WEEK 4 –

SEPTEMBER 29, 2025

AGING

AS A NEURODEGENERATIVE DISEASE

Program

Week	Date	Day		Topics 2025	Teacher
1	08.09.25	Mon		Neuroscience techniques	JG
1	12.09.25	Fri		Brain Anatomy I	JG
2	15.09.25	Mon		Brain Anatomy II	JG
2	19.09.25	Fri		Neurogenesis-Neurodevelopment	JG
	22.09.25	Jeûne Fédérale			
3	26.09.25	Fri		Glia	MB
4	29.09.25	Mon		Aging	JG
4	03.10.25	Fri		Role of misfolded protein in NDDs - Part I	ALM
5	06.10.25	Mon		Role of misfolded protein in NDDs with PD as an example - Part II	ALM
5	10.10.25	Fri		Gut-brain axis and microbiota in PD	ALM
6	13.10.25	Mon		Basal ganglia and Parkinson's disease?	BS
6	17.10.25	Fri		Basal ganglia and Parkinson's disease?	BS
	20.10.25	Mon		Teaching break	
	24.10.25	Fri		Teaching break	
7	27.10.25	Mon		Motor neurons and disease	BS
7	31.10.25	Fri		Motor neurons and disease	BS
8	03.11.25	Mon		Motor neurons and disease	BS
8	07.11.25	Fri		TBD	BS/ALM
9	10.11.25	Mon		Alzheimer's disease	JG
9	14.11.25	Fri		Alzheimer's disease	JG
10	17.11.25	Mon		Biomarkers and emerging therapeutics in PD	ALM
10	21.11.25	Fri		Meet the Patients	ALM
11	24.11.25	Mon		Neuroepigenetics	JG
11	28.11.25	Fri		Neuroepigenetics	JG
12	01.12.25	Mon		Gene therapy	BS
12	05.12.25	Fri		Gene therapy	BS
13	08.12.25	Mon		Translational approaches against neurodegenerative disorders	BS/ALM
13	12.12.25	Fri		IPSc and their potential	ALM
14	15.12.25	Mon		Mock Exam	BS/ALM/JG
14	19.12.25	Fri		Mock Exam Correction	BS/ALM/JG
				Block "Fundamentals in molecular neuroscience"	
				Block "Neurodegenerative diseases"	
				Block "Emerging concepts and therapies"	

Learning objectives

At the end of this session you will be able to

- Define aging
- Identify different theories of aging
- Describe proximate vs ultimate causes of aging
- Know about aging biomarkers
- Know about aging interventions
- Design a study to investigate causes or treatments of aging*

* exercises

Wordle

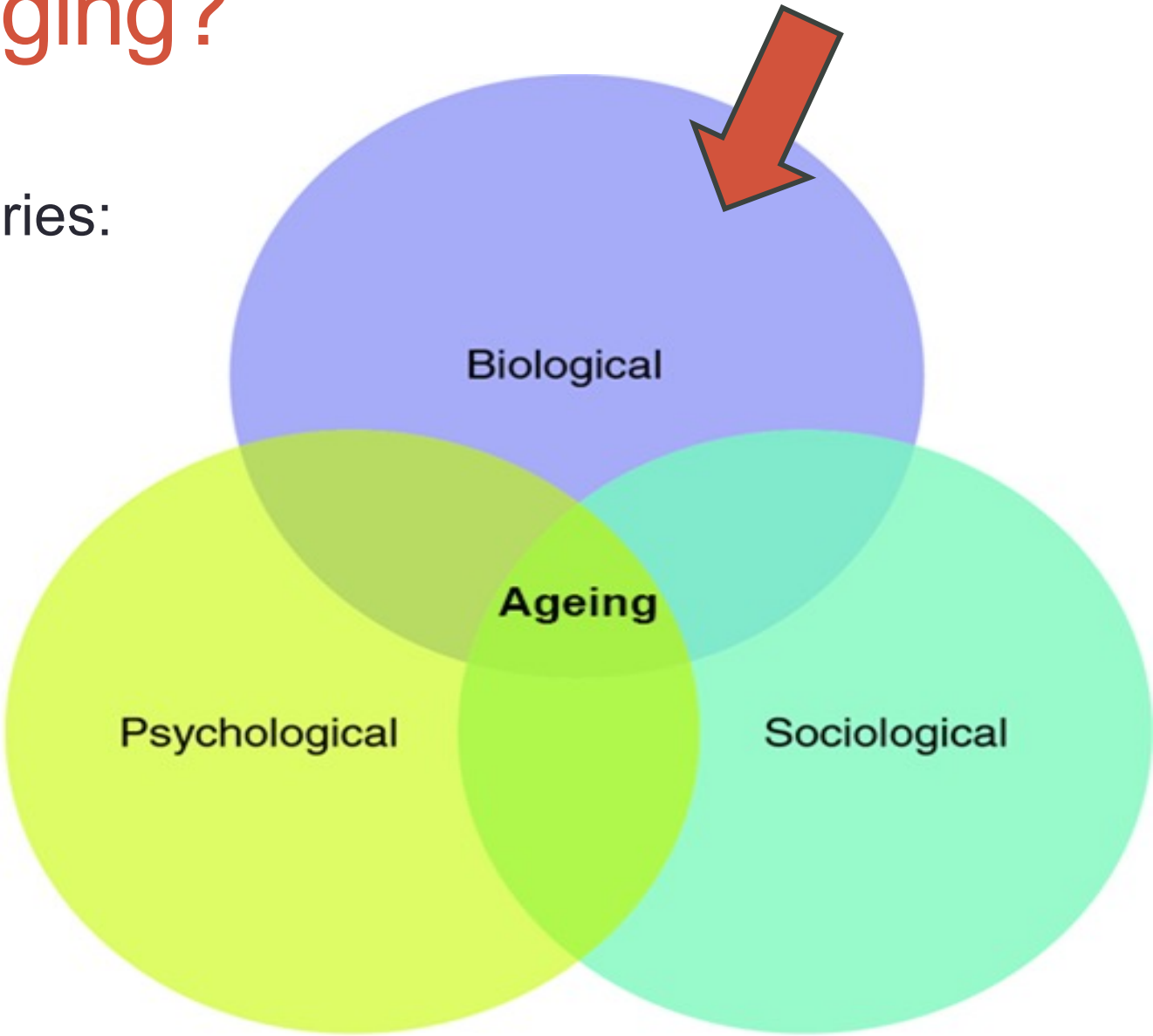

SIRT1
cellular-reprogramming
epigenetic-clock
telomeres
disposable-soma
crosslinkage
parabiosis
mutation-accumulation
ROS
resveratrol
antagonistic-pleiotropy
caloric-restriction

Today's lecture – Overview

1) Definition of aging
2) Theories of aging
   - Stochastic
   - Non-stochastic
3) Anti-Aging interventions
   - Caloric restriction
   - Cellular reprogramming
   - Parabiosis
4) Evolutionary theories of aging

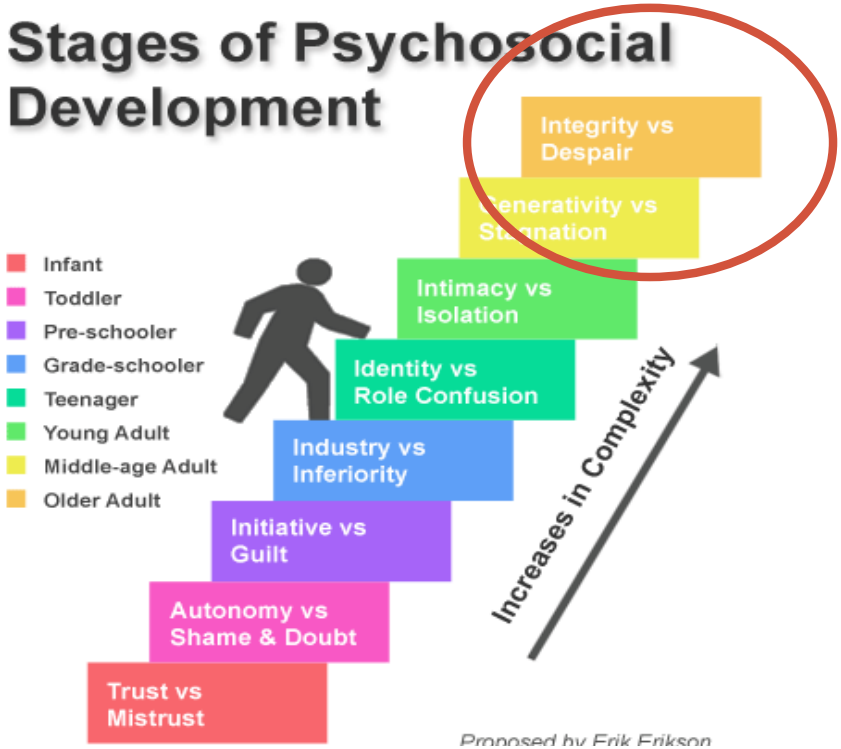
What is aging?

- Different theories:



Psychological theories

- We age in pre-defined steps (Erik Erikson, 1960):



Psychological theories

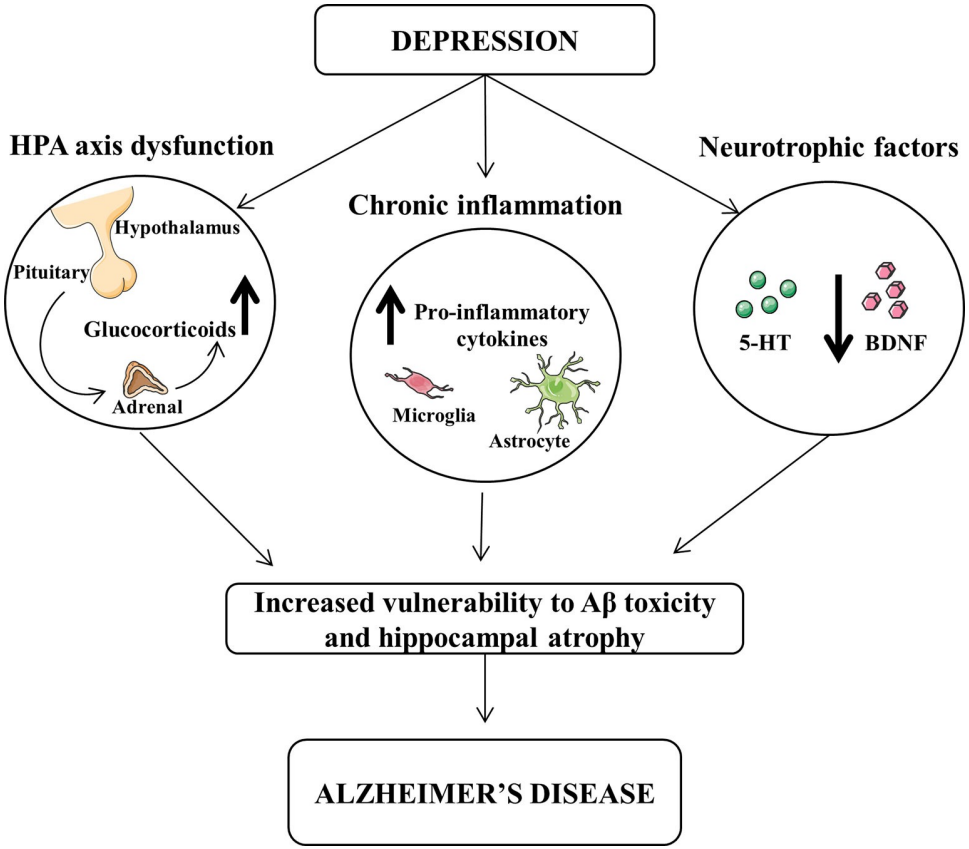
- Integrity vs despair feelings impact on the aging process per se

Psychological theories

- **Integrity ↗**
  - Acceptance
  - A sense of wholeness
  - Lack of regret
  - Feeling at peace
  - A sense of success
  - Feelings of wisdom and acceptance
- **Despair ↘**
  - Bitterness
  - Regret
  - Ruminating over mistakes
  - Feeling that life was wasted
  - Feeling unproductive
  - Depression
  - Hopelessness

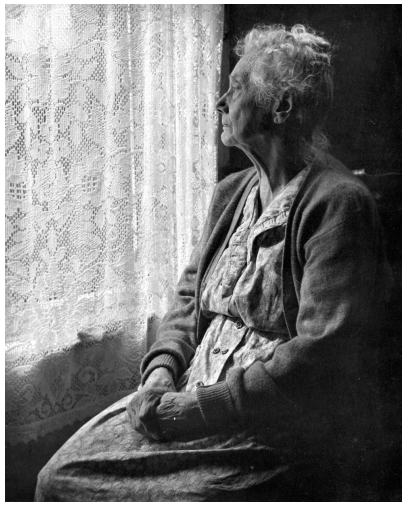
Psychological theories

- in the context of neurodegeneration:



Sociological theories

- Aging is accompanied by:
  - reduced activity
  - social disengagement
  - subculture: elderly rest among themselves



Sociological theories

- in the context of neurodegeneration:

Journal of Alzheimer's Disease Reports 7 (2023) 699–714
DOI 10.3233/ADR-230011
IOS Press

Review

The Impact of Loneliness and Social Isolation on Cognitive Aging: A Narrative Review

Abstract. Social concepts such as loneliness and social isolation are fairly new factors that have been recently gaining attention as to their involvement in changes in cognitive function and association with dementia. The primary aim of this narrative review was to describe the current understanding of how loneliness and social isolation influence cognitive aging and how they are linked to dementia. Studies have shown that there is an association between loneliness, social isolation, and reduced cognitive function, in older adults, across multiple cognitive domains, as well as a heightened risk of dementia.

Biological theories

- Aging can be defined as the time-related deterioration of the physiological functions necessary for survival and fertility.
- The aging process has two major facets.

1) Age (in numbers) itself: How long does an organism live?
2) **Senescence**, the physiological deterioration that characterizes old age.

What happens during aging, physiologically speaking?

Senescence / Biological aging

- The process by which a cell loses its ability to divide, grow, and function. This loss of function ultimately ends in death.
- Strictly degenerative without positive features.
- Characterized by the declining ability of cells to respond to stress, by increased homeostatic imbalance and increased risk of aging-associated diseases.

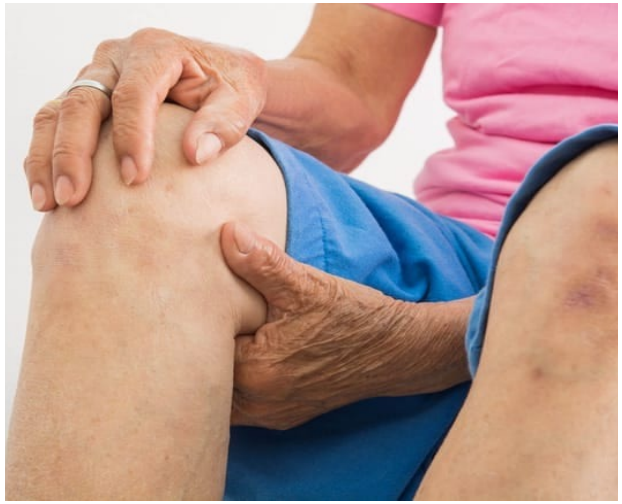
STOCHASTIC THEORIES	NON-STOCHASTIC THEORIES
WEAR AND TEAR	PROGRAMMMED
FREE RADICALS	BIOLOGICAL CLOCK
CROSS LINKAGE	NEUROENDOCRINE
SOMATIC MUTATION	IMMUNOLOGICAL

Stochastic theories of biological aging

- A stochastic or statistical perspective, which identifies episodic events that happen throughout one's life that cause random cell damage and accumulate over time, thus causing aging.

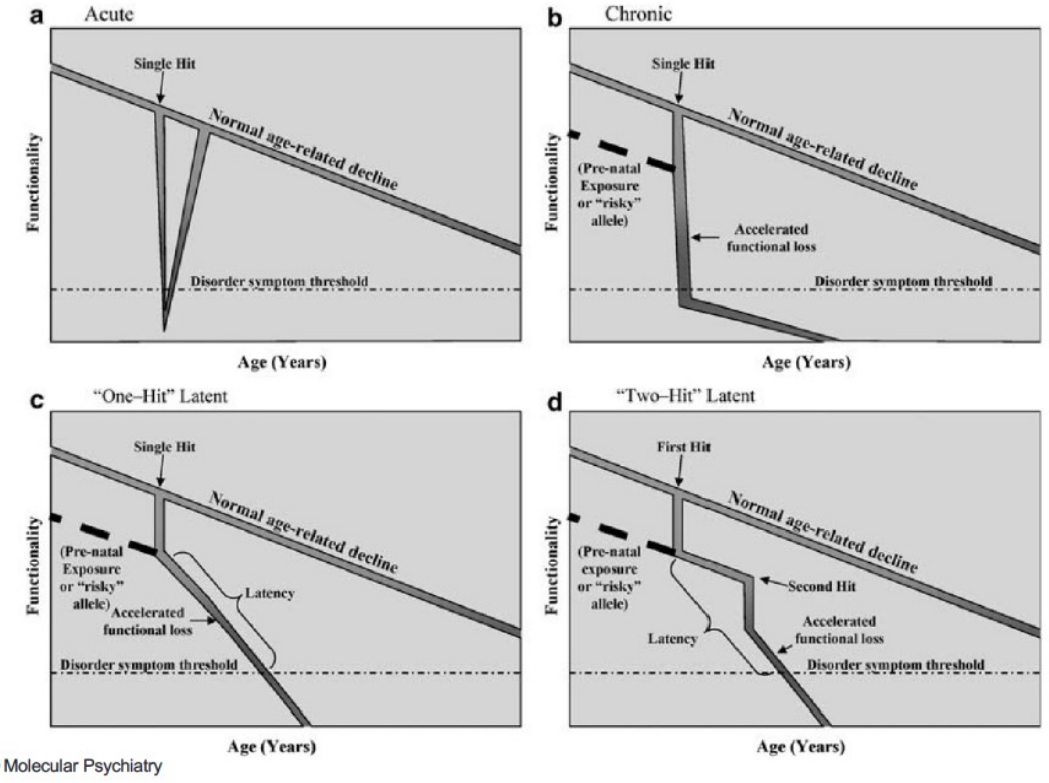
Wear and Tear

- The daily grind of life, in particular abuse or overuse, literally wears the body out, leading to disease states.
  - Example: The degeneration of cartilage and eventual grinding of bone on bone causes aging process, as wear and tear exceeds the body's ability to repair.



