,207, überall 9<0,001, außer zwischen 40:59 zu 60-79:0,013	korrR2 = 0,140, 20-39:40-59: p = 0,041; 20-39:60-79: p=0,002	ANOVA Univariat
IL6	Trend (pearson: -0,127, p=0,079)	Pearson -0,73, p=0,412	Pearson -0,201, p=0,108	Sign. (20-39:60-79, p= 0,029) korr R2=0,026	Trend means	Trend means	ANOVA Univariat
TNF	Trend (spearman -0,054, p=0,384)	spearman -0,053, p= 0,491	pearson -0,105, p=318	Trend means	Trend means	Trend means	Kruskal Wallis
miR-19b	Linear regression: p= 0,018; (spearman -0,298**, p=0,005)	Linear regression: p= 0,027 (spearman -0,352** p=0,008)	spearman -0,174, p=0,341	Sign. 20-39:40-59 p=0,047	Trend p=0,06		Kruskal Wallis
miR-let-7a-5p	Linear regression: p= 0,028 (pearson 0,236*, p=0,028)	Linear regression: p= 0,001 (pearson 0,445** p=0,001)	pearson -0,085, p=0,613	Trend means	sign. (20-39:40-59: p=0,023); sign. (20-39:60-79: p=0,028) korrR2 = 0,162	sign. (20-39:40-59: p=0,027) korrR2 = 0,145	ANOVA Univariat
miR-877	Trend (spearman 0,207, p=0,058)	Trend Linear regression: 0,054 (spearman 0,288*, p=0,047)	spearman 0,105, p=0,544	X	Trend means	X	Kruskal Wallis
miR-151a	Trend (spearman 0,151, p=0,166)	(spearman 0,295* p=0,039)	spearman 0,059, p=0,727	X	Trend means	X	Kruskal Wallis
miR-127	Trend (pearson 0,288, p=0,055)	pearson 0,196, p=0,336	Trend pearson 0,444, p=0,057	Sign. (40-59:60-79, p= 0,016) korr R2=0,133	Sign. (40-59:60-79 p=0,046) korrR2= 0,167	X	ANOVA Univariat
miR-30e-5p	Trend (spearman -0,246, p=0,163)	Trend spearman-0,436, p= 0,055	spearman 0,048 p =0,869	Trend means	Trend means	Trend means	Kruskal Wallis
miR-150	Trend (pearson -0,114, p=0,522)	pearson 0,082, p=0,731	pearson -0,416, p=0,139				
miR-21	Trend (pearson, -0,091, p=0,153)	pearson -0,094, p=0,233	pearson -0,098, p=377				
miR-101	Trend (pearson: -0,228, p=0,195)	Trend: pearson -0,317, p=0,173	pearson -0,074, p=0,803				

DIFFERENT AGING PATTERNS (AGE RELATED MIRNAS) IN METABOLIC DISEASE GROUP



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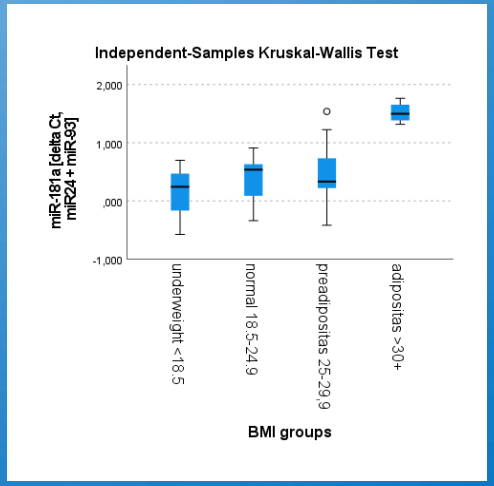
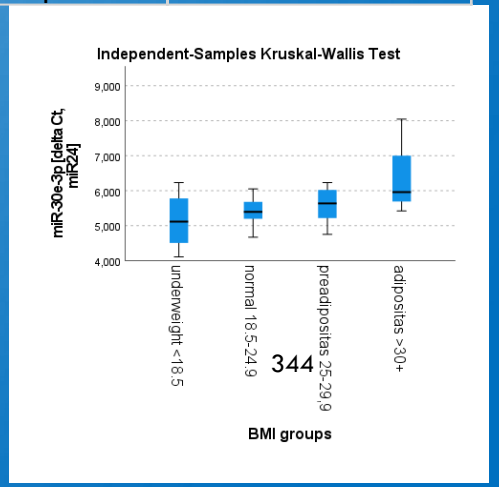
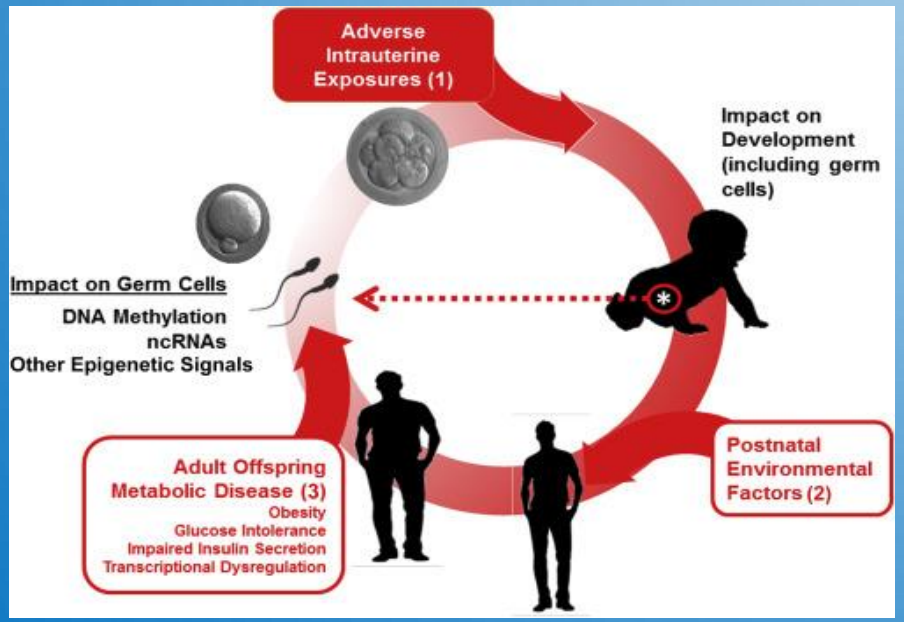
Marker	All	healthy controls	metabolic disorders
mi-181a	0,454* (Pearson)	x	0,777**
mi-378a	0,396* (Pearson), Linear regression (p=0,28)	x	0,864**
mi30e-5p	-0,339	-0,429	0,357
mi30e-3p	0,361* (spearman), Linear regression (p=0,042)	x	0,573
mi122	x	-0,359	x
mi101	x	-0,353	x
let7g	x	-0,360*	x
mi139*	p=0,007	p=0,004	
*Kruskal Wallis test between BMI groups			





CONCLUSION: COMPLEX DISEASES (AGING) CAN ARISE FROM (A MIXTURE OF) PERSONAL DIVERSE CAUSES, AN ARGUMENT IN FAVOR OF PERSONALLY SPECIFIC INTERVENTIONS (E.G. METABOLIC DISEASE)




Cell Metabolism
Perspective
Epigenetic Mechanisms of Transmission of Metabolic Disease across Generations

		Metabolic disorder
Hereditary SNPs Somatic mutatiions		Symptomatic treatment
Epigenetic (hereditary) or acuqired mismethylations, Histone modifocations or ncRNA structure		Causative treatment ? Epigenetic active additives? mTOR – Inhibitors ? Nutrition, Lifestyle
Delivery or accessed microbiota dysbiosis		Causative treatment ? pro-, pre, postbiotics? Nutrition, Lifestyle
Psycho- neuro- immune endocrine axis		

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CONEQUENCES FOR INTERVENTION: FLAGSHIP EU-FOOD4ME STUDY RESULTS PROVE „PERSONAL NUTRITION DOES BETTER THAN ON SIZE FITS ALL“, J. MATHERS

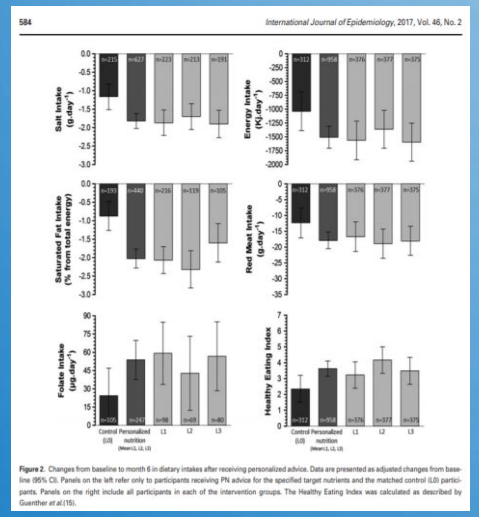
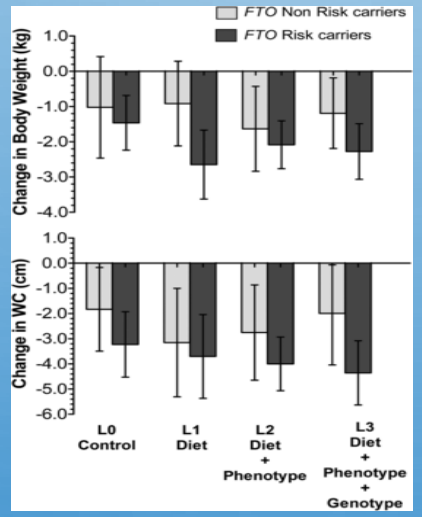


