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UniforJob ACADEMY

Accademia Eraclitea
ENTE DI RICERCA E DI ALTA FORMAZIONE ACCREDITATO

Master Universitario di primo livello in “Deglutologia geriatrica” A.A. 2023/24

L’anziano

Marco Domenicali

Medico Geriatra
Professore associato in Medicina Interna
Università di Bologna

Obiettivi Formativi

- Le basi Biologiche dell'invecchiamento
- Come si manifesta clinicamente l'invecchiamento
- Sarcopenia e Fragilità

LA DINAMICA DEMOGRAFICA

Il bilancio demografico 2022

Diversi fattori hanno influenzato la dinamica demografica nell'ultimo anno:

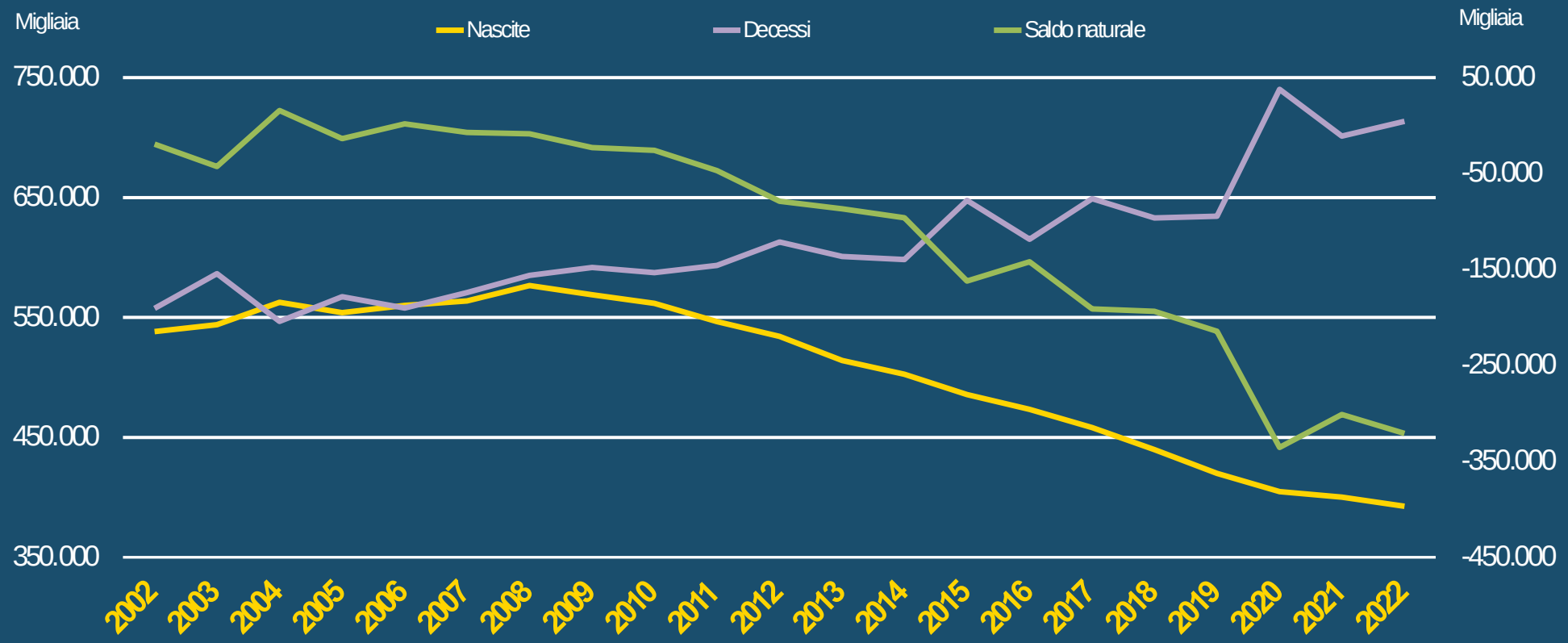
- l'uscita dallo stato di emergenza sanitaria;
- l'aumento del numero di cittadini in cerca di protezione umanitaria a seguito della guerra in Ucraina;
- l'eccesso di caldo nei mesi estivi.