Wear and Tear

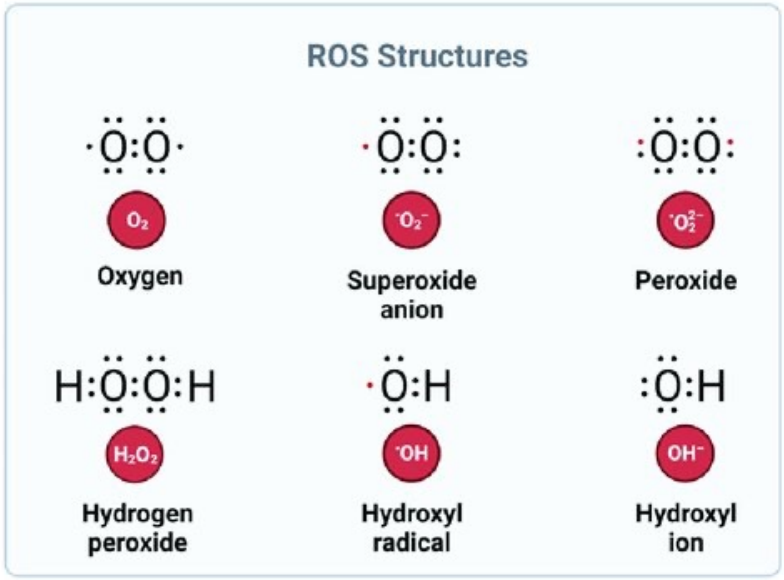
- The daily grind of life, in particular abuse or overuse, literally wears the body out, leading to disease states.
  - In neurodegeneration:
    - Multiple-hit hypothesis in AD



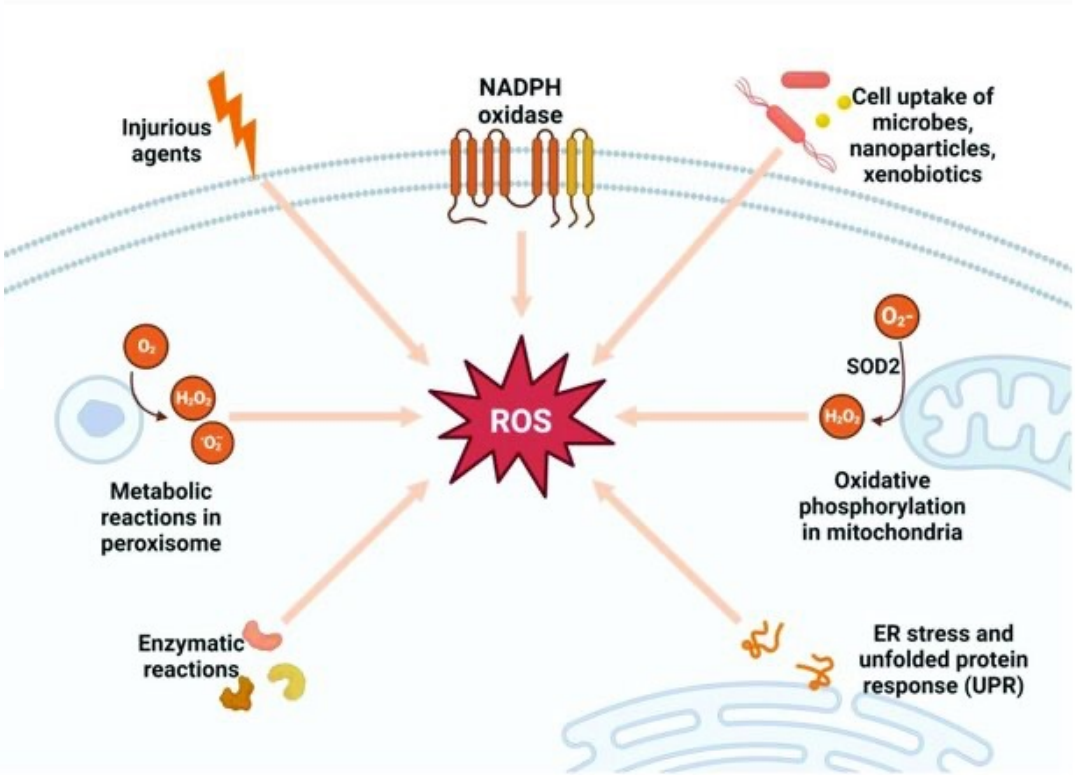
↗ Lectures Week 9

Free Radicals – Oxidative stress

- Driven by reactive oxygen species (ROS)

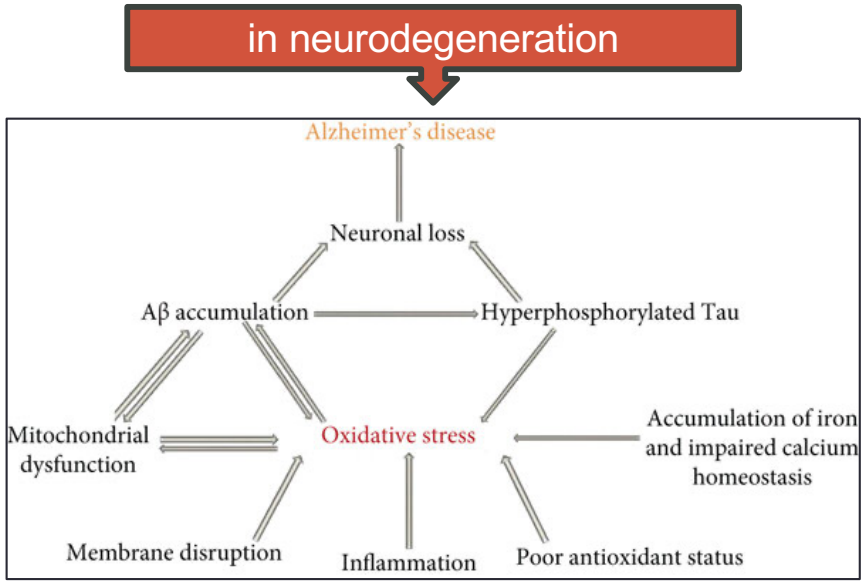


- Sources:



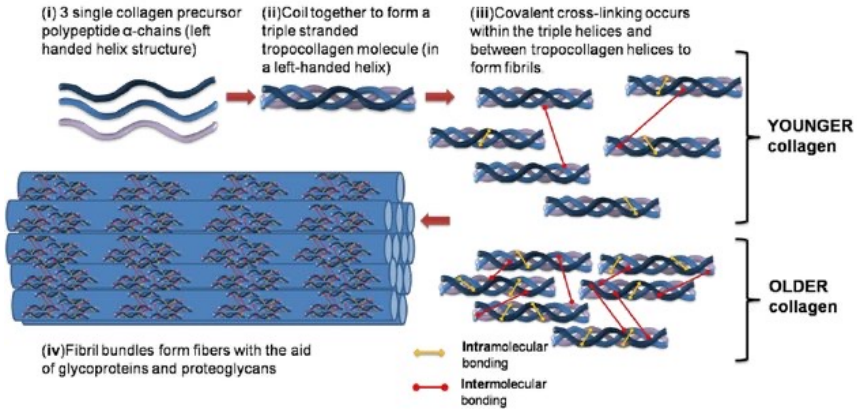
Free Radicals – Oxidative stress

- Manifold consequences of oxidative stress:



Cross Linkage

- Over time, biochemical processes create connections between structures not normally connected.
  - Collagen



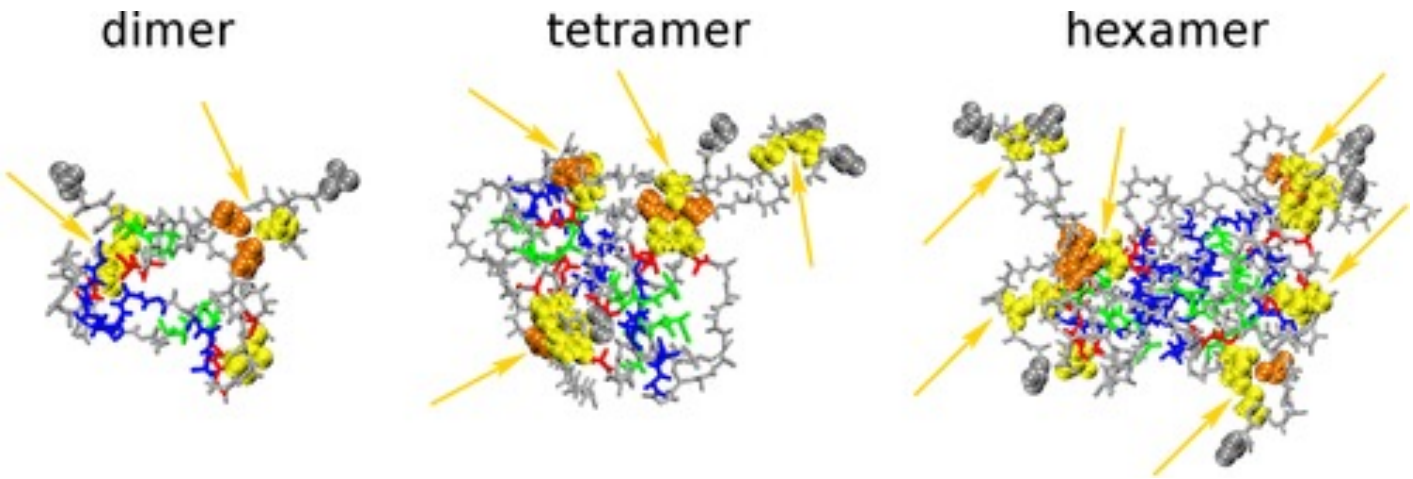
or

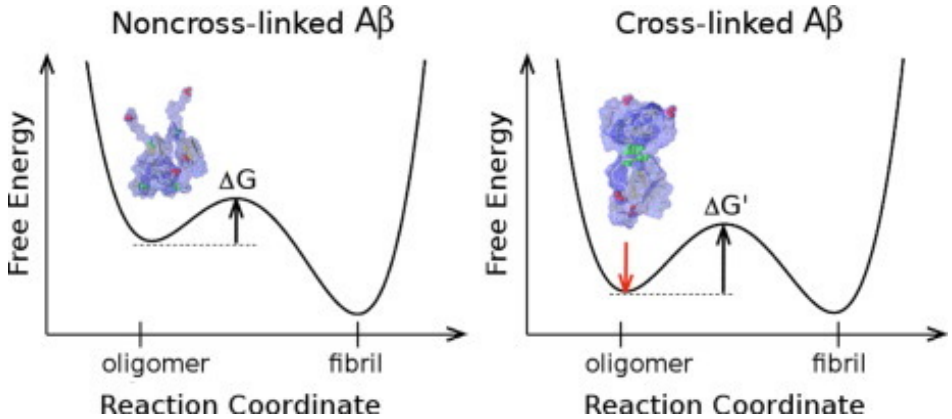
- Over time, biochemical processes loose connections between structures normally connected.
  - Elastin dries up and cracks with age. Hence skin with less elastin tends to be drier and wrinkled.

Cross Linkage

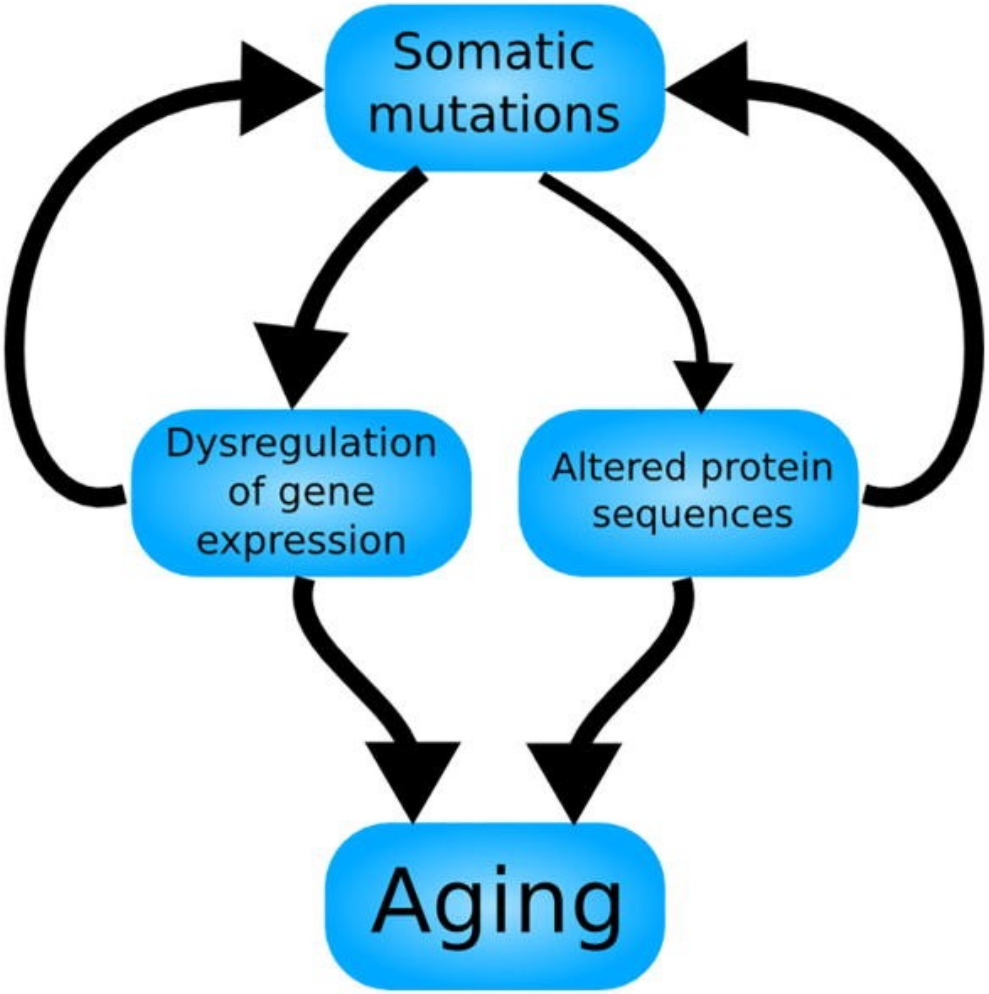
- Example of amyloid

in neurodegeneration





Somatic mutations



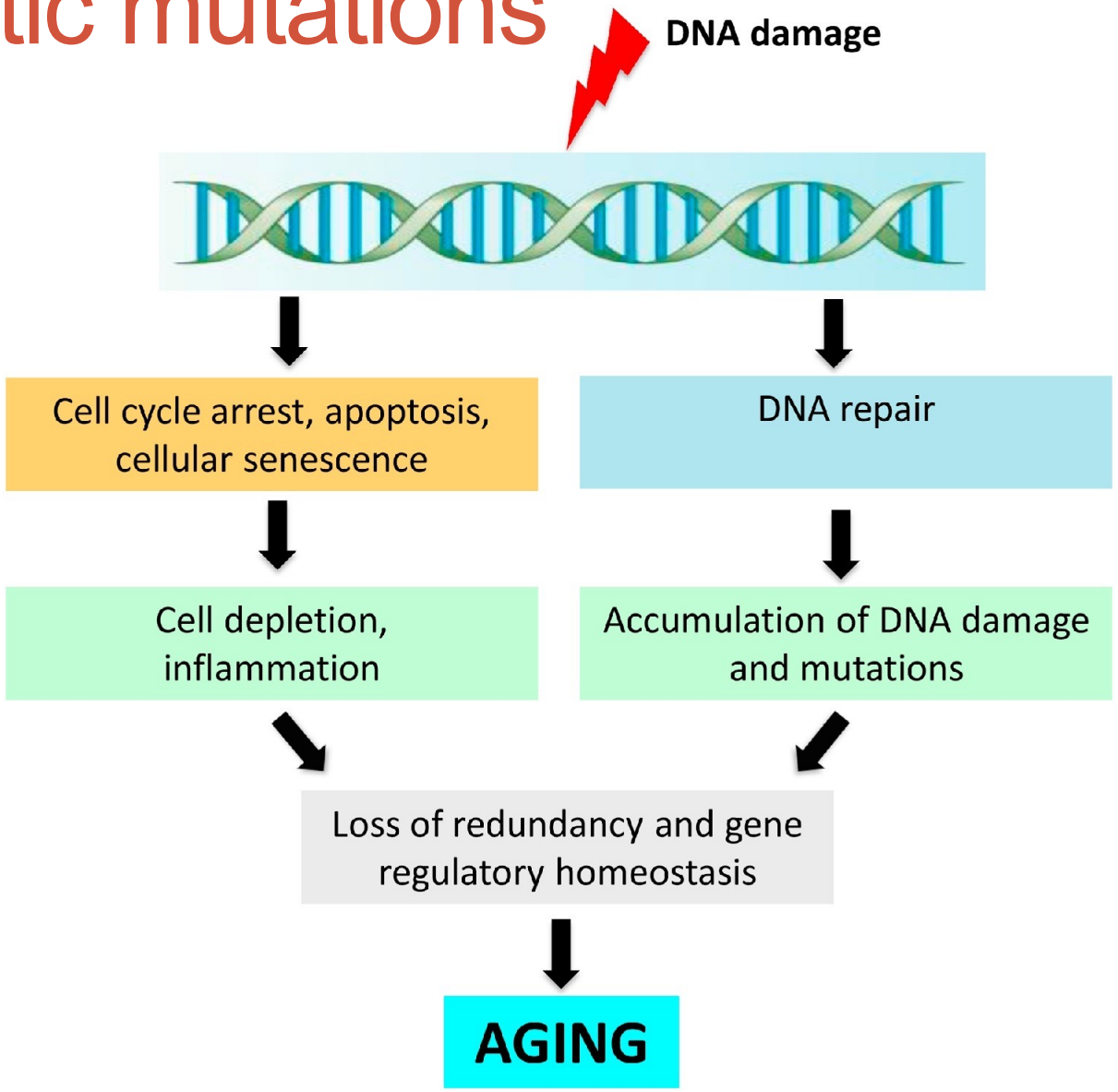
Gene regulation and DNA damage in the ageing human brain