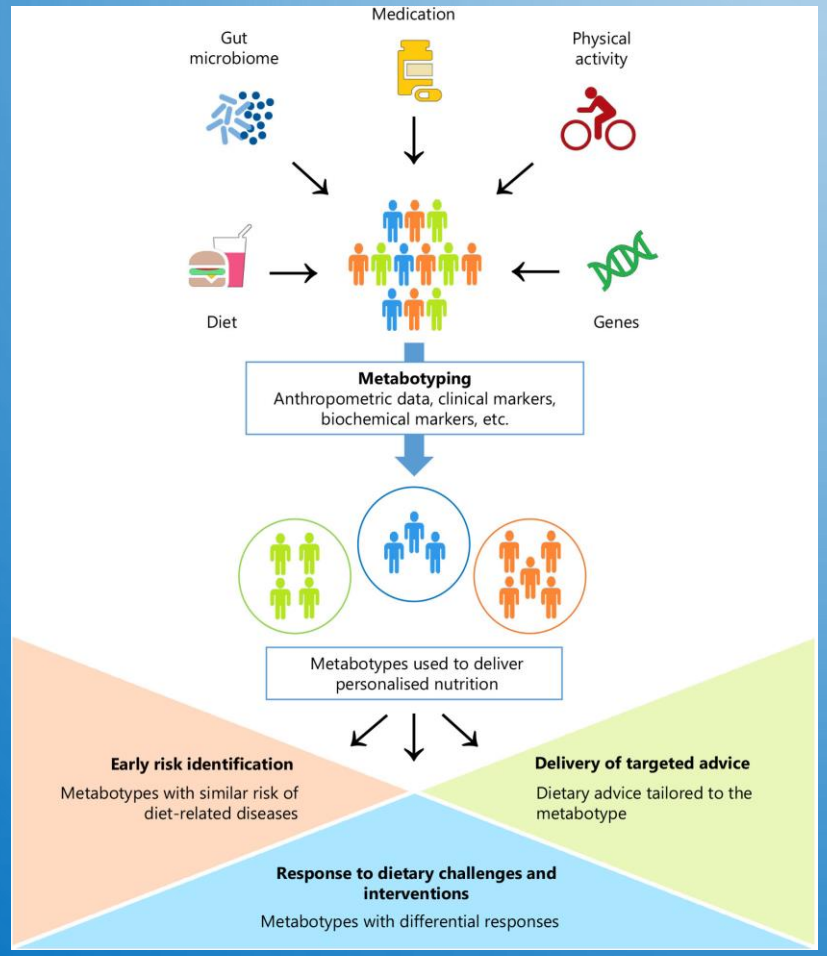
Figure 2. Changes from baseline to month 6 in dietary intakes after receiving personalized advice. Data are presented as adjusted changes from baseline (95% CI). Panels on the left refer only to participants receiving PN advice for the specified target nutrients and the matched control (L0) participants. Panels on the right include all participants in each of the intervention groups. The Healthy Eating Index was calculated as described by Guenther et al.(15).

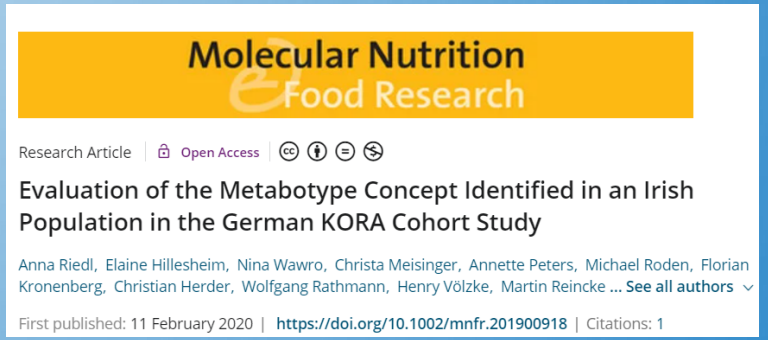


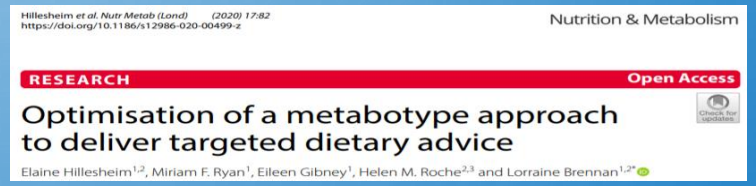
Changs of dietary intake after personalised advice Healthy eating index

Changes in adiposity markers were greater in participants who were informed that they carried the *FTO* risk allele (level 3 AT/AA carriers) than in the nonpersonalized group

DEFINITION OF METABOTYPES FROM GENETIC-, MICROBIOTA- METABOLOMICS BASED INFORMATION, METABOTYPING







CONSEQUENCES OF METABOTYPES, DIETS NEXT STEP TRACKERS

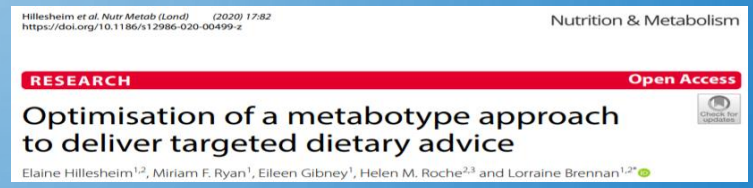
Spectrum of Possibilities for Human Metabolism

Carbo Types	Mixed Types	Protein Types
Increasing need for Carbohydrates Decreasing need for Proteins, Fats & Purines	Relatively balanced need for Carbohydrates, Proteins, Fats & Purines	Increasing need for Proteins, Fats & Purines Decreasing need for Carbohydrates

Carbo Type Characteristics:
- Casual relationship with food
- Skipping a meal is usually not a big deal
- Needs high quality Vegetable and/or Fruit nutrition at their

Mixed Types:
Can identify with some characteristics of both Carbo Types & Protein Types - but, typically

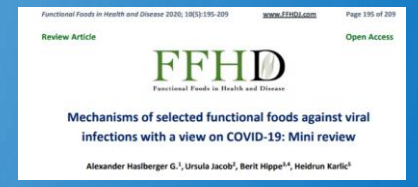
Protein Type Characteristics:
- Intense relationship with food - loves to eat & tends to eat fast
- Skipping a meal IS a big deal
- Needs some high quality animal Protein & Fat at every meal to

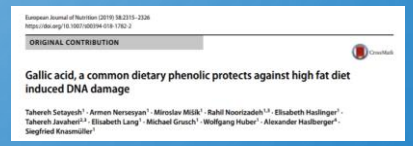

Hillesheim et al. Nutr Metab (Lond) (2020) 17:82
https://doi.org/10.1186/s12986-020-00499-z
Nutrition & Metabolism
RESEARCH
Open Access

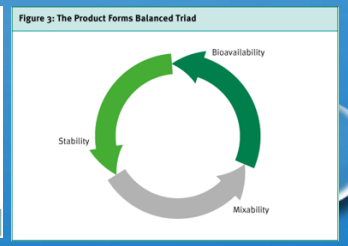
Optimisation of a metabotype approach to deliver targeted dietary advice

Elaine Hillesheim[1,2], Miriam F. Ryan[1], Eileen Gibney[1], Helen M. Roche[2,3] and Lorraine Brennan[1,2*]

Personalisation of additives for Prevention
Monitoring basic hallmarks of health/aging. Use of mixes of supplements, functional foods which address specific mechanisms „Achilles Fersen Concept“







HealthBioCare GmbH

Precision Probiotics + Prebiotics with Viome's Gut Intelligence™ Test

For gut health

AND WHAT HAPPENS TO OUR PYRAMIDE? BUT ALREADY THE DIETARY REFERENCE VALUES1992 US USDA-PYRAMIDE, USED AN INDIVIDUALISED APPROACH, AGE, LIFESTYLE (WORK)

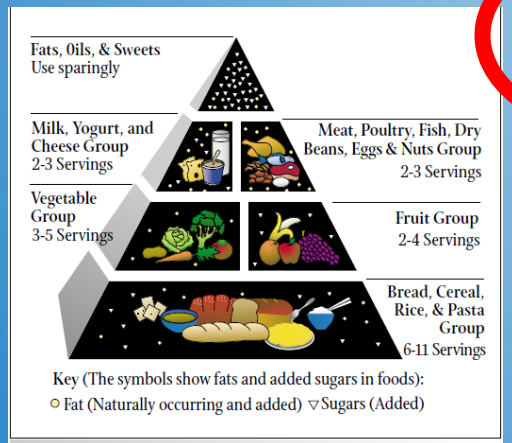


FIGURE 2
1992 FOOD PYRAMID

TABLE 1
MYPYRAMID FOOD PLAN FOR A 38-YEAR-OLD MALE WHO EXERCISES AN AVERAGE OF 30-60 MINUTES PER DAY.