58 MILIONI 851 MILA

RESIDENTI

Nascite, decessi (scala sinistra) e saldo naturale (scala destra)

Anni 2002–2022, valori assoluti in migliaia (a)



Fonte: Istat, Ricostruzione intercensuaria della popolazione residente (2002-2018); Movimento e calcolo della popolazione residente annuale (2019-2022)

(a) Nel 2022 i dati sono provvisori

L'INVERNO DEMOGRAFICO: CULLE SEMPRE PIÙ VUOTE

La persistente bassa fecondità è uno dei tratti distintivi dell'evoluzione demografica del nostro Paese e ha prodotto negli ultimi decenni una consistente erosione della platea dei potenziali genitori, a cui si deve un effetto importante del calo delle nascite.

393 MILA NASCITE NEL 2022
MINIMO STORICO DALL'UNITÀ D'ITALIA

1,24 NUMERO MEDIO DI FIGLI PER DONNA NEL 2022

LA LONGEVITÀ E L'INVECCHIAMENTO DELLA POPOLAZIONE

L'Italia è uno dei paesi con il più alto livello di sopravvivenza nel panorama europeo e con un persistente processo di invecchiamento.

L'età media della popolazione è salita da 45,7 anni all'inizio del 2020 a 46,4 anni all'inizio del 2023.

SPERANZA DI VITA ALLA NASCITA

80,5 ANNI UOMINI

84,8 ANNI DONNE

ANZIANI

24,1%

al 1° gennaio 2023, le persone con 65 anni e più rappresentano ormai quasi un quarto della popolazione totale

ADULTI

63,4%

gli individui in età attiva, cioè coloro che hanno tra 15 e 64 anni, sono 37milioni 339 mila

RAGAZZI

12,5%

si riduce il numero dei più giovani: i ragazzi fino a 14 anni sono 7 milioni 334 mila

Più forte il decremento demografico e l'invecchiamento nelle aree interne

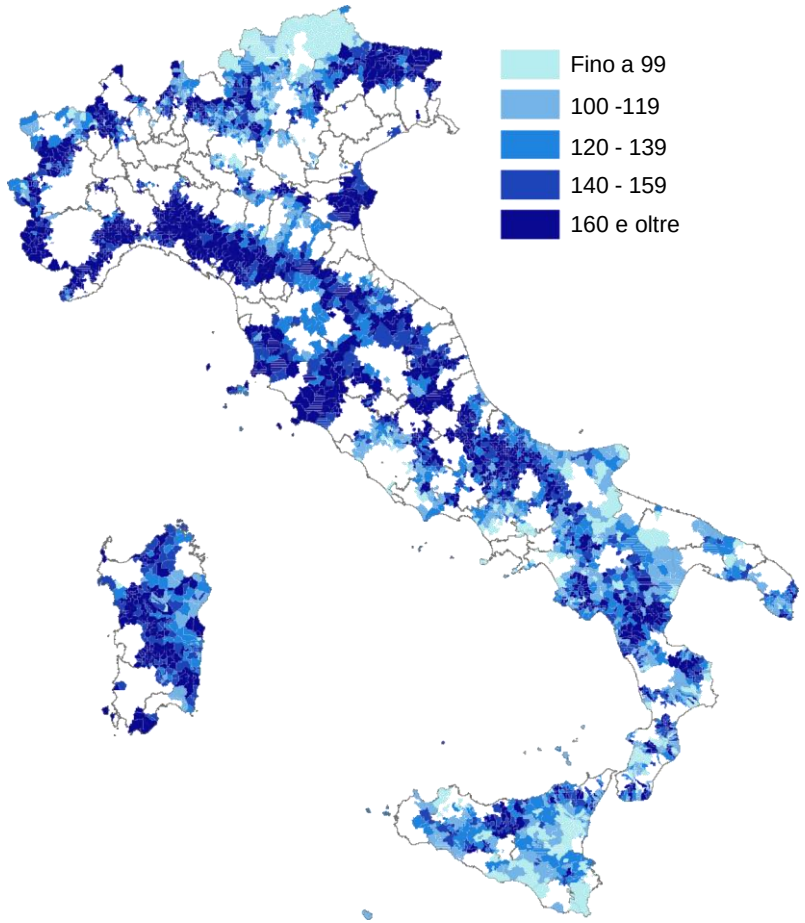
Rapporto tra popolazione di 65 anni e più e popolazione di 15-34 anni al 1° gennaio 2023 (valori percentuali) nei comuni delle aree interne e centrali (a)