Tao Lu[1], Ying Pan[1], Shyan-Yuan Kao[1], Cheng Li[2], Isaac Kohane[3], Jennifer Chan[4] & Bruce A. Yankner[1]

[1]*Department of Neurology and Division of Neuroscience, The Children's Hospital and Harvard Medical School, Enders 260,300 Longwood Avenue, Boston, Massachusetts 02115, USA*
[2]*Department of Biostatistics, Harvard School of Public Health, and* [3]*Department of Medicine, The Children's Hospital and Harvard Medical School, and*
[4]*Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA*

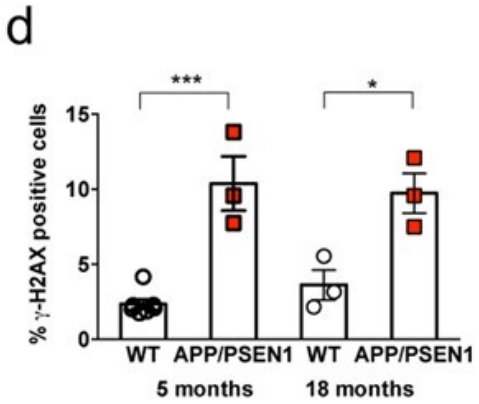
The ageing of the human brain is a cause of cognitive decline in the elderly and the major risk factor for Alzheimer's disease[1]. The time in life when brain ageing begins is undefined[2–4]. Here we show that transcriptional profiling of the human frontal cortex from individuals ranging from 26 to 106 years of age defines a set of genes with reduced expression after age 40. These genes play central roles in synaptic plasticity, vesicular transport and mitochondrial function. This is followed by induction of stress response, antioxidant and DNA repair genes. DNA damage is markedly increased in the promoters of genes with reduced expression in the aged cortex. Moreover, these gene promoters are selectively damaged by oxidative stress in cultured human neurons, and show reduced base-excision DNA repair. Thus, DNA damage may reduce the expression of selectively vulnerable genes involved in learning, memory and neuronal survival, initiating a programme of brain ageing that starts early in adult life.

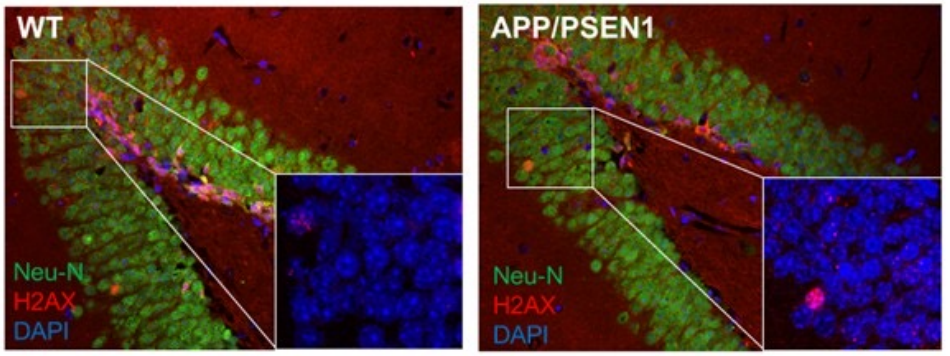
Somatic mutations



Somatic mutations

in neurodegeneration

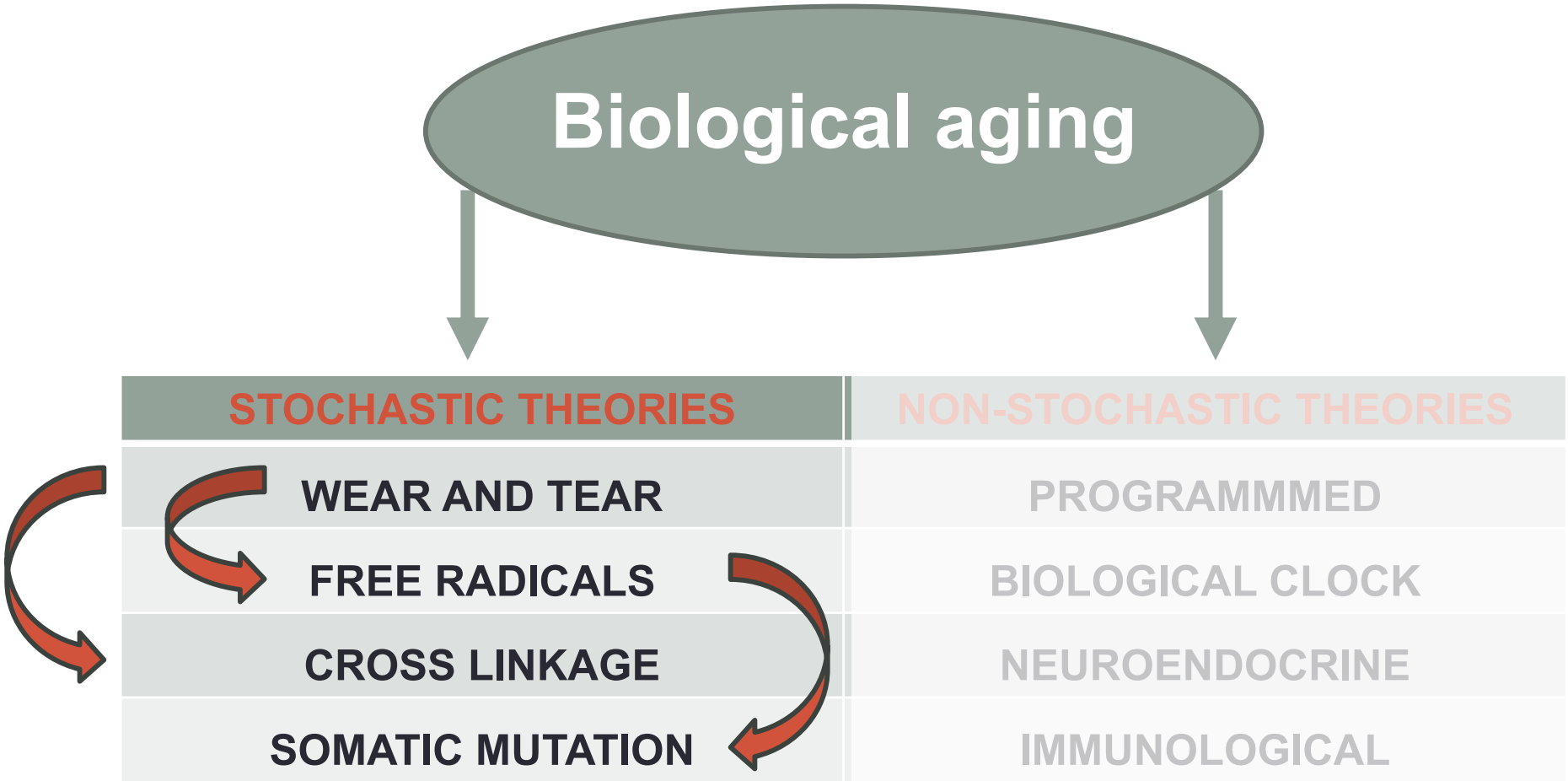




APP/PS1: A common mouse model of familial Alzheimer's disease
γH2Ax: Phosphorylated histone H2A, a sign of double stranded DNA breaks
NeuN: A marker of neuronal cells

Which of the following happen(s) during aging?

A. Oxidative stress
B. Generation of free radicals
C. Accumulation of mutations
D. Telomere shortening
E. A, B and C
F. A, B, C and D



These theories are not mutually exclusive!

STOCHASTIC THEORIES	NON-STOCHASTIC THEORIES
WEAR AND TEAR	PROGRAMMMED
FREE RADICALS	BIOLOGICAL CLOCKS
CROSS LINKAGE	NEUROENDOCRINE
SOMATIC MUTATION	IMMUNOLOGICAL

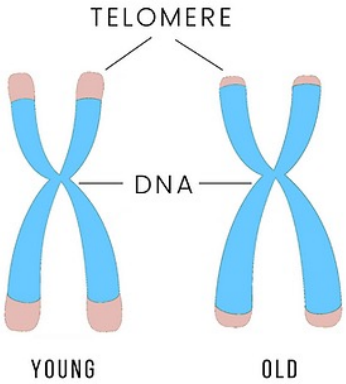
Non-stochastic / programmed theories of biological aging

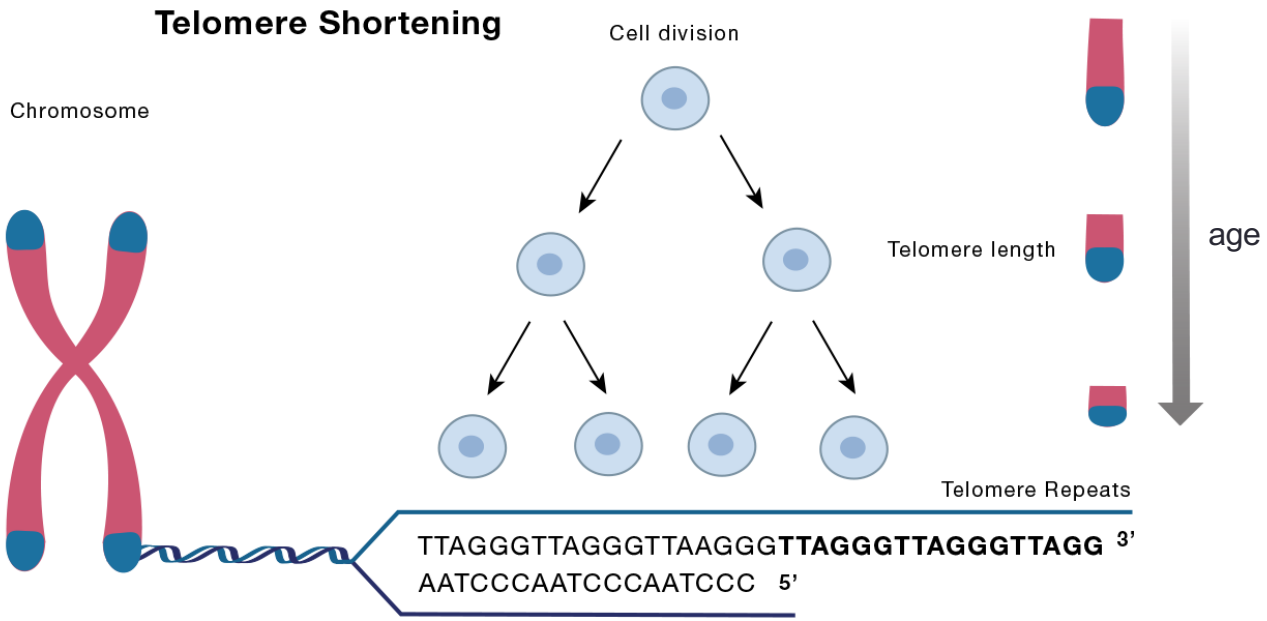
- Non-stochastic theories view aging as a series of predetermined events happening to all organisms within a time framework.

- Cells divide until they can no longer divide, whereupon the cell's **infrastructure** recognizes this inability to further divide and triggers the apoptosis sequence or death of the cell (Hayflick limit, 1961)

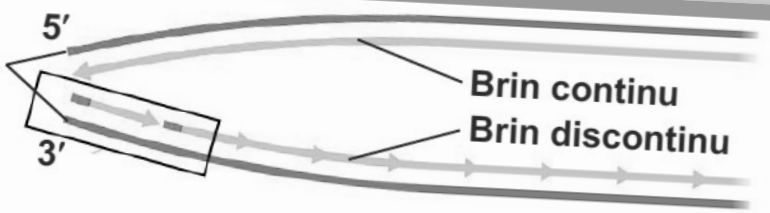
Telomere shortening is programmed

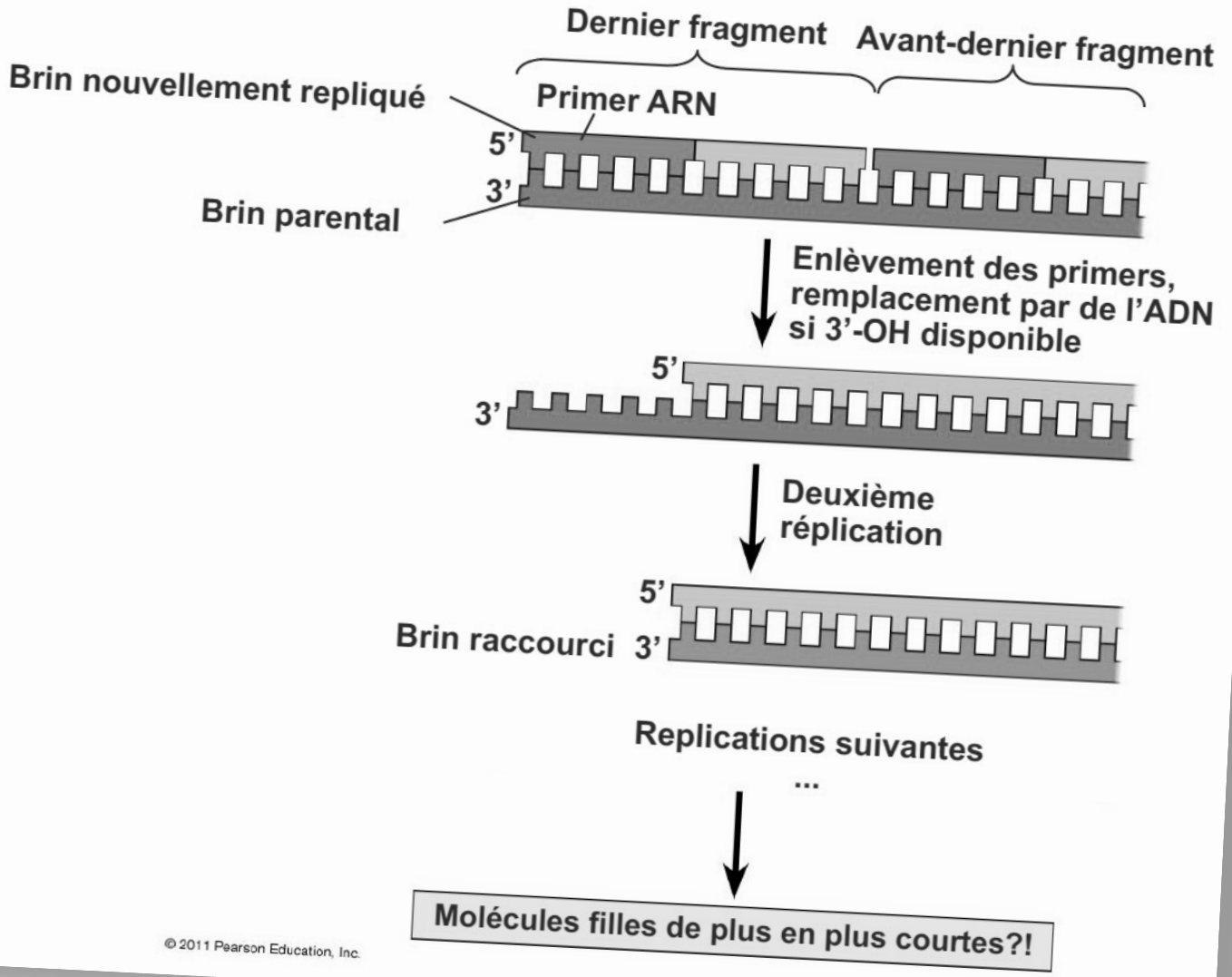
- One such ”infrastructure” is telomere shortening





3’ end problem:





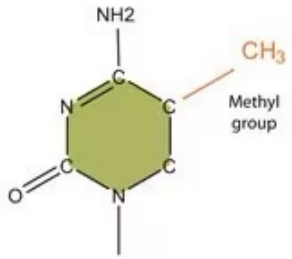
Bio-ENG110

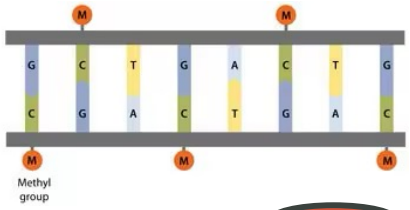
Biological clocks

- Each cell, or perhaps the entire organism, has a genetically programmed aging code that is stored in the organism's DNA.
- Cause or effect unclear!
  - Best understood example: Epigenetic clocks

Epigenetic clocks

- With age, there are increased levels of changes in **DNA methylation**, an epigenetic modification
  - occurs on C (cytosine) bases of the DNA, at position 5