Food group	Recommendation (per day)
Grains	9 oz. (half should be whole grains)
Vegetables	3.5 cups
Fruits	2 cups
Milk	3 cups
Meat and beans	6.5 oz.
Oil	8 tsp.
Discretionary	410 calories (extra fats and sugars)
Total daily calories	2,600

TABLE 2
SAMPLE MENU THAT MEETS THE MYPYRAMID RECOMMENDATIONS FOR HEALTHY EATING FOR A 38-YEAR-OLD MALE WHO EXERCISES AN AVERAGE OF 30-60 MINUTES PER DAY.*

Breakfast Bagel with fruit other than raisins, 1 large (3.5" to 3.75" diameter) Orange juice, 1.5 cup
Snack Black beans, cooked, no fat added, 1 cup Rice, brown, medium-grain, cooked, .5 cup Bread, multigrain, toasted, 2 large slices
Lunch McDonald's garden salad French fries, from frozen, deep-fried, 1 small fast-food order Milk, 1%, 1 cup

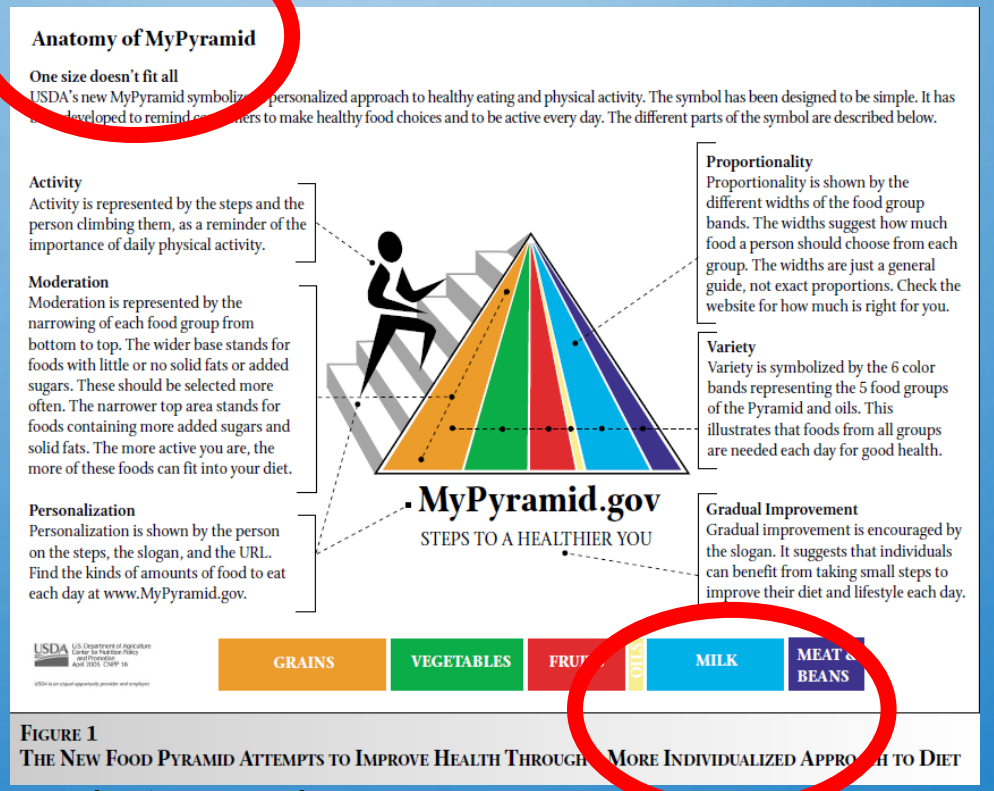
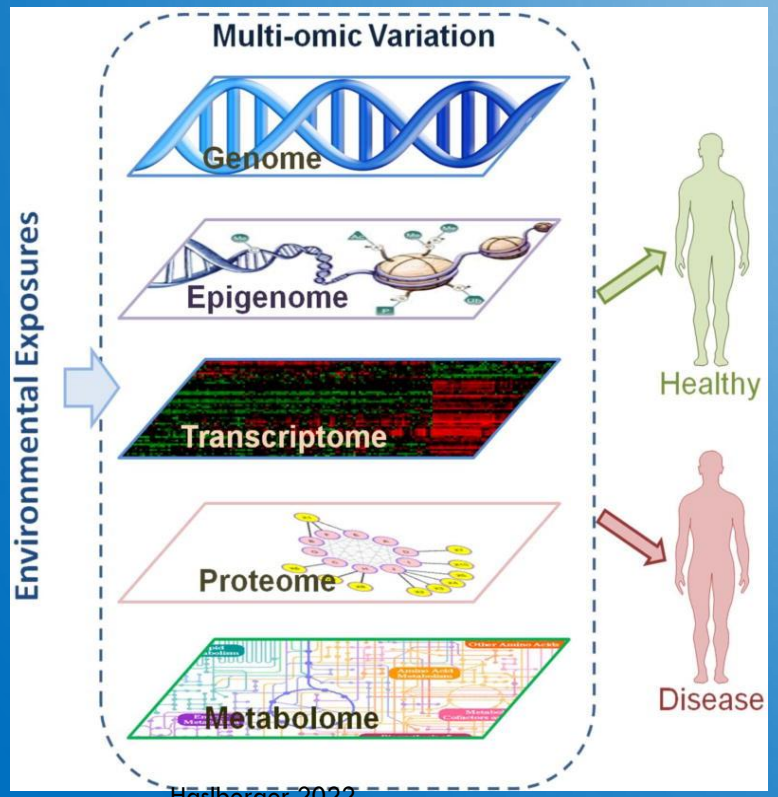


FIGURE 1
THE NEW FOOD PYRAMID ATTEMPTS TO IMPROVE HEALTH THROUGH A MORE INDIVIDUALIZED APPROACH TO DIET

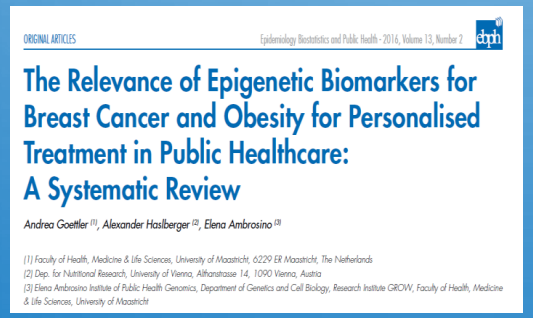
John Neustadt
Integrative Medicine 2005

IMPORTANCE OF GOOD MARKERS, NUTRITION: FOLLOWING THE WAY OF PERSONALISED, PREZISION MEDICINE, CFDNA) ?