La riduzione della popolazione giovane ha un impatto più rilevante nelle aree interne, soprattutto in quelle del Centro-Sud.

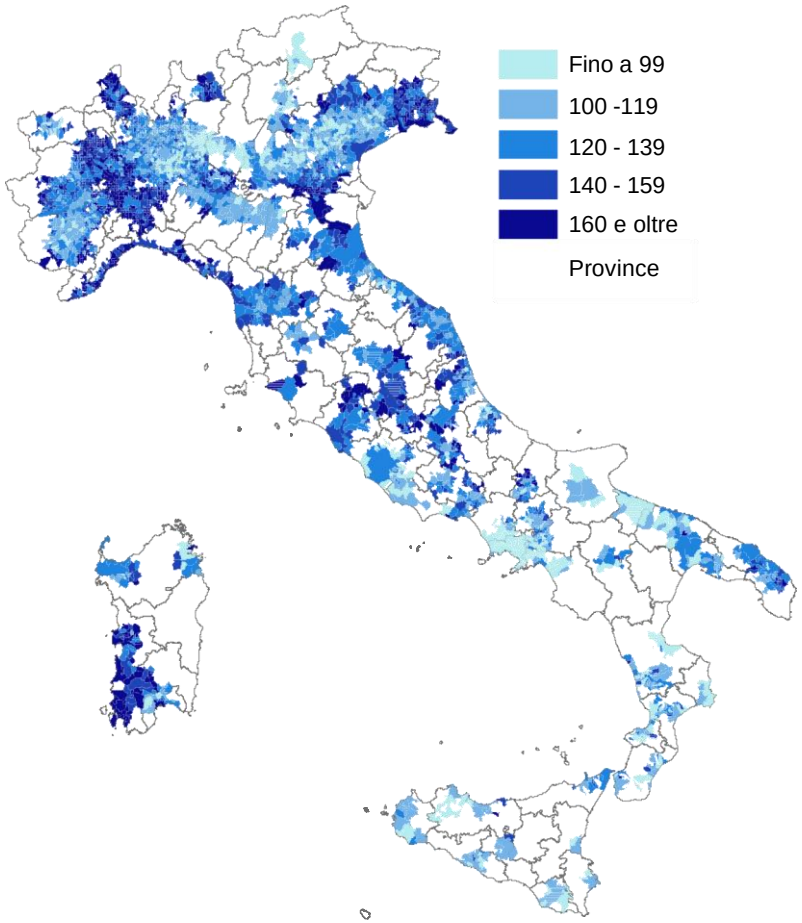
Fonte: Istat, Sistema di nowcast per indicatori demografici

(a) Dati stimati

AREE INTERNE



AREE CENTRALI



Perché invecchiamo?

Storia della longevità

Alcuni animali della preistoria, come alcuni tipi di rettili (vedi il caso della testuggine Chelonoidis abingdonii Lonesome George), ma anche le più antiche varietà di dinosauri, potevano vivere oltre i 100 anni[1].