↗ Lectures Week 11

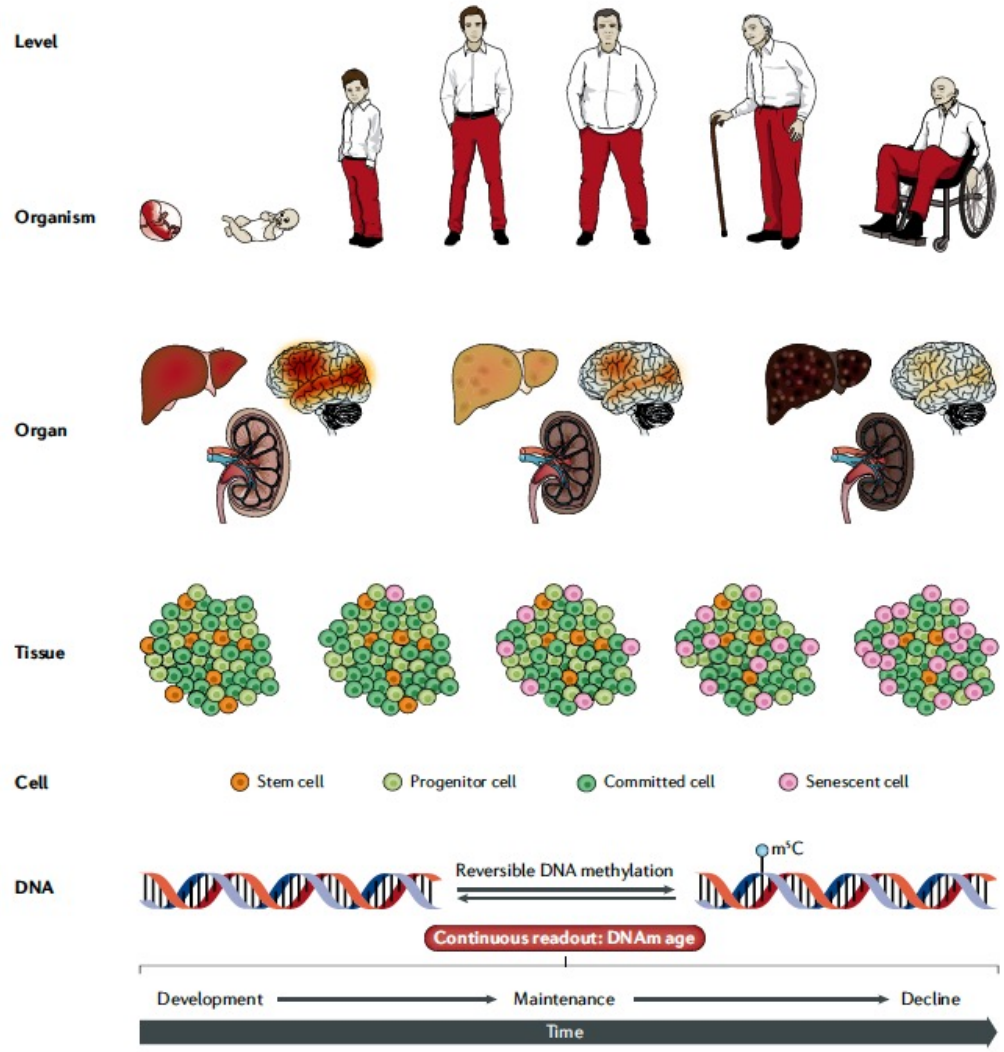


Fig. 3 | **Tissue function versus DNA methylation-based age.** DNA methylation-based (DNAm) age is a continuous readout of molecular processes that play a role in development, tissue maintenance and, ultimately, decline. DNAm age increases as stem and progenitor cells undergo differentiation to produce more committed cells for growth during the early developmental years and for replenishment of committed cells during the maintenance years (after 20 years). The precise mechanisms linking the innate molecular processes to the decline in tissue function probably relate to subtle changes in cell composition, for example, a decline in somatic stem cells, and/or the loss of cellular identity. Independently, senescent cells, which are not measured by the multi-tissue DNAm age estimator, begin to accumulate in later years owing to numerous factors unrelated to epigenetic ageing. In time, these collective changes at the cellular level compromise tissue fitness, leading to the decline of organ functions and the manifestation of physical ageing. m^5C, 5-methylcytosine.

Epigenetic clocks

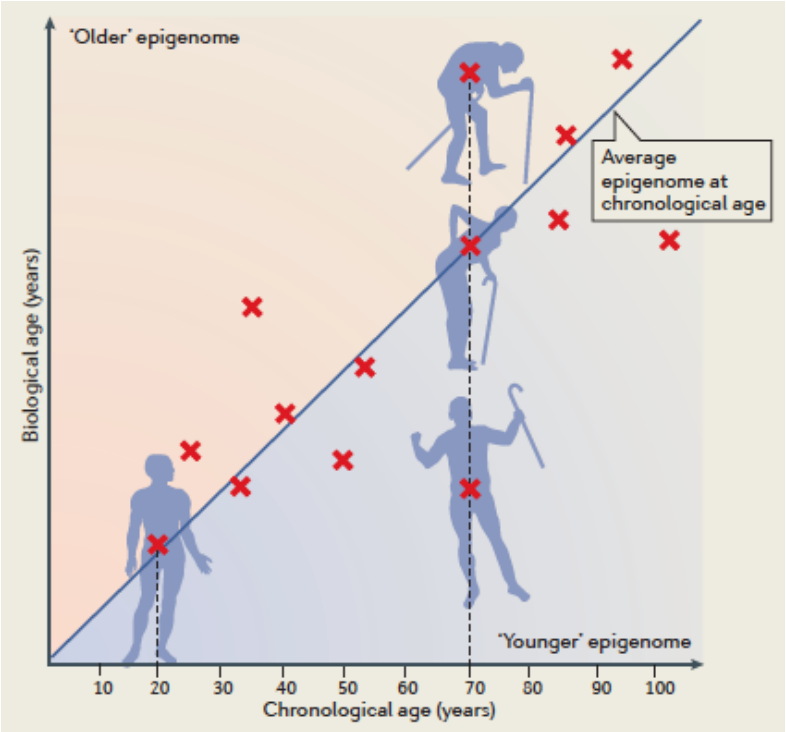
- These DNA methylation changes reflect biological age, rather than chronological age

EPIGENETICS

DNA methylation-based biomarkers and the epigenetic clock theory of ageing

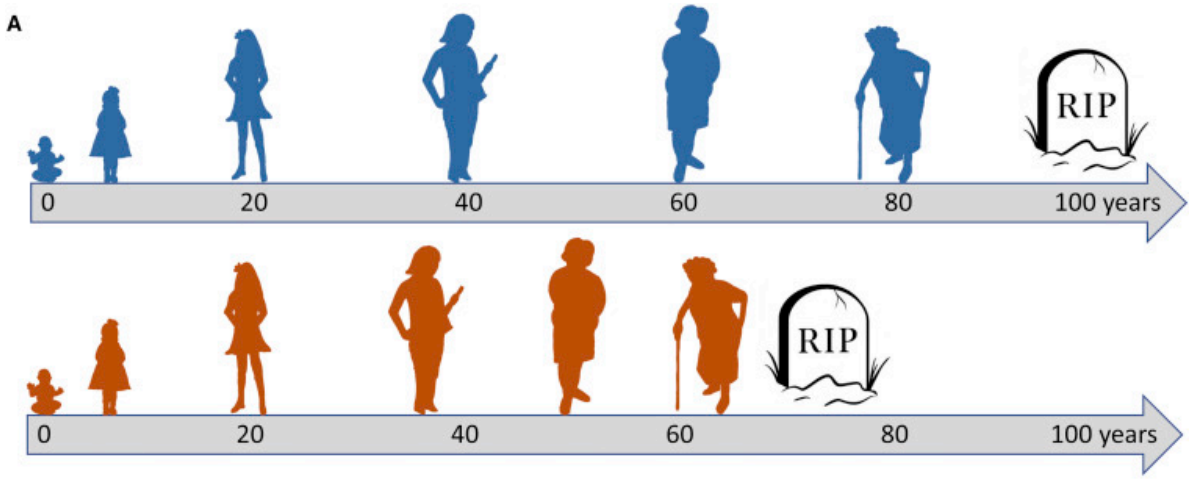
Steve Horvath[1,2] and Kenneth Raj[3]*

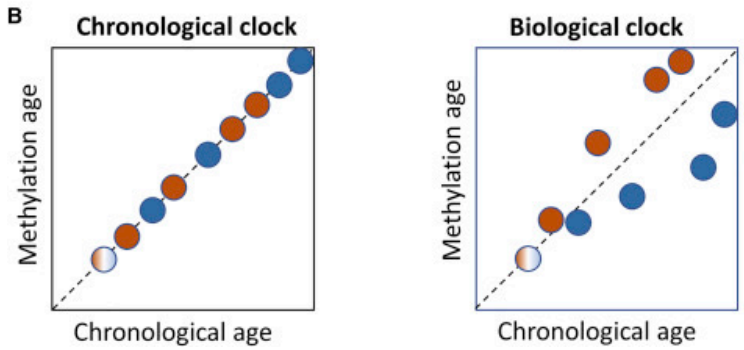
Abstract | Identifying and validating molecular targets of interventions that extend the human health span and lifespan has been difficult, as most clinical biomarkers are not sufficiently representative of the fundamental mechanisms of ageing to serve as their indicators. In a recent breakthrough, biomarkers of ageing based on DNA methylation data have enabled accurate age estimates for any tissue across the entire life course. These 'epigenetic clocks' link developmental and maintenance processes to biological ageing, giving rise to a unified theory of life course. Epigenetic biomarkers may help to address long-standing questions in many fields, including the central question: why do we age?



Epigenetic clocks

- These DNA methylation changes reflect biological age, rather than chronological age





Epigenetic clocks

- Multiple such clocks exist nowadays
  - Different performance in different tissues

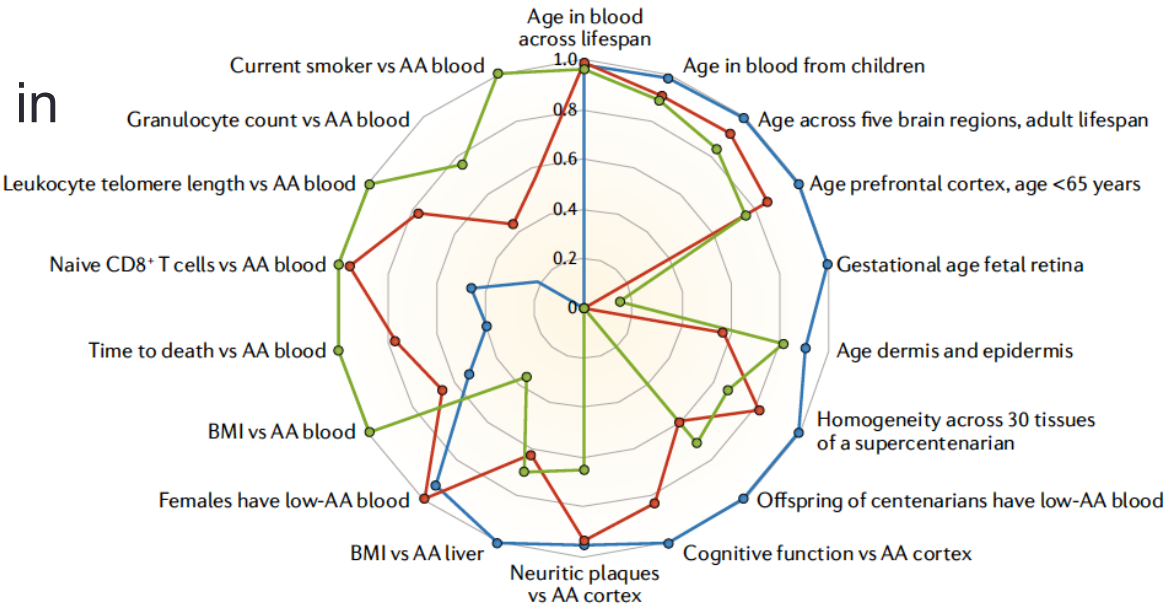
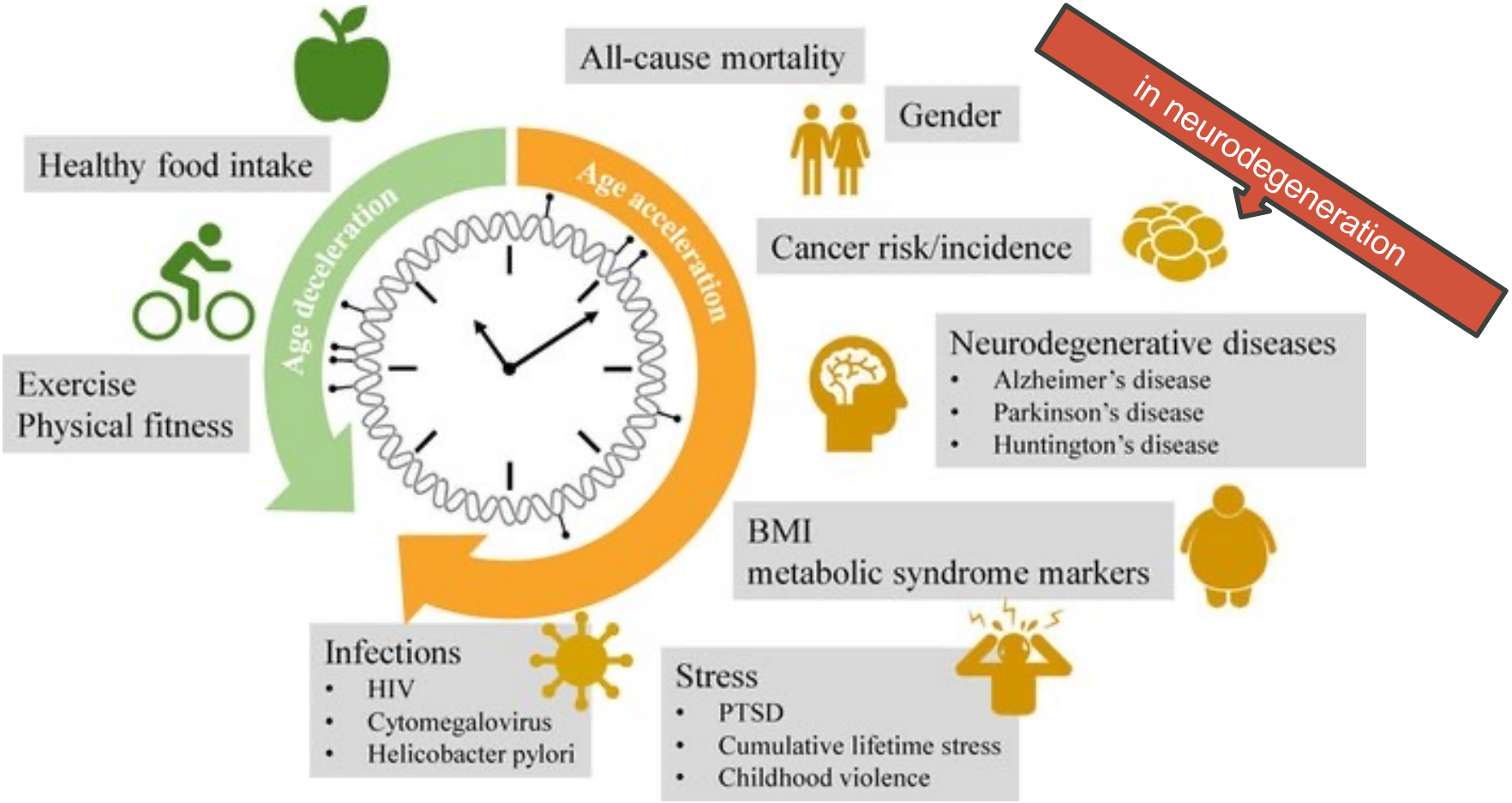


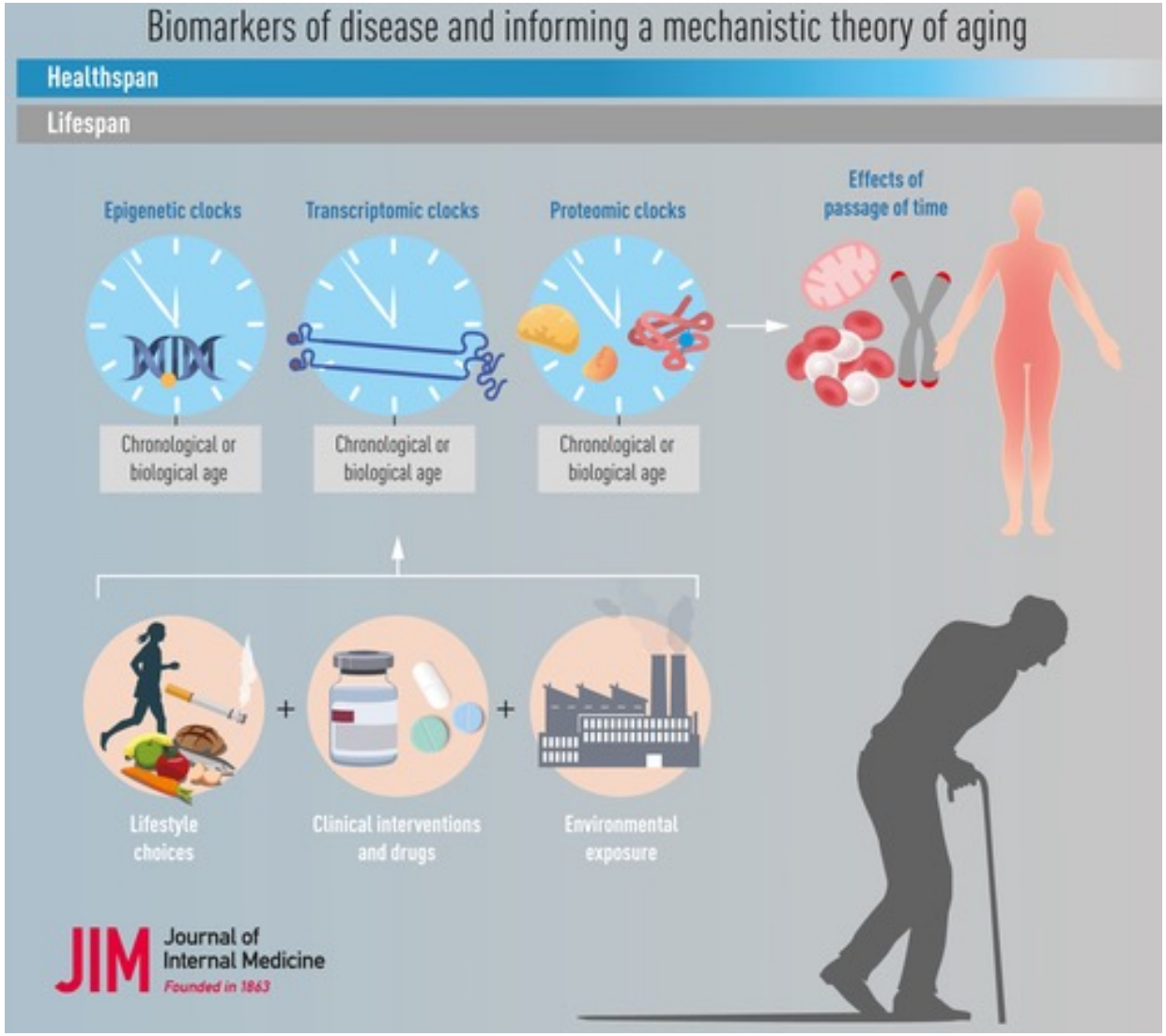
Fig. 1 | **Comparison of three DNA methylation-based biomarkers of ageing.** The multi-tissue DNA methylation-based (DNAm) age estimator (blue line), also known as Horvath's clock, stands out in terms of its correlation with chronological age across multiple tissue types, its high accuracy in children, its strong correlation with gestational age (differentiation day) in neuronal cell culture models and the homogeneity of its age estimates across tissues, for example, 30 tissue samples collected from a supercentenarian (>110 years)[56]. The phenotypic age estimator (green line), or DNAm PhenoAge stands out in terms of its predictive accuracy for time to death, its association with smoking status and its association with various markers of immunosenescence[59]. In general, DNAm PhenoAge and DNAm age as calculated by the single-tissue age estimator known as Hannum's clock (red line) outperform other blood-based biomarkers in regard to lifespan prediction. Supplementary information contains the data and details on the construction of this radar plot. AA stands for (epigenetic) age acceleration, for example, 'AA blood' denotes age acceleration in blood. BMI, body mass index.