Epigenetic markers, quite stable, eg condens events over longer time spans

Metabolomic marker reflect more immediate events

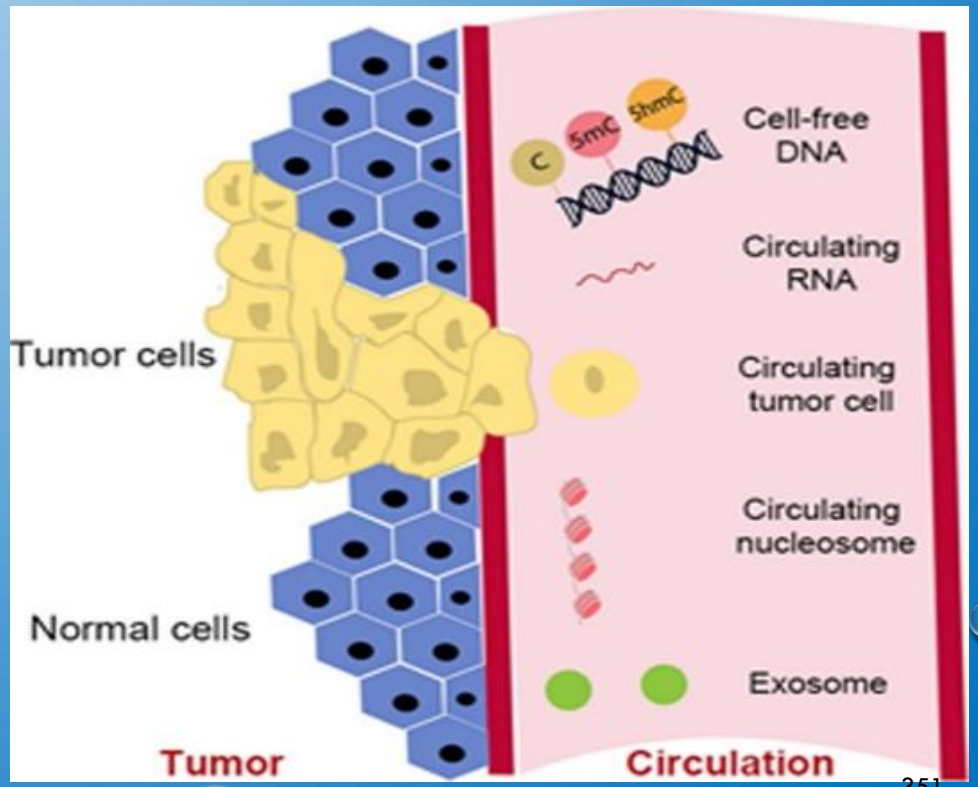

ORIGINAL ARTICLES

Epidemiology Biostatistics and Public Health - 2016, Volume 13, Number 2

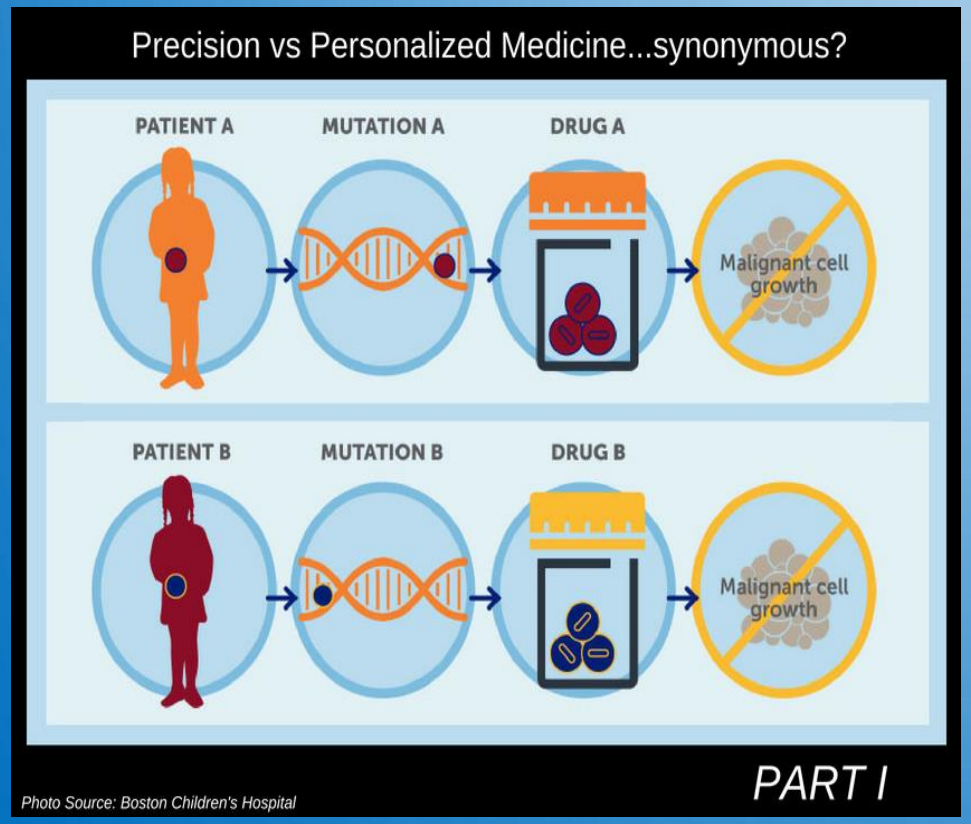
The Relevance of Epigenetic Biomarkers for Breast Cancer and Obesity for Personalised Treatment in Public Healthcare: A Systematic Review

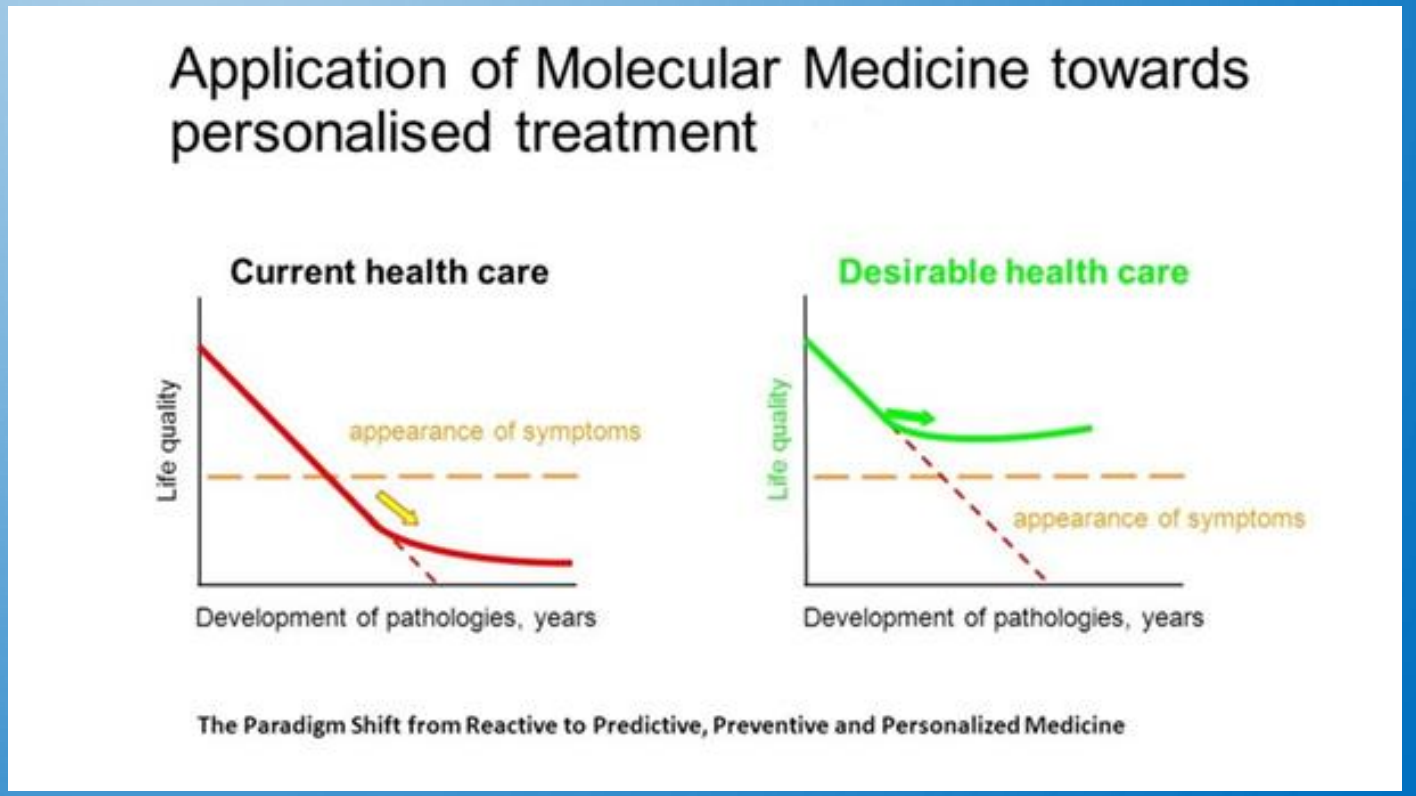
Andrea Goettler [1], Alexander Haslberger [2], Elena Ambrosino [3]

[1] Faculty of Health, Medicine & Life Sciences, University of Maastricht, 6229 ER Maastricht, The Netherlands
[2] Dep. for Nutritional Research, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
[3] Elena Ambrosino Institute of Public Health Genomics, Department of Genetics and Cell Biology, Research Institute GROW, Faculty of Health, Medicine & Life Sciences, University of Maastricht



Discussion: Prevention, intervention: personal or precision medicine, synonyme? personal or precision nutrition, synonyme?