WIKIPEDIA
The Free Encyclopedia

Nei tempi recenti, gli organismi viventi appartenenti al regno Animalia ritenuti più longevi del pianeta Terra sono delle piccole creature marine dell'ordine degli idrozoi, del genere Hydra, ovvero delle particolari meduse chiamate Turritopsis dohrnii, nella varietà denominata Turritopsis nutricula e, per la loro particolarità appunto, chiamate semplicemente meduse immortali. Le meduse immortali hanno un'altissima capacità di rigenerazione e, dopo aver raggiunto lo stadio maturo di medusa, ritornano allo stadio iniziale di polipo, rendendole, in tal modo, praticamente immortali[2].

Età media di morte	Nome dell'animale e classe tassonomica[9]
Immortale	*Turritopsis nutricula* (o medusa immortale), *Hydrozoa*
11000-15000 anni	*Hyalospongia monorhaphididae* (o medusa vitrea)[10], *Hyalospongiae*
2200 anni	*Xestospongia muta*, *Demospongiae*
2000 anni	Corallo nero *Antipatharia* della Nuova Zelanda, *Anthozoa*
1500 anni	*Dendrilla membranosa*, *Demospongiae*
507 anni	*Arctica islandica* "Ming"[11], *Bivalvia*
400 anni	Squalo della Groenlandia[11], *Chondrichthyes*
344 anni	Testuggine africana, o sulcata, *Centrochelys sulcata*
240 anni	Cozza d'acqua dolce, *Bivalvia*
210 anni	Balena della Groenlandia[11], *Mammalia*
205 anni	*Sebastes aleutianus*[11], *Actinopterygii*
200 anni	*Mesocentrotus franciscanus*[11], *Echinoidea*
180 anni	Vongola dalla proboscide, *Bivalvia*
177 anni	Tartaruga delle Galapagos[11], *Reptilia*
170 anni	*Lamellibrachia luymesi*, *Polychaeta*
160 anni	Anguilla svedese, *Actinopterygii*
157 anni	*Sebastes borealis*[11], *Actinopterygii*
150 anni	Aragosta mediterranea, *Decapoda* Pesce specchio atlantico[11], *Osteichthyes* Storione di lago[11], *Actinopterygii* Tartaruga gigante di Aldabra[11], *Reptilia*
140 anni	*Allocyttus verrucosus*[11], *Actinopterygii* Carpa giapponese, *Actinopterygii*
130 anni	Storione bianco, *Actinopterygii*
110 anni	Tuatara[12], *Reptilia*
105 anni	Orca "Granny", *Mammalia*
100 anni	Tardigrado, *Tardigrada*
80 anni	Cacatua Ciuffogiallo[13], *Aves* Pappagallo cenerino, *Aves* Coccodrillo australiano[14], *Reptilia* Uomo, *Mammalia*

- Sono da citare con particolare attenzione, per la loro longevità, anche i tardigradi[3], minuscoli (circa 0,5 mm) ed innocui esseri, ma altresì resistenti ad ambienti molto estremi; si è notato che essi possono vivere a lungo poiché, oltre che ad epocali periodi di ibernazione, possono "riattivarsi" legandosi al DNA di batteri e funghi[4].

- Tra i vertebrati invece, il primato di longevità spetterebbe allo squalo della Groenlandia (di media più di 400 anni; curioso rilevare che esso giunge alla maturità sessuale attorno ai 150 anni d'età) seguito dalla balena della Groenlandia[5], un cetaceo che può vivere sui 200 anni[6], mentre l'orca Granny raggiunse un primato di 105 anni[7][8].