Epigenetic clocks

- These clocks reflect age-related influences

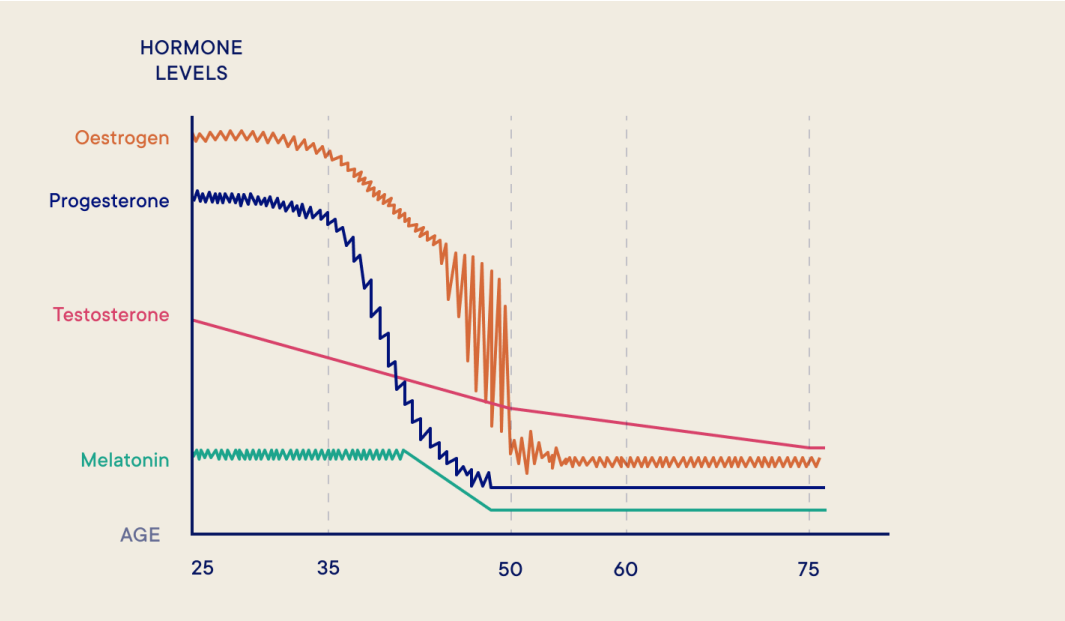


Other **biological** clocks exist as well



Neuroendocrine theory

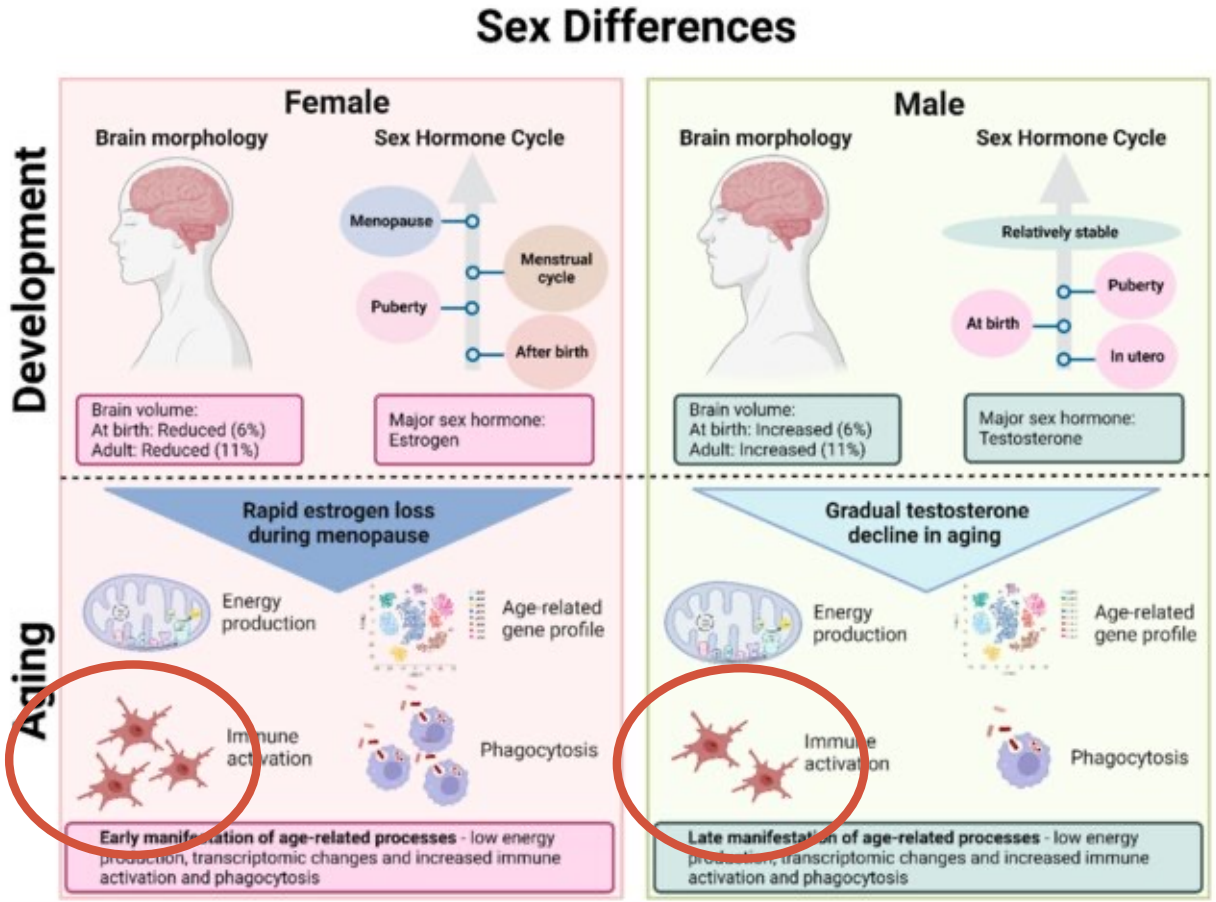
- Hormonal changes contribute to aging
  - Example in females: Post-menopausal drop in estrogen



  - Example in males: Age-related decreased testosterone levels

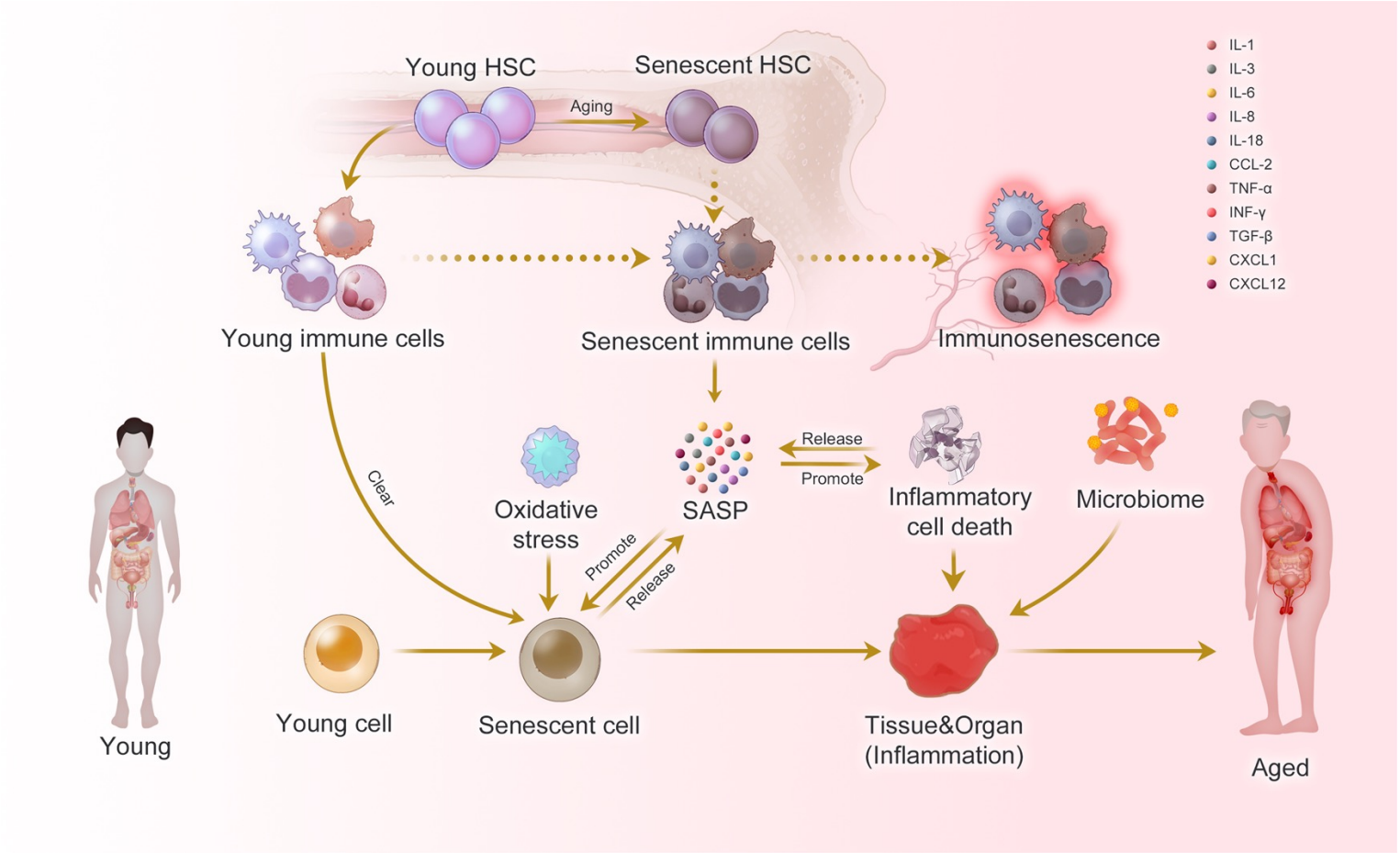
Neuroendocrine theory

- Hormonal changes contribute to aging



Immunological theory

- Compromised immune system and function with age



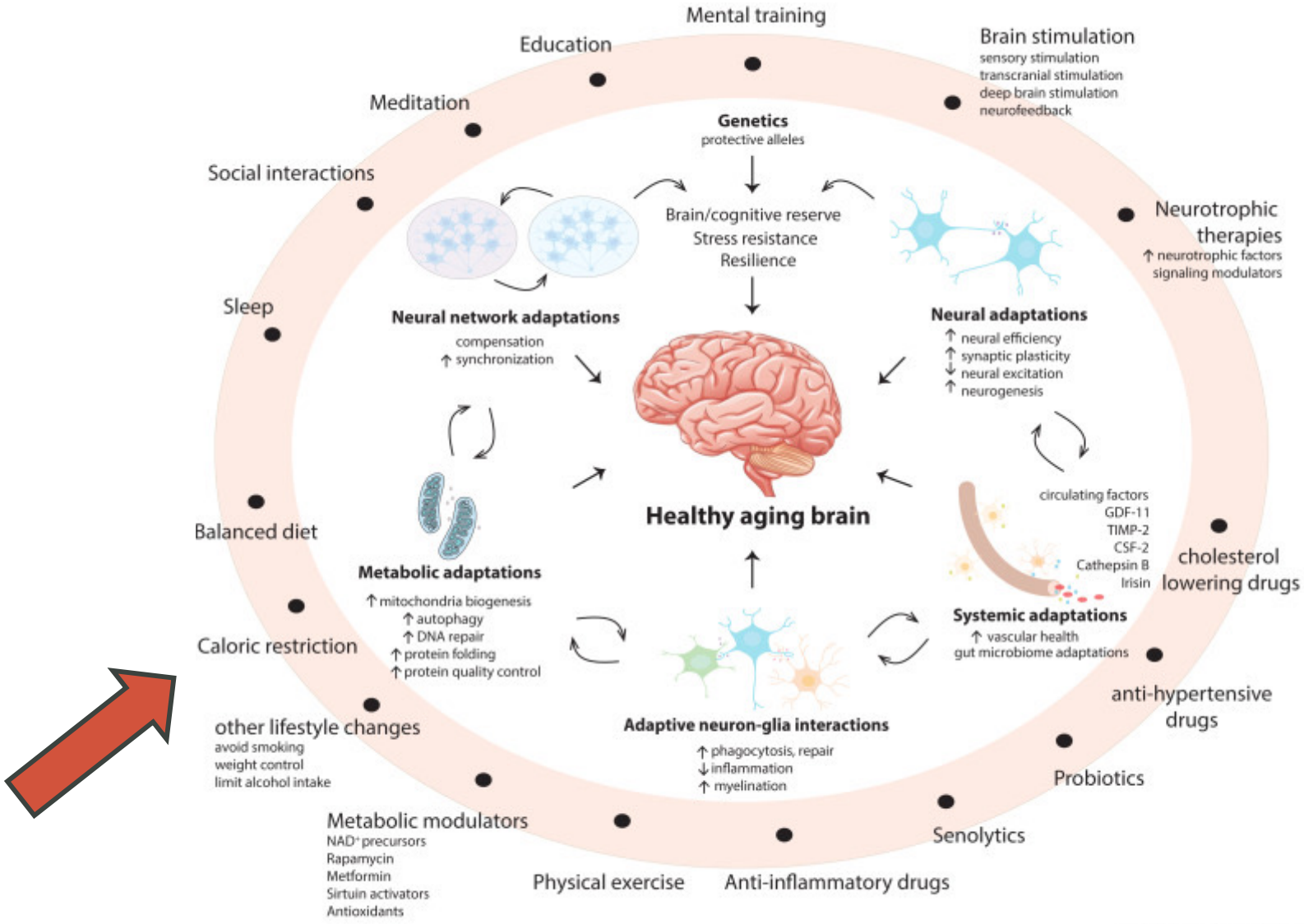
HSC, hematopoetic stem cell
IL, interleukin
SASP, senescence-associated secretory proteins

Irrespective of the theory, there are conserved physiological hallmarks of aging:

✓ = occurrence in neurodegenerative disorders too!

How can aging be prevented?