PRECISION, PERSONALISED NUTRITION, WHERE WE ARE, WHERE TO GO

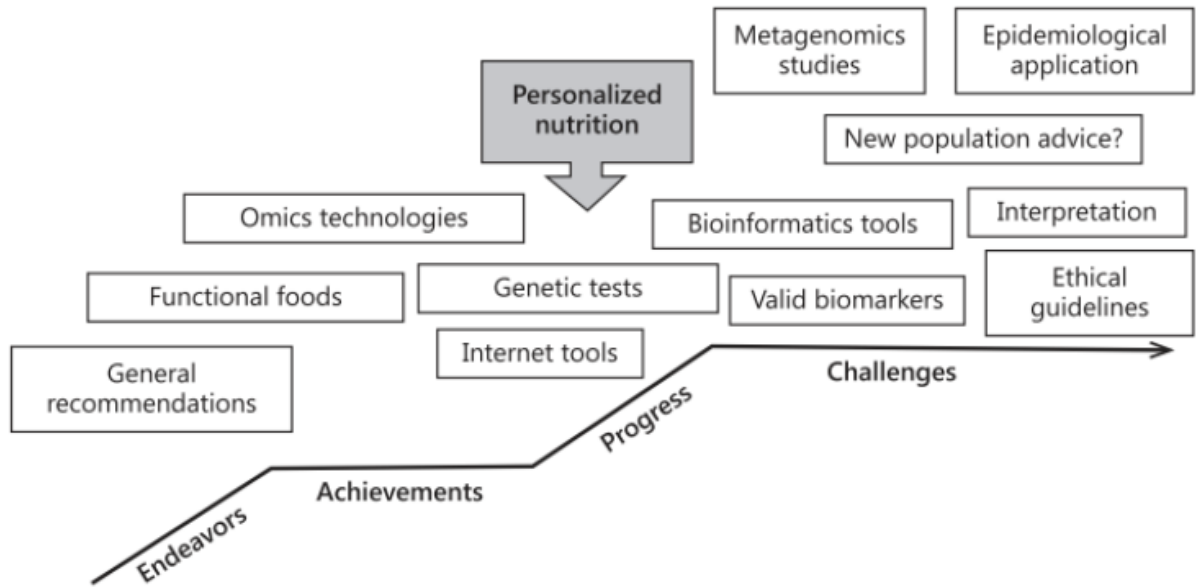


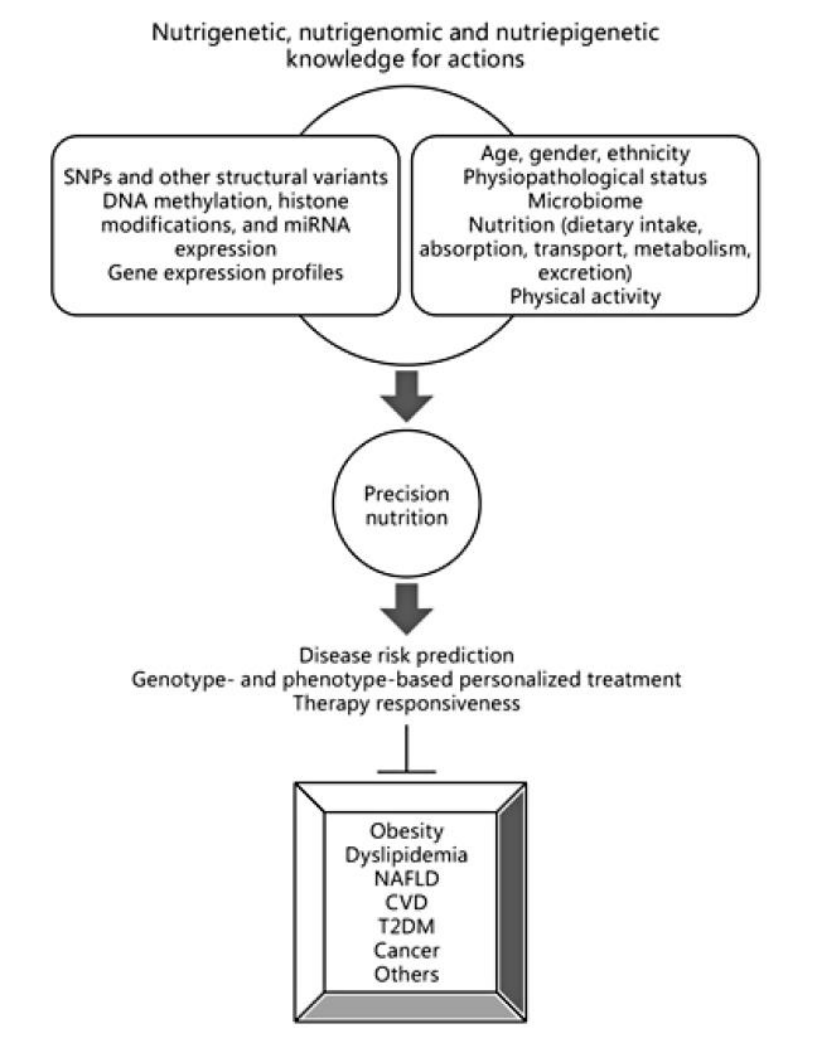
Fig. Achievements already made and challenges faced by personalised nutrition (Prasad et al., 2016)

Personalisierte Ernährung und Einteilung/ Klassifizierung von metabolischen Typen basierend auf genetischen, epigenetischen und mikrobiologischen Analysen

Personalized nutrition and classification of metabolic types based on genetics, epigenetics and gut microbiota

Stephanie Lilja, Diana Gessner, Christina Schnitzler, Nicola Stephanou-Rieser,
Claudia Nichterl, Angelika Pointner, Elena Tomeva, Marlene Remely, Alexander Haslberger

PRECISION-, PERSONALISED NUTRITION, THE WAY WE MAY GO

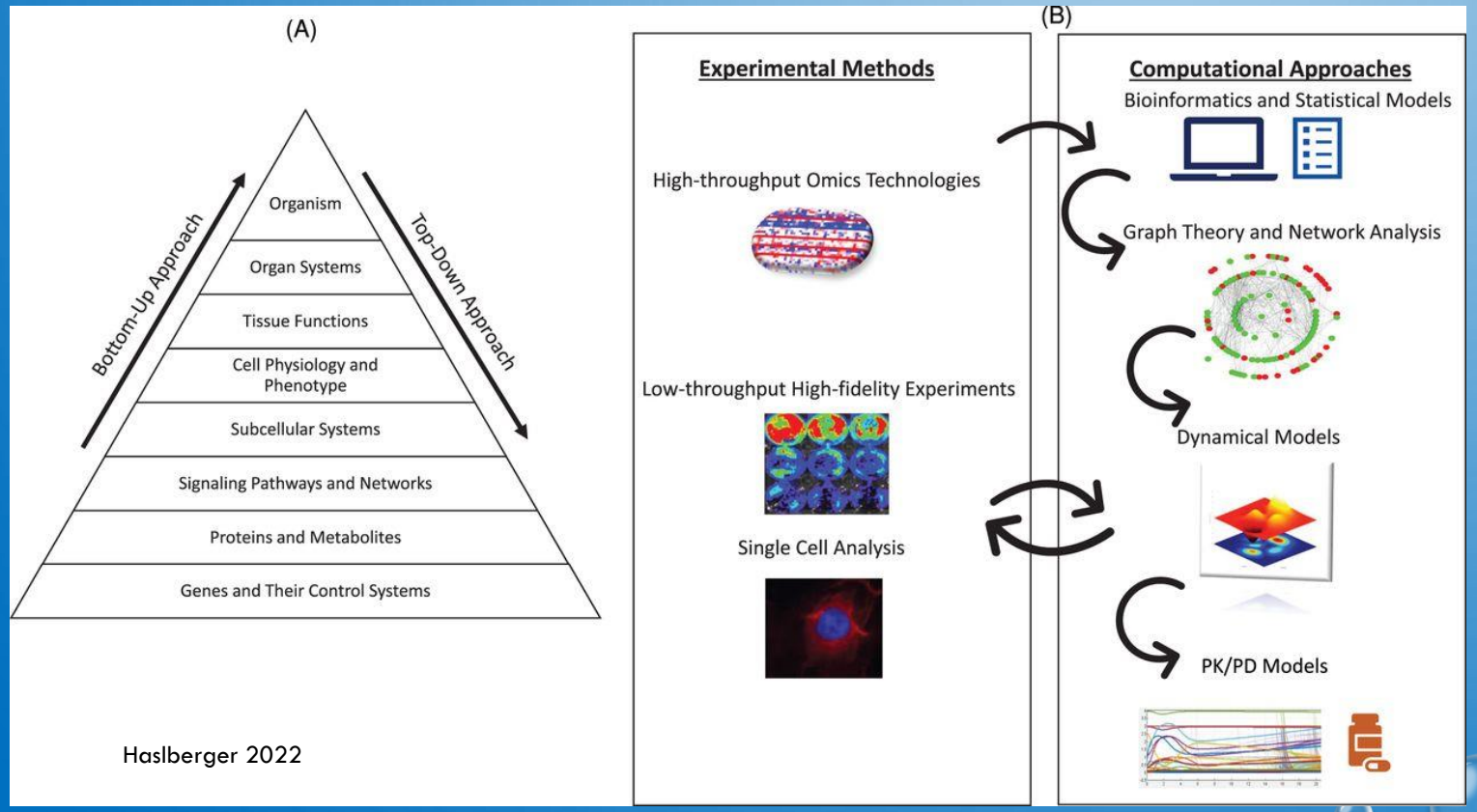


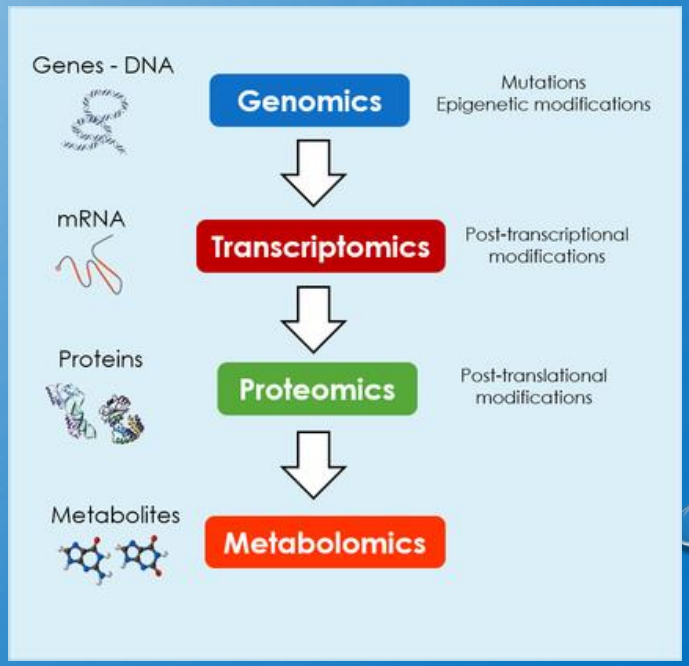
Mobile apps and wearable devices facilitate real-time assessment of dietary intake and provide feedback which can improve glycaemic control and diabetes management.