1.^ *Copia archiviata*, su *curiosone.tv*. URL consultato il 7 giugno 2017 (archiviato dall'url originale il 22 ottobre 2016).
2.^ La medusa immortale: eternamente giovane e sana – Conoscenze al Confine
3.^ http://www.scienzainrete.it/contenuto/partner/i-tardigradi-questi-sconosciuti-e-questi-fenomeni
4.^ http://www.greenreport.it/news/aree-protette-e-biodiversita/i-tardigradi-sono-immortali-perche-rubano-il-dna-a-piante-batteri-e-funghi/
5.^ https://www.greenme.it/informarsi/animali/15368-balene-groenlandia-longevita-dna-genoma
6.^ http://scienze.fanpage.it/chris-16-anni-ha-ucciso-una-balena-di-200-anni-e-una-tradizione-choc-in-groenlandia/
7.^ http://best5.it/post/i-5-animali-piu-longevi-del-pianeta/
8.^ http://gizzeta.it/i-dieci-animali-piu-longevi-del-mondo/
9.^ https://www.italiavox.it/2011/10/animali-centenari-le-creature-piu-longeve-della-terra/
10.^ http://www.ilgiornale.it/news/politica/5-minuti-11mila-anni-ogni-animale-ha-sua-vita-1296046.html
11.^ Salta a:a b c d e f g h i j k https://www.focus.it/ambiente/animali/animali-piu-longevi-del-pianeta?gimg=59425#img59425
12.^ http://www.lorologiaiomiope.com/lultimo-dei-rincocefali-il-tuatara-shenodon-punctatus/

Esistono esseri immortali

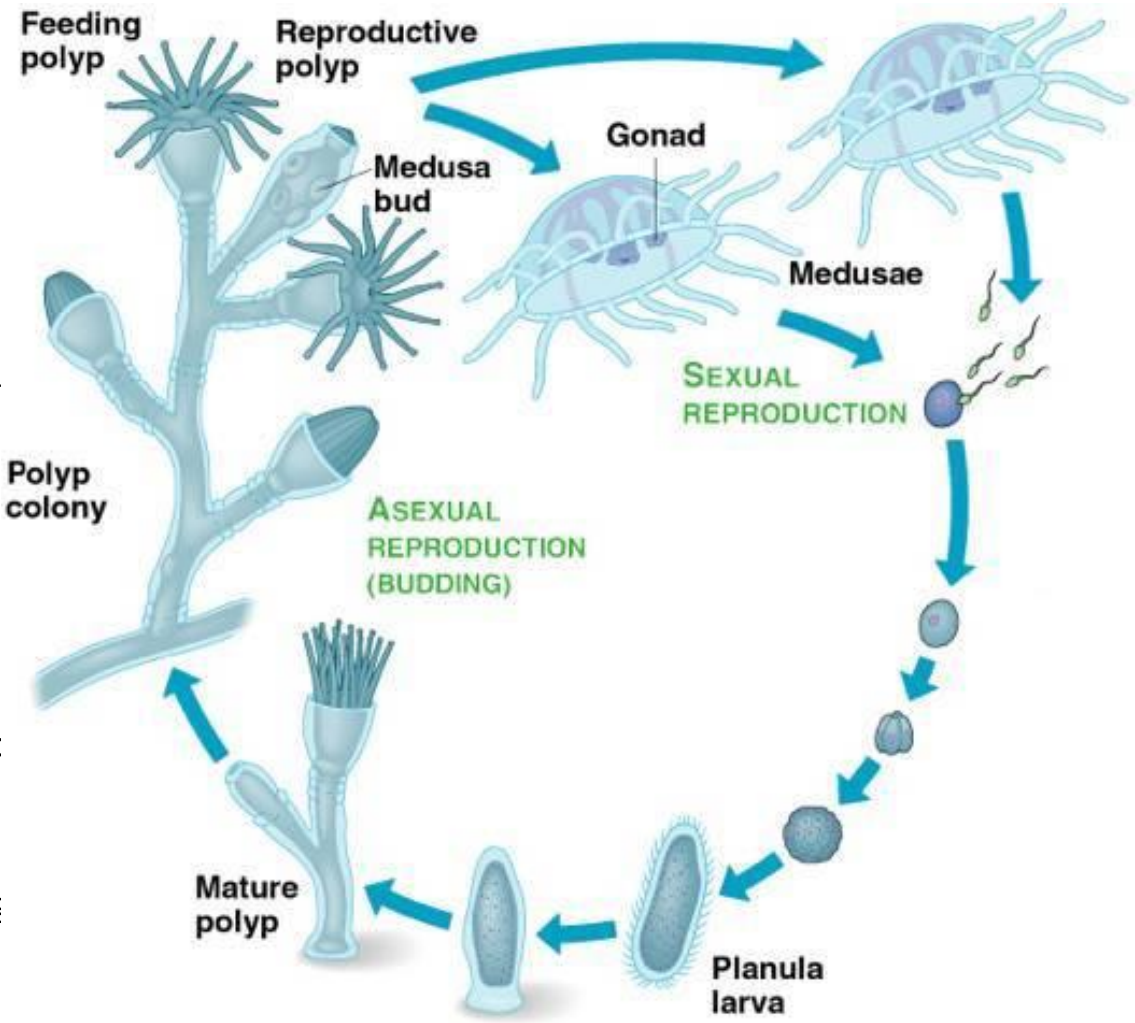
Turritopsis nutricula (medusa immortale)