Anti-aging interventions



Today's lecture – Overview

1) Definition of aging
2) Theories of aging
   - Stochastic
   - Non-stochastic
3) Anti-Aging interventions
   - Caloric restriction
   - Parabiosis
   - Cellular reprogramming
4) Evolutionary theories of aging

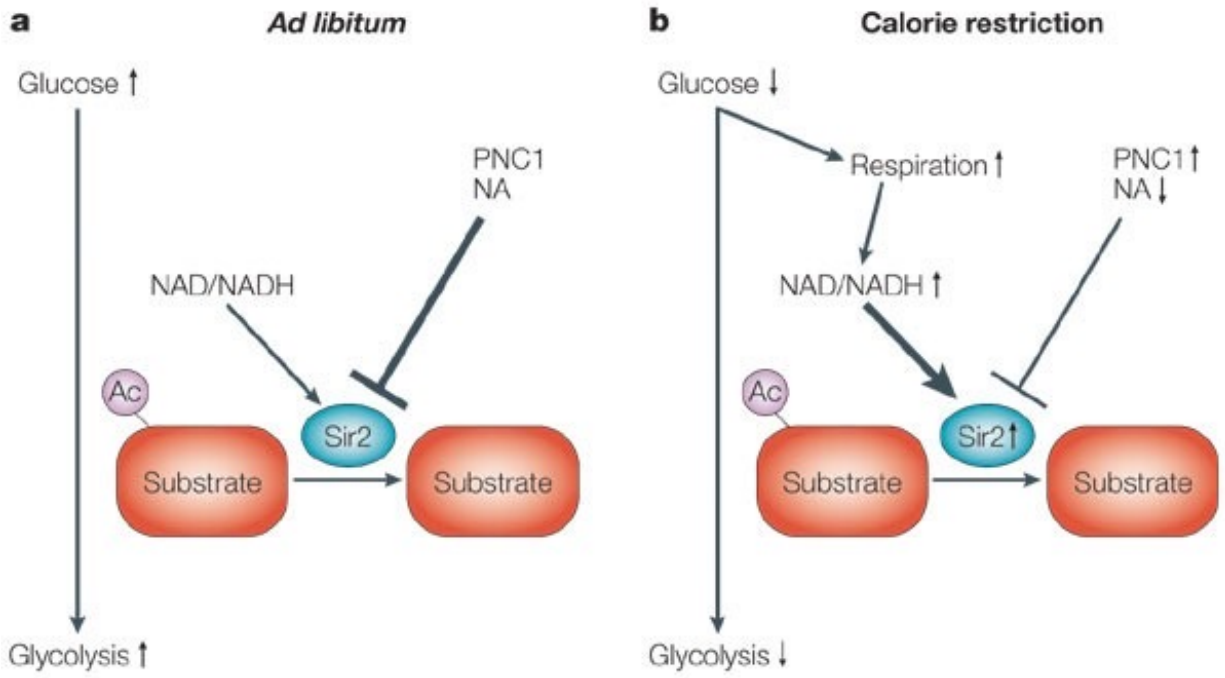
Caloric restriction

- = reduced caloric intake by ~ 30%

	Life-span increase	
	Dietary restriction	Mutations/ drugs
 Yeast	3-fold	10-fold (with starvation/ DR)
 Worms	2- to 3-fold	10-fold
 Flies	2-fold	60–70%
 Mice	30–50%	30–50% (~100% in combination with DR)
 Monkeys	Trend noted	Not tested
 Humans	Not determined	Not determined (GHR-deficient subjects reach old age)

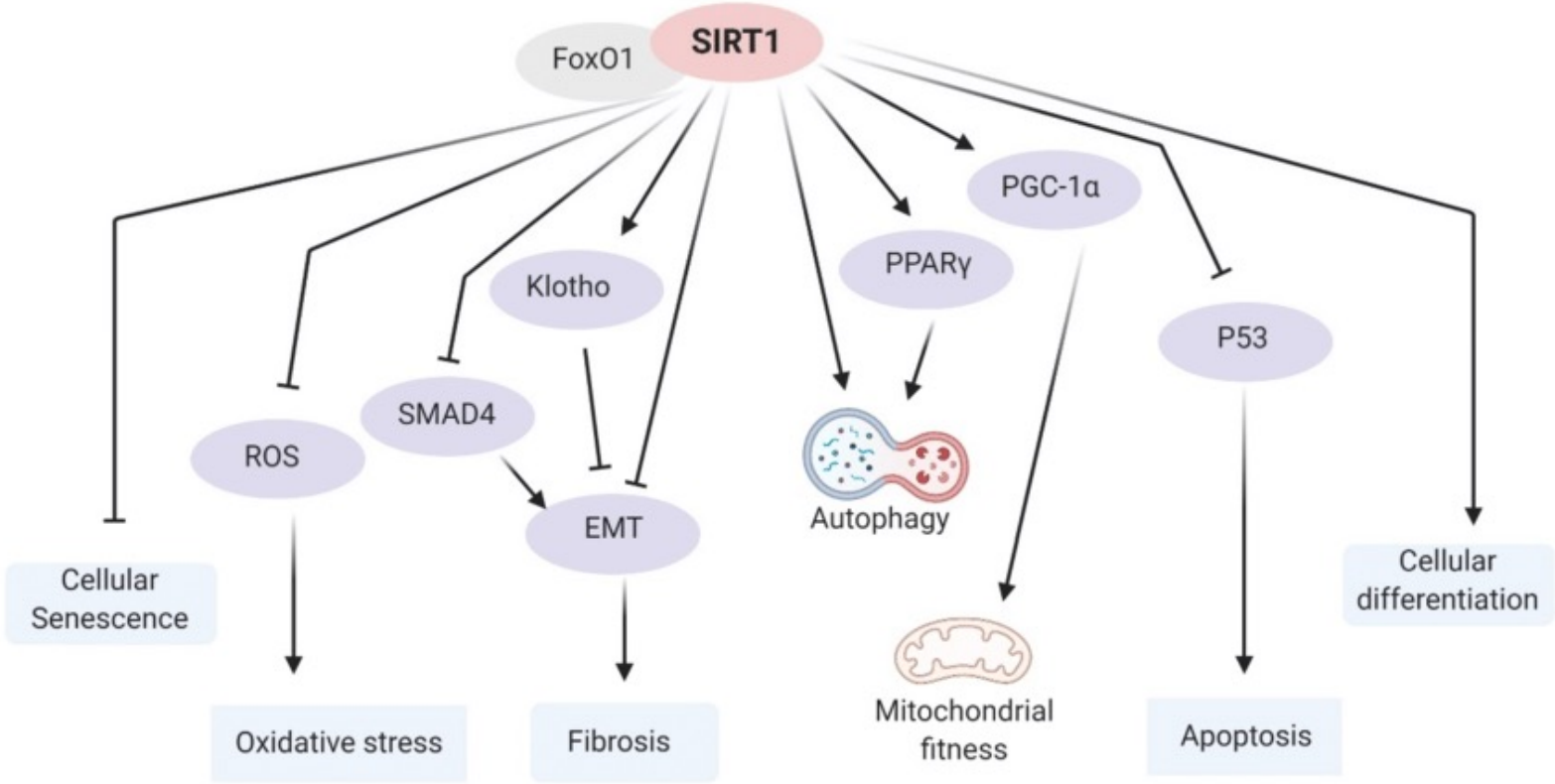
Caloric restriction

- mode of action
  - alteration of NAD/NADH balance, a metabolic co-enzyme
  - activation of SIRT1



Caloric restriction

- mode of action
  - alteration of NAD/NADH balance, a metabolic co-enzyme
  - activation of **SIRT1**



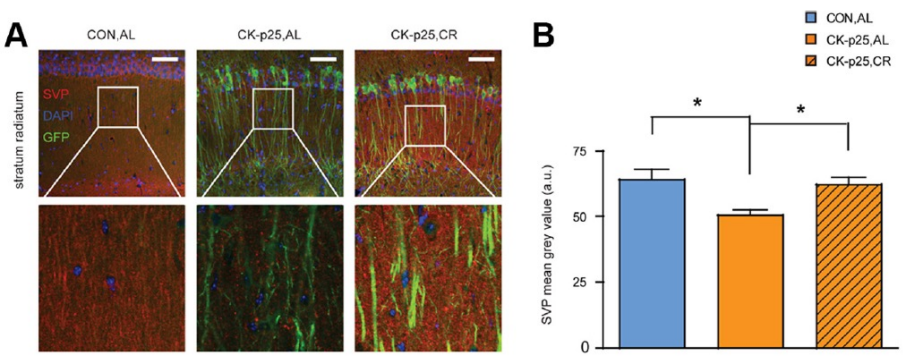
Caloric restriction

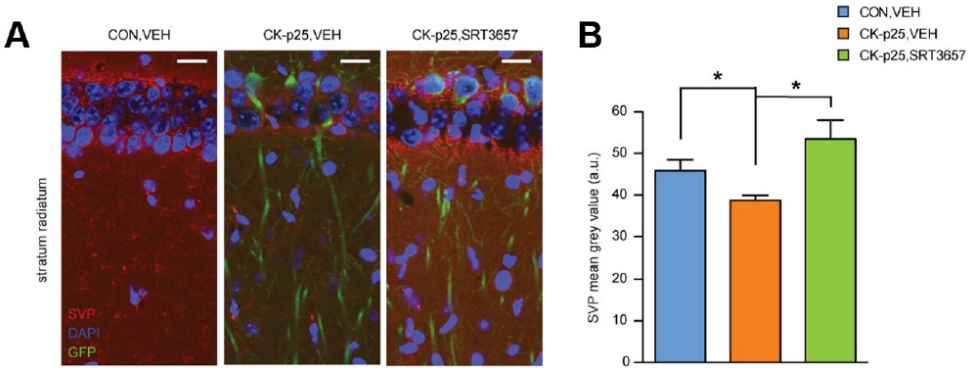
in neurodegeneration

- against AD:

Neurobiology of Disease

A Dietary Regimen of Caloric Restriction or Pharmacological Activation of SIRT1 to Delay the Onset of Neurodegeneration

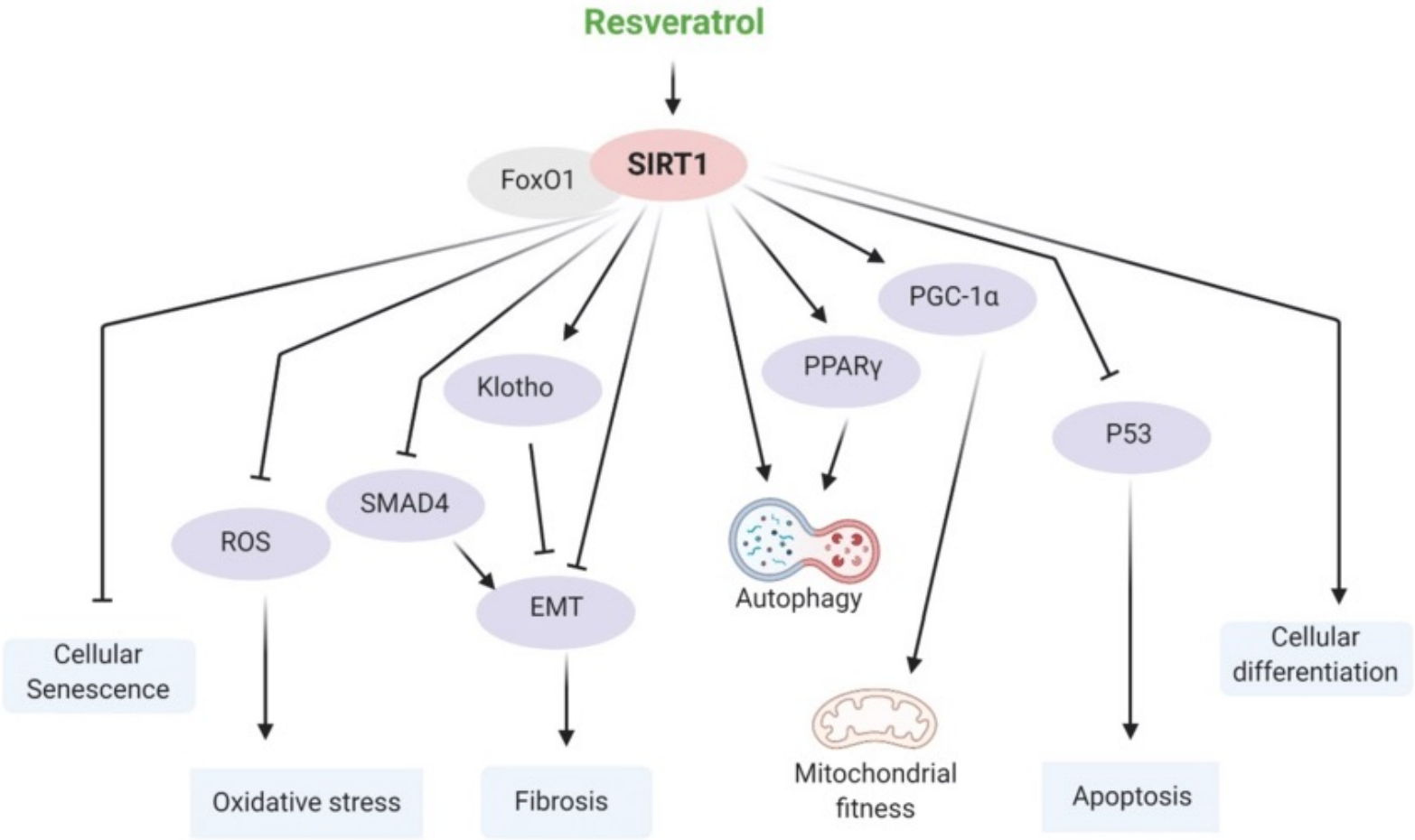




AL, ad libitum
CK-p25, a mouse model of Alzheimer's disease
CR, caloric restriction
SRT, SIRT1 activating compound
SVP, synaptophysin
VEH, vehicle treatment

Caloric restriction

- A natural activator of SIRT1: Resveratrol?



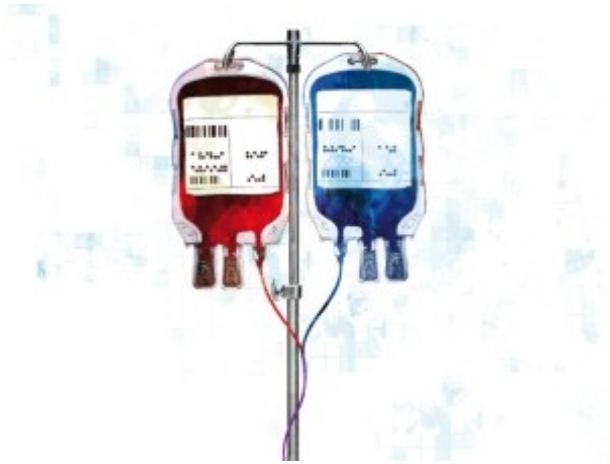
Caloric restriction

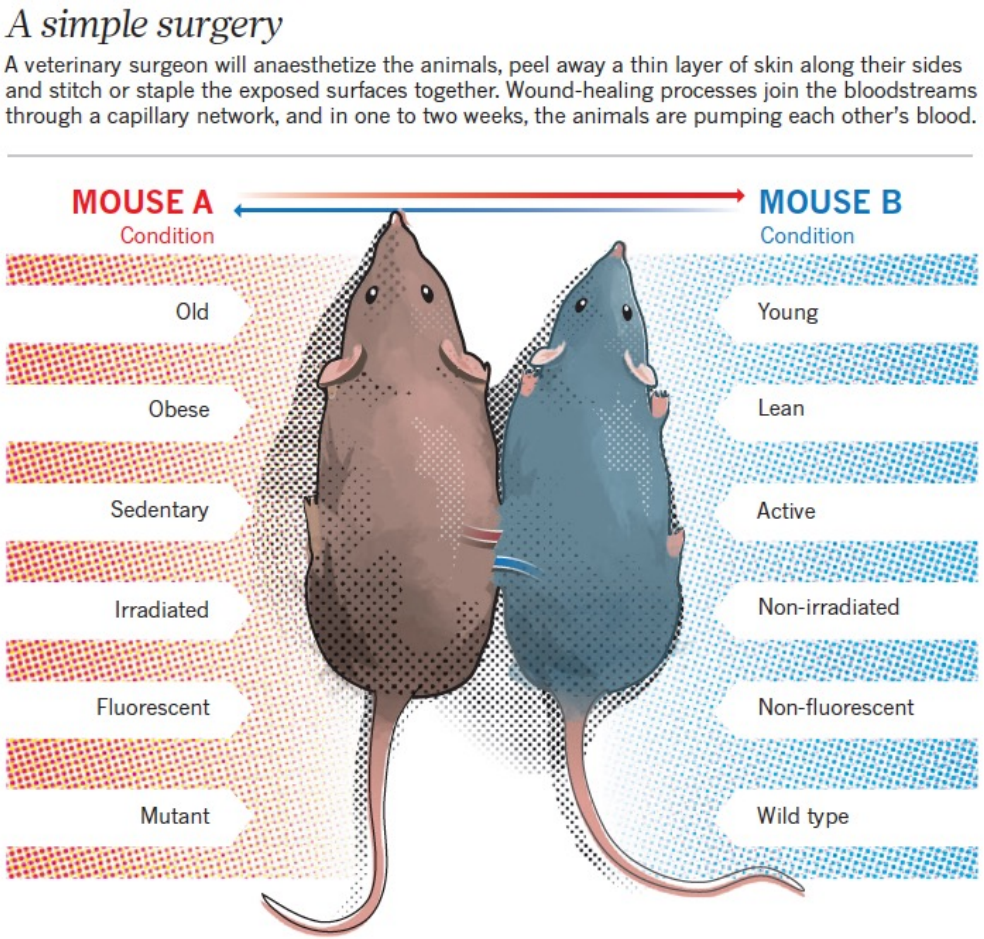
- Resveratrol is found in red wine...
- But...

Red wine may be much more potent than was thought in extending human lifespan, researchers say in a new report that is likely to give impetus to the rapidly growing search for longevity drugs. The study is based on dosing mice with resveratrol, an ingredient of some red wines. . . . [In a related study] scientists used a dose on mice equivalent to just 35 bottles a day.
—*The Times*.