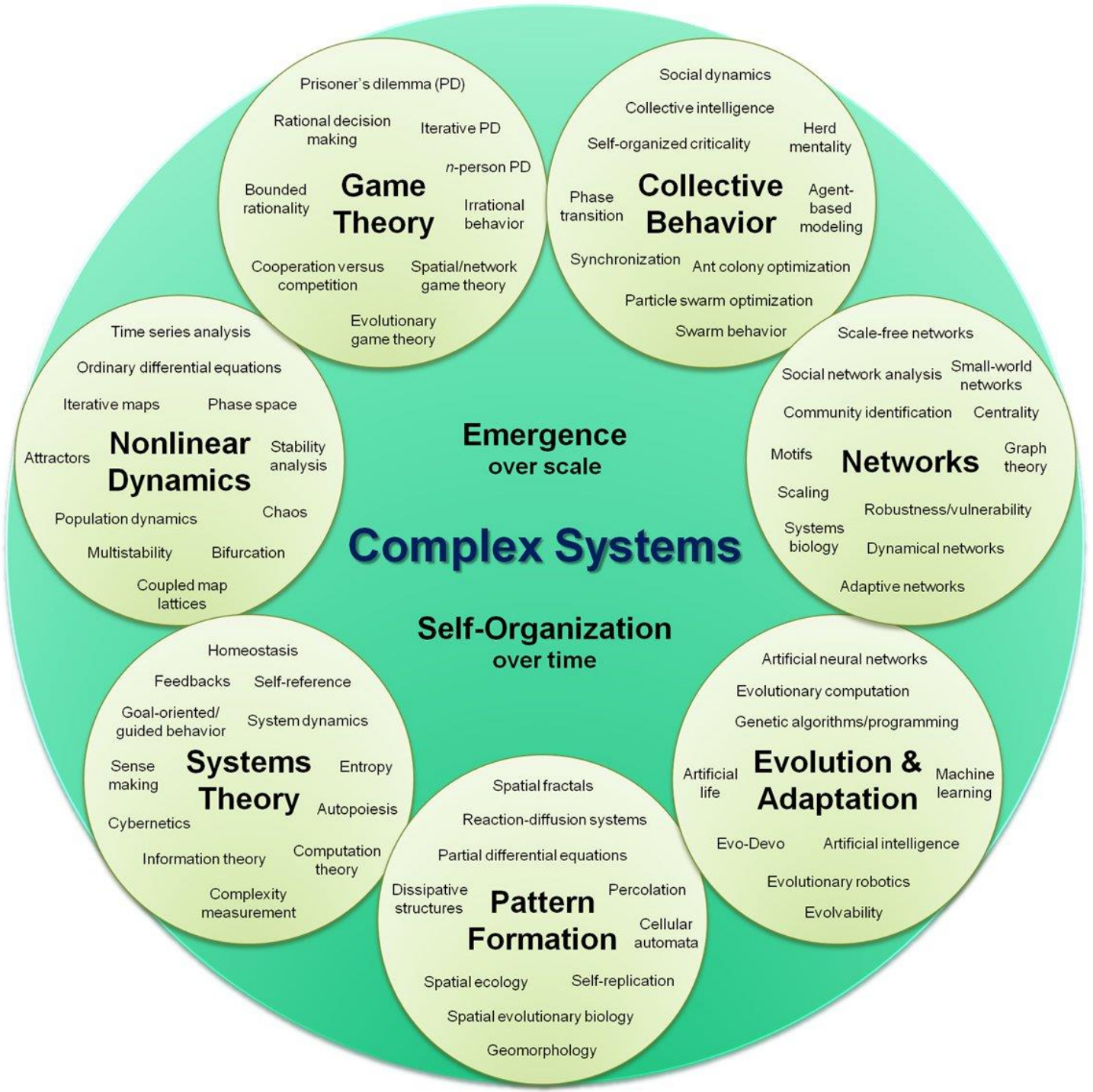
By integrating these technologies with big data analytics, precision nutrition has the potential to provide personalised nutrition guidance for more effective prevention and management of complex metabolic diseases

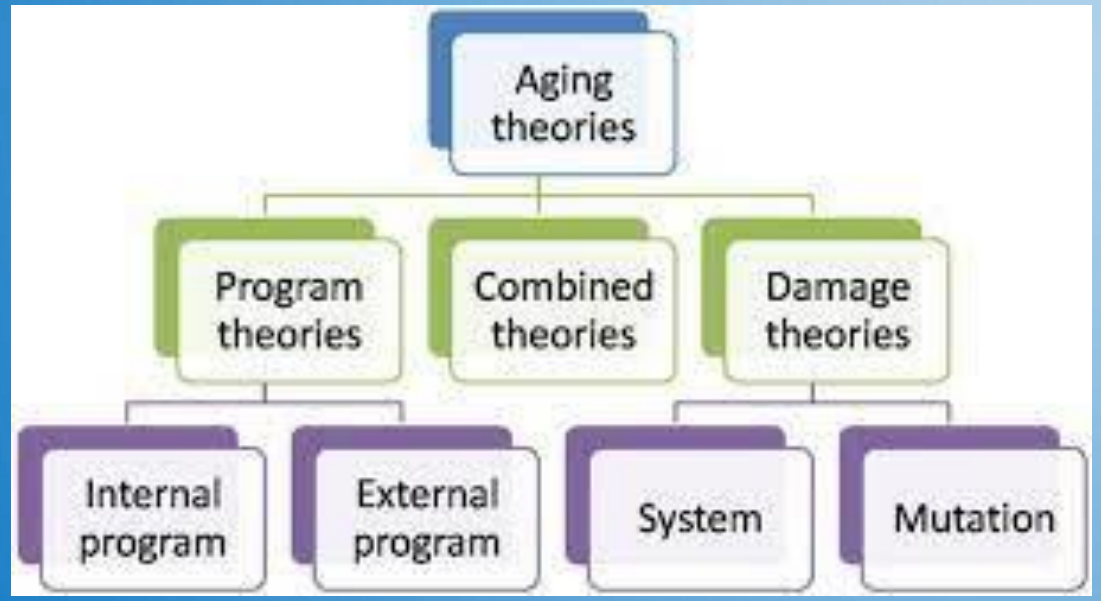
(D. D. Wang & Hu, 2018).

SYSTEM THEORY AND OMICS





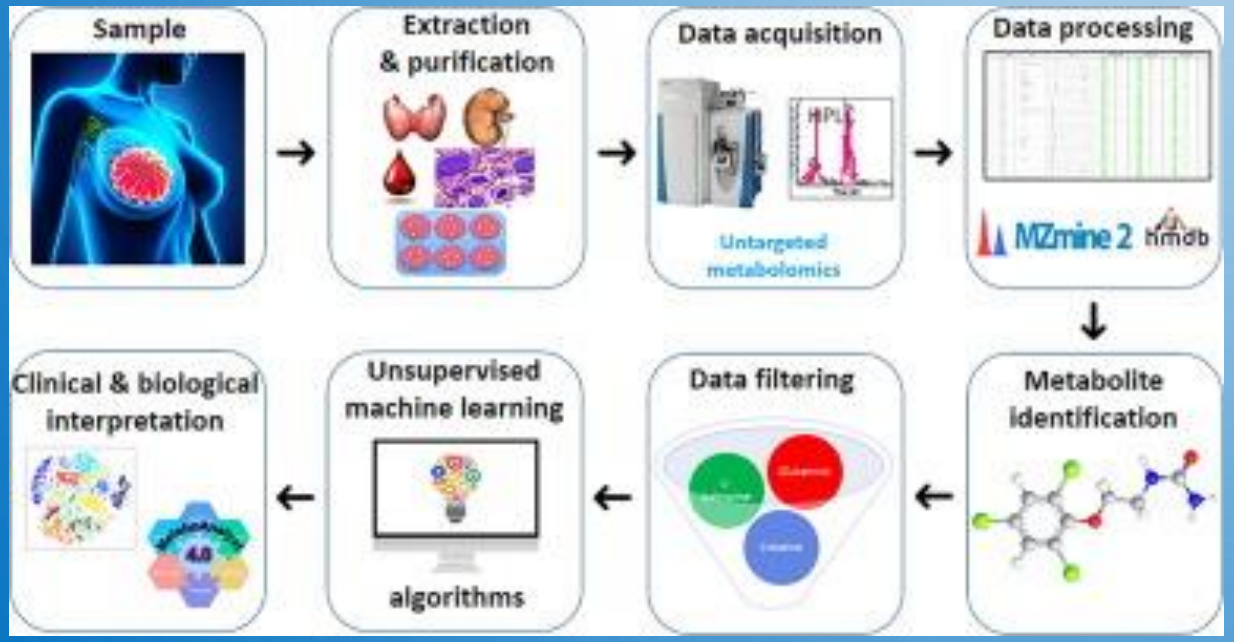

Complex Systems
Emergence
over scale
Self-Organization
over time
Game Theory
Prisoner's dilemma (PD)
Rational decision making
Iterative PD
n-person PD
Bounded rationality
Irrational behavior
Cooperation versus competition
Spatial/network game theory
Evolutionary game theory
Collective Behavior
Social dynamics
Collective intelligence
Self-organized criticality
Herd mentality
Phase transition
Agent-based modeling
Synchronization
Ant colony optimization
Particle swarm optimization
Swarm behavior
Networks
Scale-free networks
Social network analysis
Small-world networks
Community identification
Centrality
Motifs
Graph theory
Scaling
Robustness/vulnerability
Systems biology
Dynamical networks
Adaptive networks
Nonlinear Dynamics
Time series analysis
Ordinary differential equations
Iterative maps
Phase space
Attractors
Stability analysis
Population dynamics
Chaos
Multistability
Bifurcation
Coupled map lattices
Evolution & Adaptation
Artificial neural networks
Evolutionary computation
Genetic algorithms/programming
Artificial life
Machine learning
Evo-Devo
Artificial intelligence
Evolutionary robotics
Evolvability
Systems Theory
Homeostasis
Feedbacks
Self-reference
Goal-oriented/ guided behavior
System dynamics
Sense making
Entropy
Autopoiesis
Cybernetics
Information theory
Computation theory
Complexity measurement
Pattern Formation
Spatial fractals
Reaction-diffusion systems
Partial differential equations
Dissipative structures
Percolation
Cellular automata
Spatial ecology
Self-replication
Spatial evolutionary biology
Geomorphology