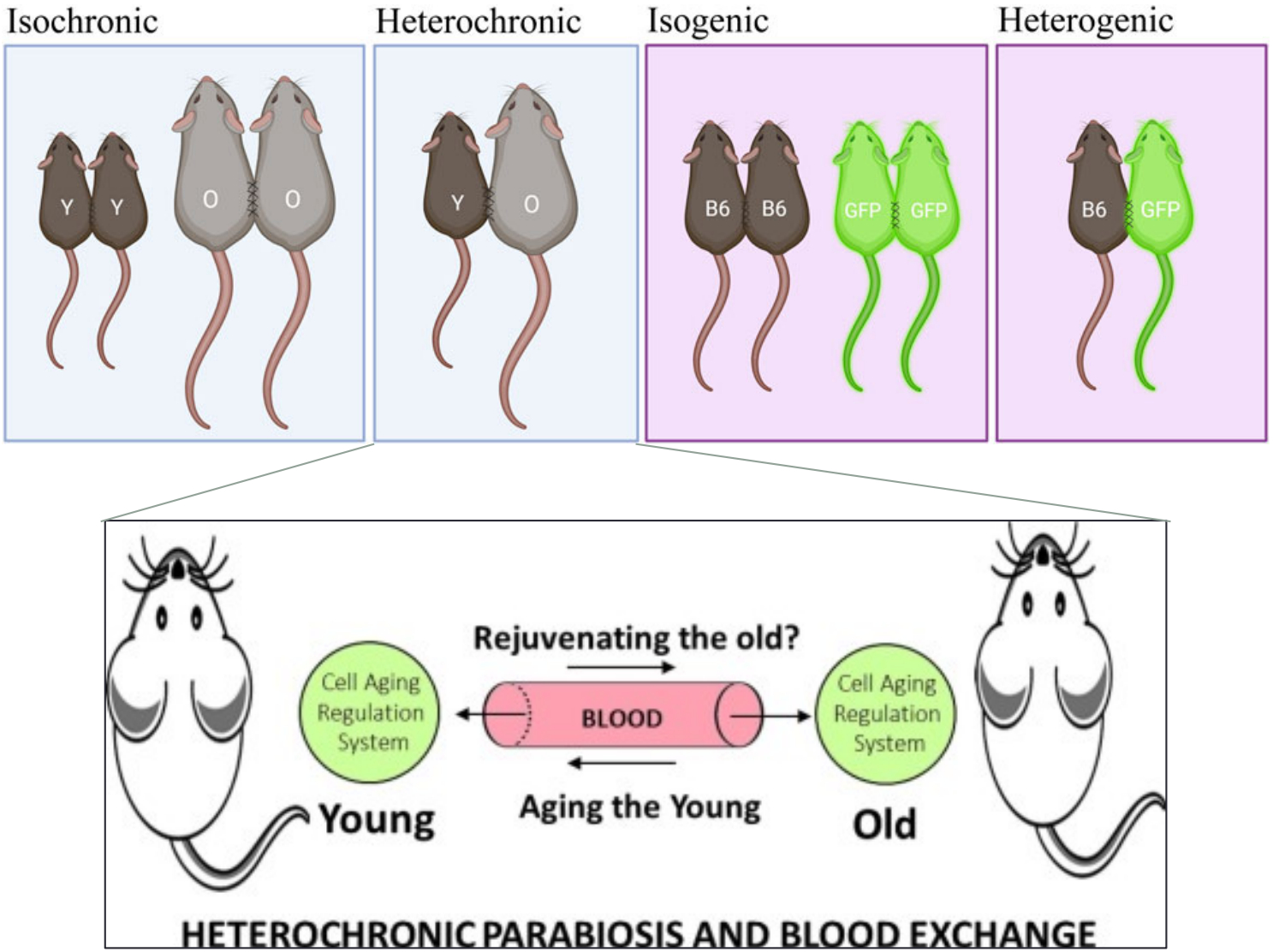
Parabiosis

- Connecting the blood system between two animals





Parabiosis



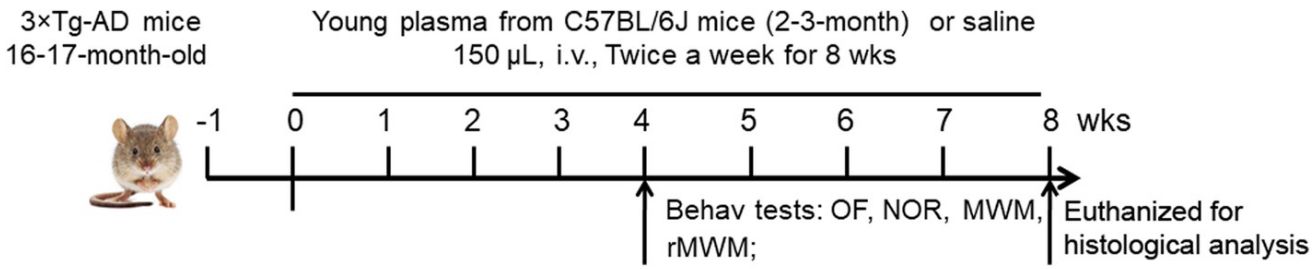
Parabiosis

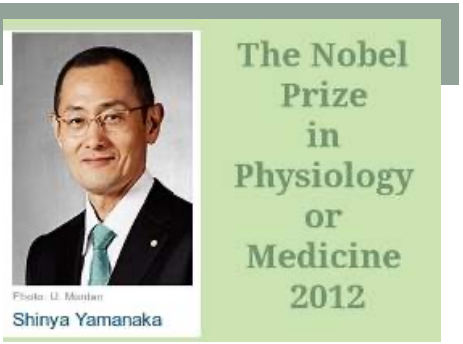
in neurodegeneration

- Unclear effects against neurodegeneration

Preclinical Assessment of Young Blood Plasma for Alzheimer Disease

Jinte Middeldorp, PhD; Benoit Lehallier, PhD; Saul A. Villeda, PhD; Suzanne S. M. Miedema, MSc; Emily Evans; Eva Czirr, PhD; Hui Zhang, PhD; Jian Luo, MD, PhD; Trisha Stan, PhD; Kira I. Mosher, PhD; Eliezer Masliah, MD, PhD; Tony Wyss-Coray, PhD





Cellular reprogramming

- Expression of 4 transcription factors, Oct4, Sox2, Klf4, c-Myc leads to induced pluripotent stem cells (iPS)

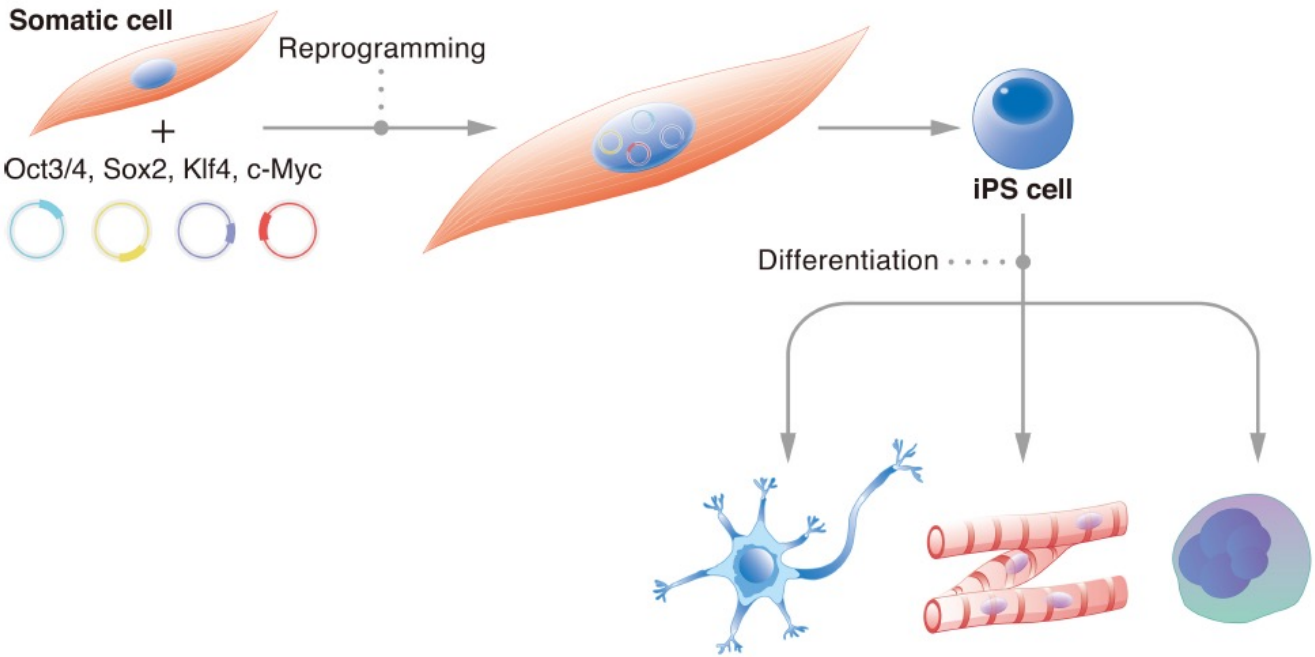
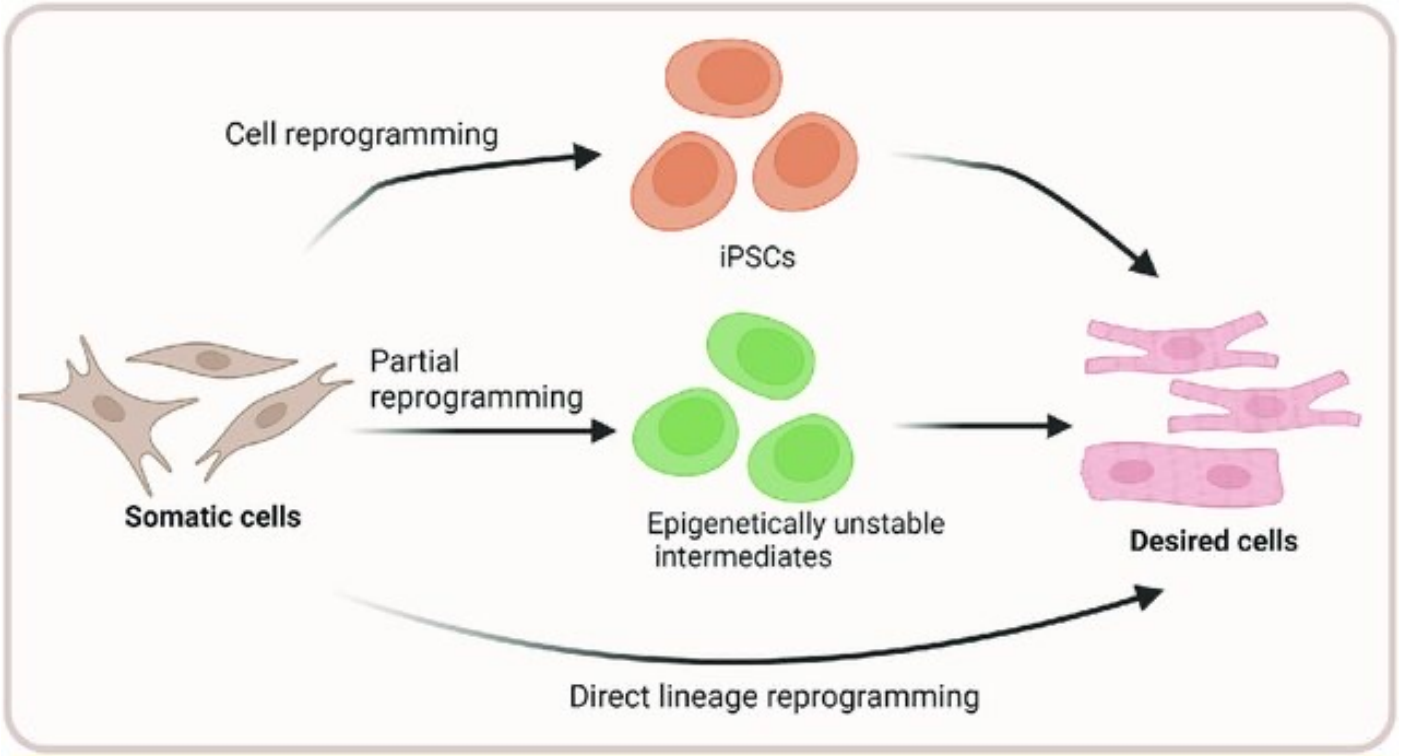


Figure 1. iPSCs describe cells that have been reprogrammed to the pluripotent state. In the illustration, a somatic cell has had OSKM exogenously expressed to initiate the reprogramming mechanism. The result is an iPSC, which in proper culture conditions can be induced to differentiate into any cell type.

Cellular reprogramming



iPSCs

- With pluripotent states
- Similar to ESCs
- With epigenome rejuvenation
- Personalized medicine
- Modeling of diseases
- Potential in cell transplatantion, gene editing, drug screening

Partial reprogramming

- Intermediate states without pluripotency
- Short-term induction of OSKM
- With epigenome rejuvenation
- No cell identity changes
- Suitable for *in vitro* manipulations
- *In vivo* amelioration of age-associated hallmarks

Lineage reprogramming

- No intermediate pluripotent states
- Conducted by lineage-specific transcription factors
- Transition between different epigenetic states
- More efficient and fast
- Suitable for *in vivo* tissue repair
- Avoiding risks for tumorigenesis

Partial cellular reprogramming

- Expression of 3 transcription factors, Oct4, Sox2, Klf4

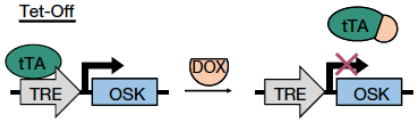
Article

Reprogramming to recover youthful epigenetic information and restore vision

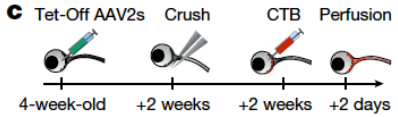
https://doi.org/10.1038/s41586-020-2975-4
Received: 31 July 2019
Accepted: 22 October 2020
Published online: 2 December 2020
Check for updates

Yuancheng Lu[1], Benedikt Brommer[2,3,11], Xiao Tian[1,11], Anitha Krishnan[3,4,11], Margarita Meer[5,6,11], Chen Wang[2,3], Daniel L. Vera[1], Qiurui Zeng[1], Doudou Yu[1], Michael S. Bonkowski[1], Jae-Hyun Yang[1], Songlin Zhou[2,3], Emma M. Hoffmann[3,4], Margarete M. Karg[3,4], Michael B. Schultz[1], Alice E. Kane[1], Noah Davidsohn[7], Ekaterina Korobkina[3,4], Karolina Chwalek[1], Luis A. Rajman[1], George M. Church[7], Konrad Hochedlinger[8], Vadim N. Gladyshev[5], Steve Horvath[9], Morgan E. Levine[6], Meredith S. Gregory-Ksander[3,4,12], Bruce R. Ksander[3,4,12], Zhigang He[2,3,12] & David A. Sinclair[1,10,12]

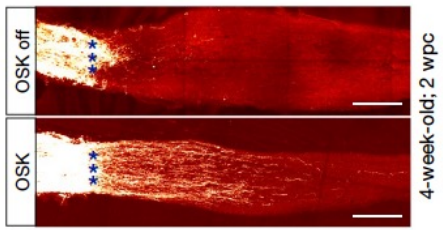
Transgenic system



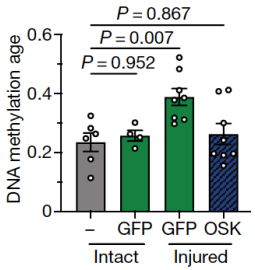
Experimental setup for optic nerve crush



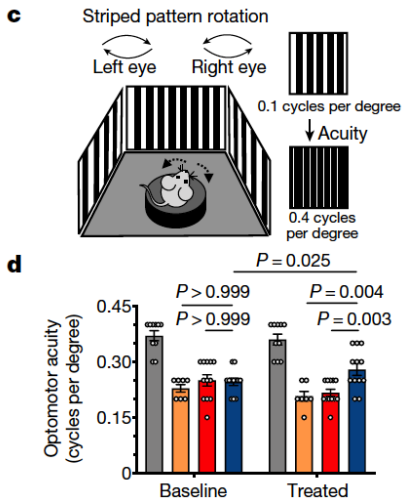
Regrowth of retinal ganglion cells at crush site



Epigenetic age (of retinal ganglion cells)



Restored vision

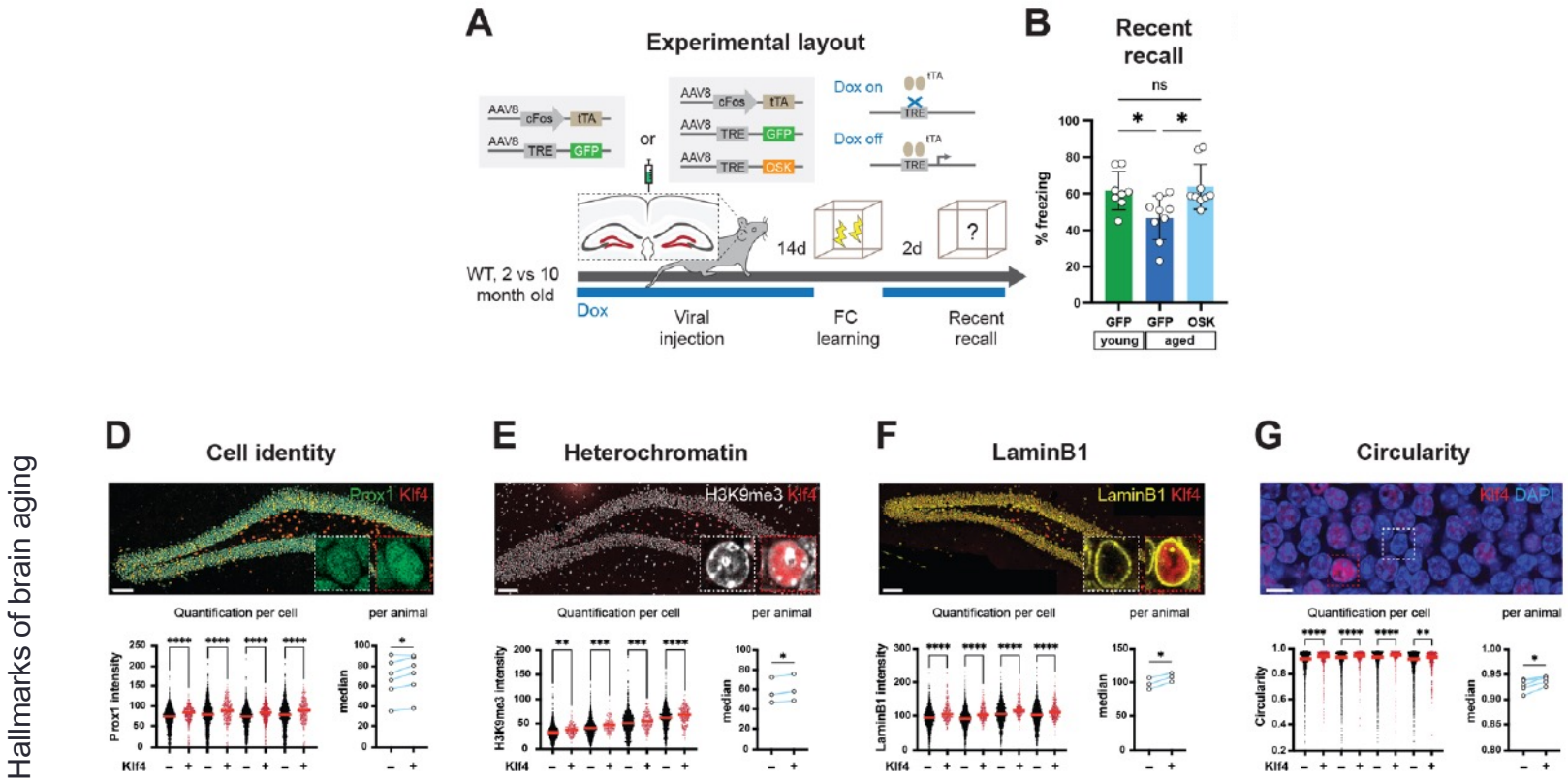


AAV, adeno-associated virus; CTB, cholera toxin B (a tracer); Dox, doxycline; tTA, tetracycline-controlled transactivator; wpc, weeks post-crush

in neurodegeneration

Partial cellular reprogramming

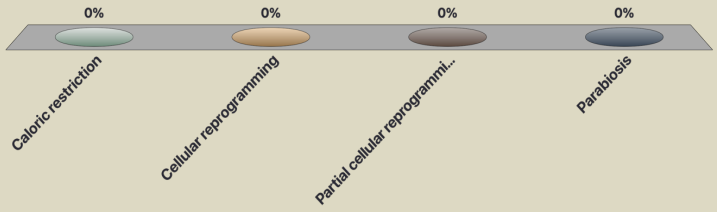
- Expression of 3 transcription factors, Oct4, Sox2, Klf4



Berdugo-Vega et al., unpublished data

Which anti-aging interventions has the best evidence against AD?