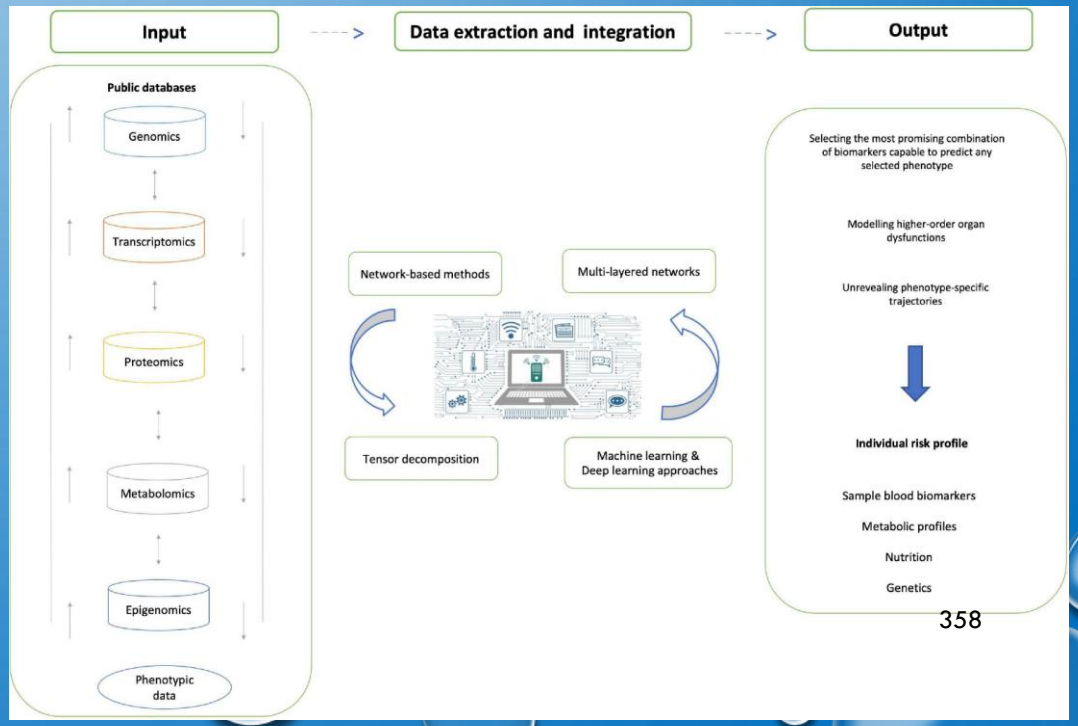


Definition of aging and non-aging systems in reliability theory

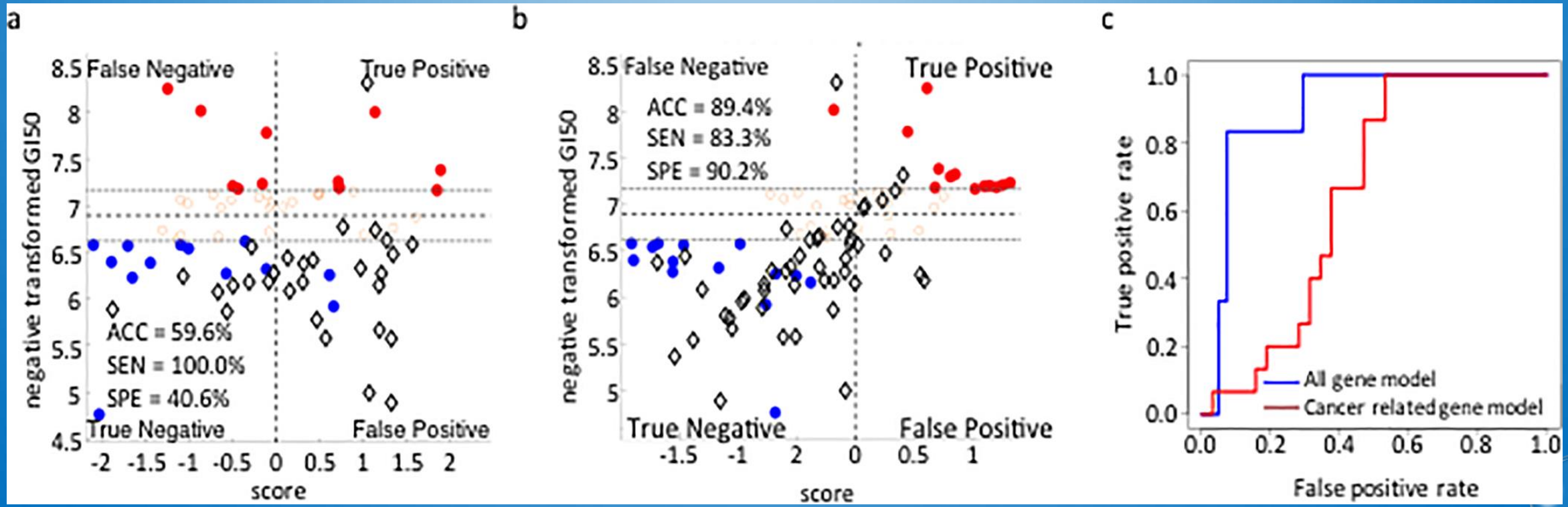
- **Aging: increasing risk of failure with the passage of time (age).**
- **No aging: 'old is as good as new' (risk of failure is not increasing with age)**
- **Increase in the calendar age of a system is irrelevant.**

DATA PROCESSING INTERATION

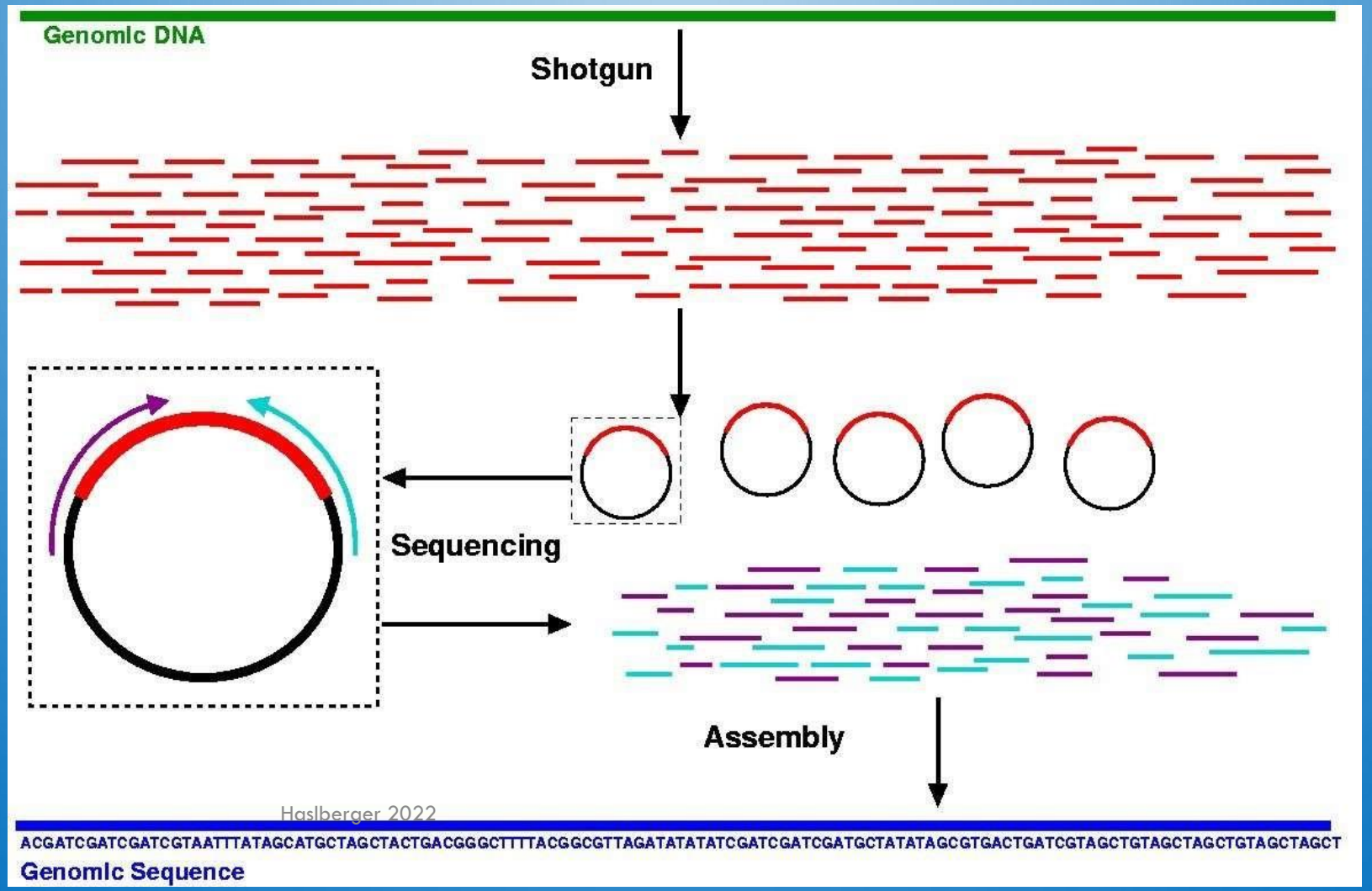




SELF LEARNING ALGORITHMS



SHOTGUN METHOD



SANGER METHOD

Sanger sequencing

- Low-throughput, but accurate and can handle up to 1000bp
- Still standard for small-scale laboratory use