A. Caloric restriction
B. Cellular reprogramming
C. Partial cellular reprogramming
D. Parabiosis



Today's lecture – Overview

1) Definition of aging
2) Theories of aging
   - Stochastic
   - Non-stochastic

} Proximate / physiological causes

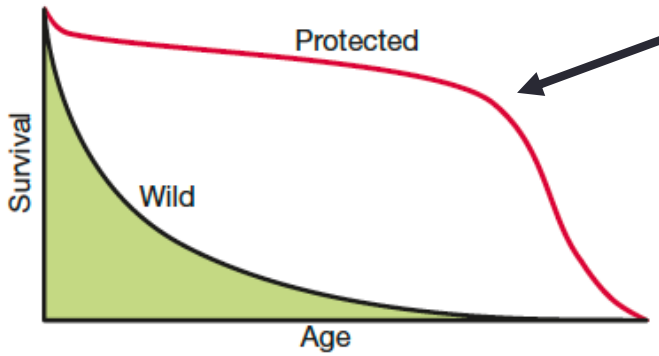
3) Anti-Aging interventions
   - Caloric restriction
   - Cellular reprogramming
4) Evolutionary theories of aging

} Ultimate causes

Evolutionary theories

- Here, we are interested in the question of why aging exists, rather than how we age psychologically/ sociologically/ biologically speaking

- Aging exists even in a (hypothetical) protected environment



- So, the question is, why does this drop happen?

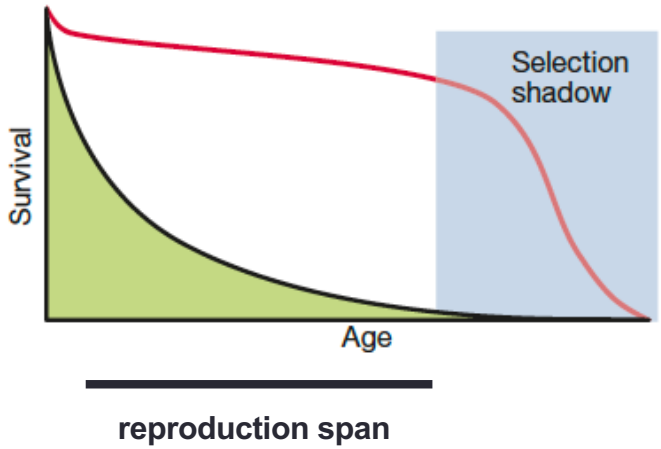
Evolutionary theories

- 3 theories:
  1) Mutation accumulation theory
  2) Antagonistic pleiotropy
  3) Disposable soma

1) Mutation (damage) accumulation theory

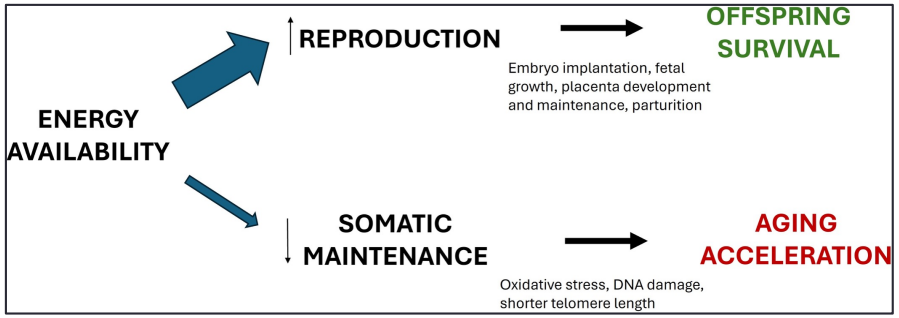
- Selection pressure to survive decreases with increased lifespan

- Why?
  - The aim of life is not longevity, but reproduction
  - Thus, there is a ”selection shadow” after having reached the age of reproduction to maintain organismal fitness

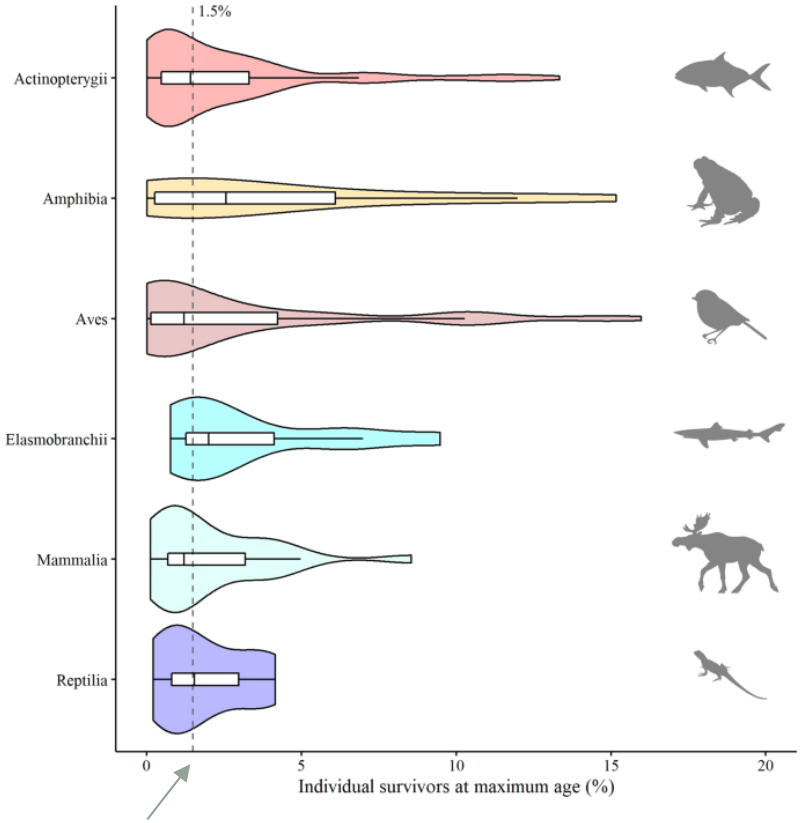


1) Mutation (damage) accumulation theory

- In other words, there is a selection trade-off between reproduction and longevity because of a finite amount of energy



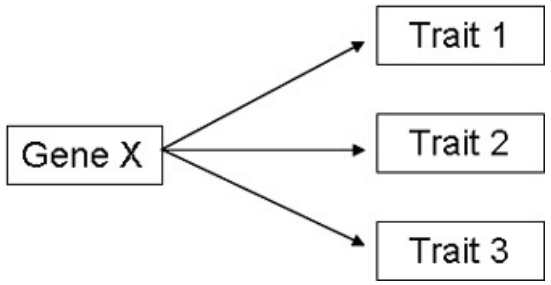
Evidence? Survival to maximum age



Average age per species

2) Antagonistic pleiotropy theory

- Pleiotropy=A single gene controls multiple traits



- The presence of this gene might be beneficial for reproductive fitness, but detrimental for survial

2) Antagonistic pleiotropy theory

- Evidence?

EVOLUTIONARY BIOLOGY

Evidence for the role of selection for reproductively advantageous alleles in human aging

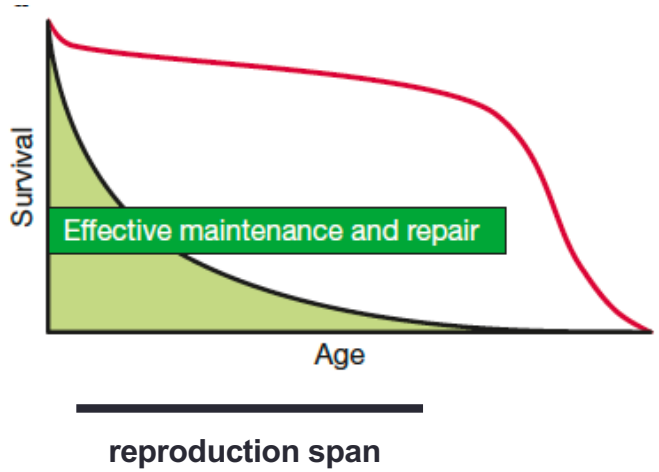
Erping Long[1,2] and Jianzhi Zhang[2]*

The antagonistic pleiotropy hypothesis posits that natural selection for pleiotropic mutations that confer earlier or more reproduction but impair the post-reproductive life causes aging. This hypothesis of the evolutionary origin of aging is supported by case studies but lacks unambiguous genomic evidence. Here, we genomically test this hypothesis using the genotypes, reproductive phenotypes, and death registry of 276,406 U.K. Biobank participants. We observe a strong, negative genetic correlation between reproductive traits and life span. Individuals with higher polygenetic scores for reproduction (PGS_R) have lower survivorships to age 76 (SV_{76}), and PGS_R increased over birth cohorts from 1940 to 1969. Similar trends are seen from individual genetic variants examined. The antagonistically pleiotropic variants are often associated with cis-regulatory effects across multiple tissues or on multiple target genes. These and other findings support the antagonistic pleiotropy hypothesis of aging in humans and point to potential molecular mechanisms of the reproduction–life-span antagonistic pleiotropy.

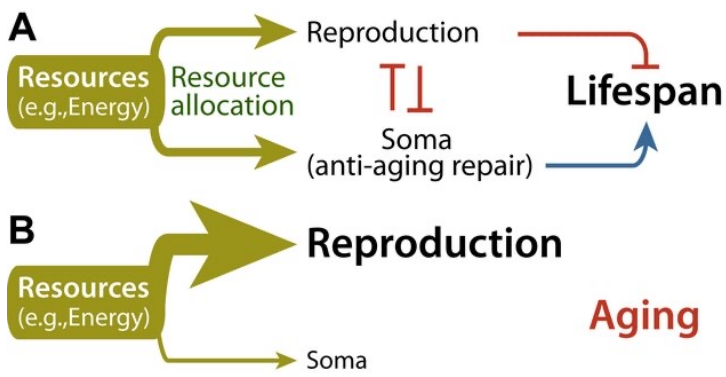
PGS_R calculated primarily with onset and end of reproduction

3) Disposable soma theory

- The soma – as opposed to the germline – is disposable



- Resources for maintenance and repair are invested during the reproductive span, but not beyond



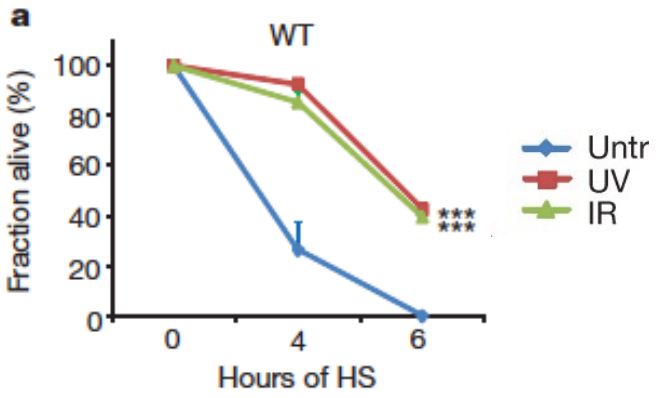
3) Disposable soma theory

- Evidence?

DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance

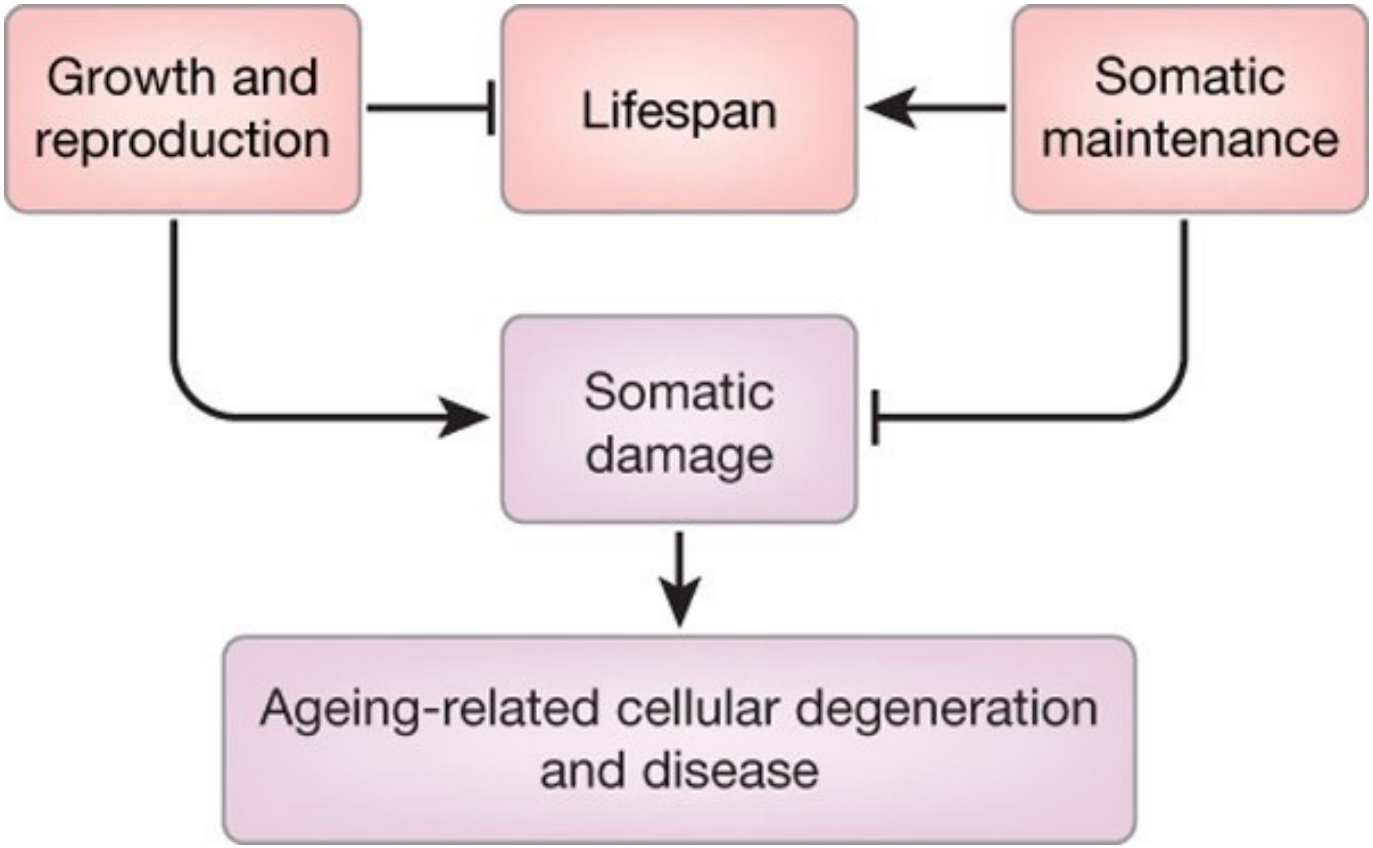
Maria A. Ermolaeva[1], Alexandra Segref[1], Alexander Dakhovnik[1], Hui-Ling Ou[1], Jennifer I. Schneider[1], Olaf Utermöhlen[2,3], Thorsten Hoppe[1] & Björn Schumacher[1,4]

DNA damage responses have been well characterized with regard to their cell-autonomous checkpoint functions leading to cell cycle arrest, senescence and apoptosis[1]. In contrast, systemic responses to tissue-specific genome instability remain poorly understood. In adult *Caenorhabditis elegans* worms germ cells undergo mitotic and meiotic cell divisions, whereas somatic tissues are entirely post-mitotic. Consequently, DNA damage checkpoints function specifically in the germ line[2], whereas somatic tissues in adult *C. elegans* are highly radio-resistant[3]. Some DNA repair systems such as global-genome nucleotide excision repair (GG-NER) remove lesions specifically in germ cells[4]. Here we investigated how genome instability in germ cells affects somatic tissues in *C. elegans*. We show that exogenous and endogenous DNA damage in germ cells evokes elevated resistance to heat and oxidative stress. The somatic stress resistance is mediated by the ERK MAP kinase MPK-1 in germ cells that triggers the induction of putative secreted peptides associated with innate immunity. The innate immune response leads to activation of the ubiquitin–proteasome system (UPS) in somatic tissues, which confers enhanced proteostasis and systemic stress resistance. We propose that elevated systemic stress resistance promotes endurance of somatic tissues to allow delay of progeny production when germ cells are genomically compromised.



HS, heat shock; wt, wild-type

Putting it all together...




SIRT1
cellular-reprogramming
epigenetic-clock
telomeres
disposable-soma
crosslinkage
parabiosis
mutation-accumulation
ROS
resveratrol
antagonistic-pleiotropy
caloric-restriction