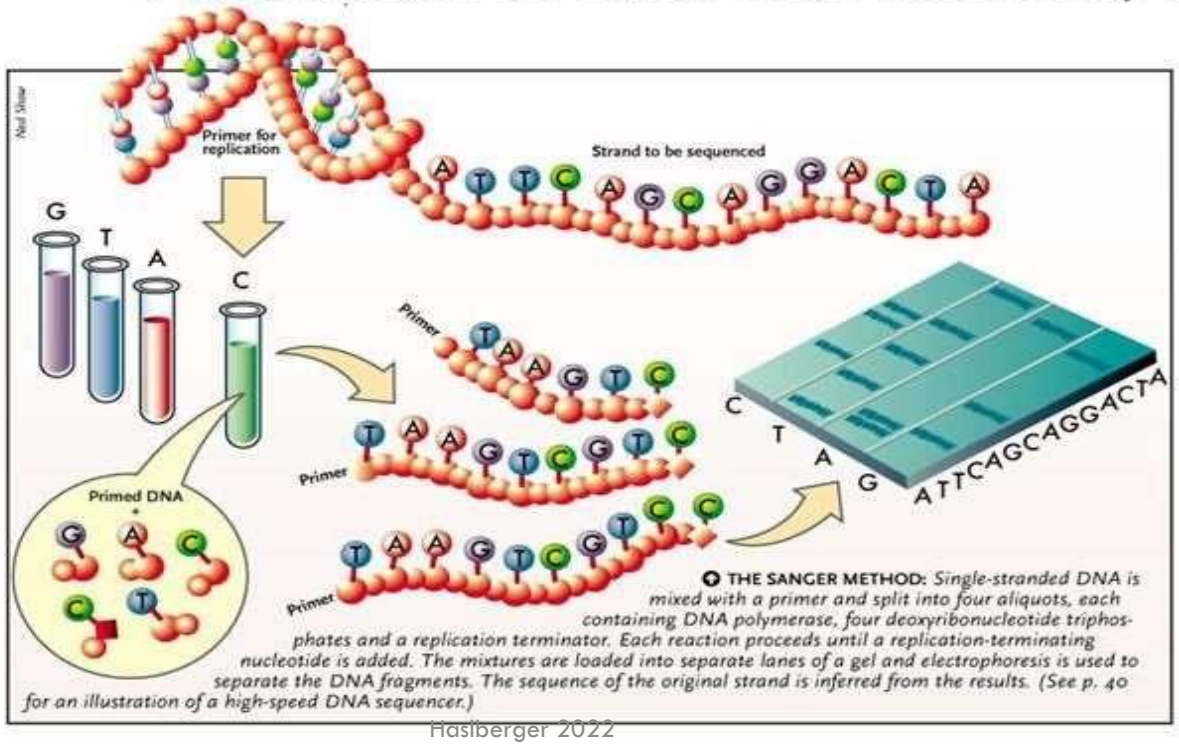


Image credit: the-scientist.com

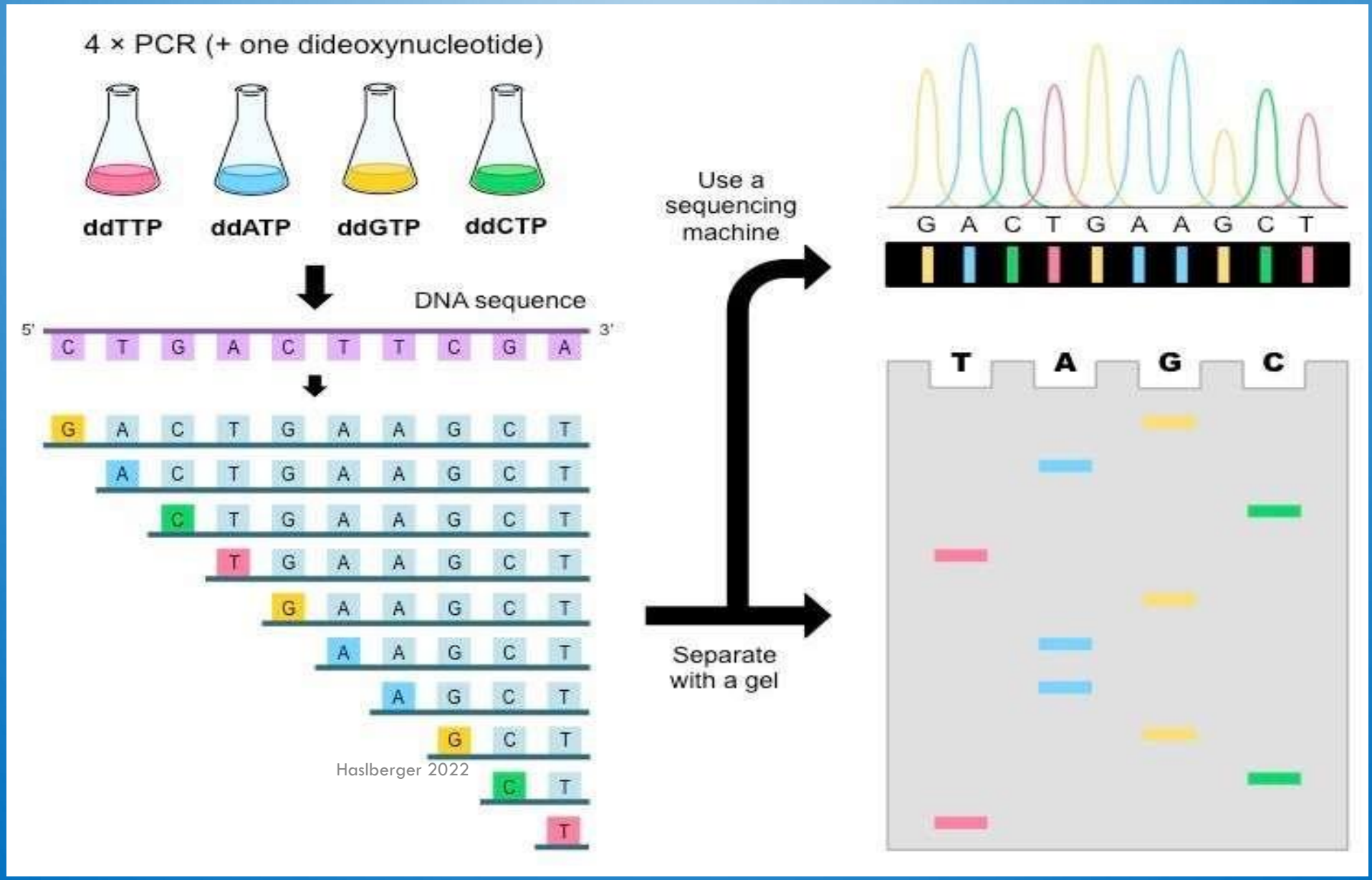
Components:

- DNA to be sequenced
- Primer
- Free nucleotides that allow further extension (dNTP, circles):
  - N=A, C, G or T, all four types are present
- Free nucleotides that terminate extension (ddNTP, rhombuses):
  - N=A, C, G or T, only one type is present
- DNA polymerase

See these videos for animations:
http://www.youtube.com/watch?v=oYpIlbI0qF8
http://www.youtube.com/watch?v=6ldtdWjDwes

Hasiberger 2022

SANGER SEQUENCING



MOVIES

(85) Overview of qPCR - YouTube

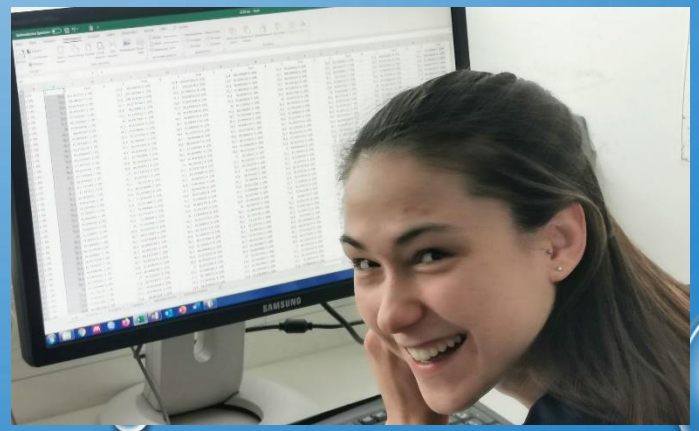
(85) Illumina Sequencing by Synthesis - YouTube

(85) Gene Therapy - YouTube

(85) Genome Editing with CRISPR-Cas9 - YouTube

(85) Gene Editing Inside the Body Using CRISPR - YouTube

https://youtu.be/DDiQGn72Z8M



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www.alexander-haslberger.at

www.my-personal.health