Turritopsis nutricula è uno **cnidario** appartenente alla classe *Hydrozoa* di 4-5mm di diametro, diffuso principalmente nell'Atlantico occidentale e nei Caraibi. Lo **stadio medusoide** è a forma di campana e può presentare fino a 80-90 tentacoli negli individui adulti, mentre i giovani esemplari ne hanno solo 8; il celenteron (intestino), ben visibile attraverso l'ombrella trasparente, è color cremisi e a sezione trasversale cruciforme. Lo **stadio polipoide** forma invece colonie tramite gemmazione e i vari individui, tutti geneticamente identici, si dispongono in rami verticali ancorati a stoloni che decorrono lungo il substrato.

Come quello di tutti gli altri idrozoi, dunque, il **ciclo biologico** di *Turritopsis nutricula* è dato dall'alternanza di uno stadio polipoide sessile a riproduzione asessuata e di uno stadio medusoide bentonico (sospeso nella colonna d'acqua) a riproduzione sessuata. Ma se una medusa di idrozoo generalmente muore dopo aver liberato i propri gameti, in *T. nutricula* si osserva, al contrario, un fatto alquanto bizzarro: l'individuo adulto è infatti in grado di **regredire** allo stadio sessualmente immaturo di polipo e di creare, a partire da esso, una nuova colonia fisiologicamente attiva. In sostanza, sembra che le meduse di *T. nutricula* siano letteralmente in grado di riavvolgere il tempo tornando allo stadio giovanile in una sorta di *rewind* biologico e di (ri)vivere quindi nuovamente la loro vita.

Ringiovanimento

- Nel corso degli anni sono stati condotti molti studi in laboratorio per analizzare il processo di *ringiovanimento* della *T. nutricula* e la maggior par di questi concorda nel suddividerlo in quattro fasi fondamentali.
- Le meduse immortali adulte, messe in condizione di scarso nutrimento, iniziano a rimpicciolirsi e la campana si contrae verso il corpo centrale (Fig. 4/4-5). I tentacoli si accorciano e la mesoglea viene riassorbita fino a scomparire completamente (Fig. 4/6-7).
- Gli esemplari di *T. nutricula*, regredite allo stato larvale, hanno un'evoluzione strettamente dipendente dalla temperatura dell'acqua di coltura: se la temperatura è di circa 22°C si può osservare la formazione di stoloni entro 3 giorni; se la temperatura è inferiore ai 14°C le larve riescon resistere fino a 3 mesi senza perdere la loro capacità di produrre stoloni (Fi 4/8).
- I polipi, generati dagli stoloni, sono in grado di nutrirsi di artemia salina di produrre gemme di meduse nel giro di 2 giorni dalla loro formazione (Fig 4/9).
- Le meduse adulte sono pronte a rilasciare uova mature e spermatozoi nell'acqua di coltura e a dar vita a una nuova generazione di *T. nutricula*.
- Ad oggi, però, non è stato possibile vedere questo processo di ringiovanimento nelle meduse immortali che vivono negli oceani perché avviene in condizioni difficili da osservare e in tempi estremamente rapidi.

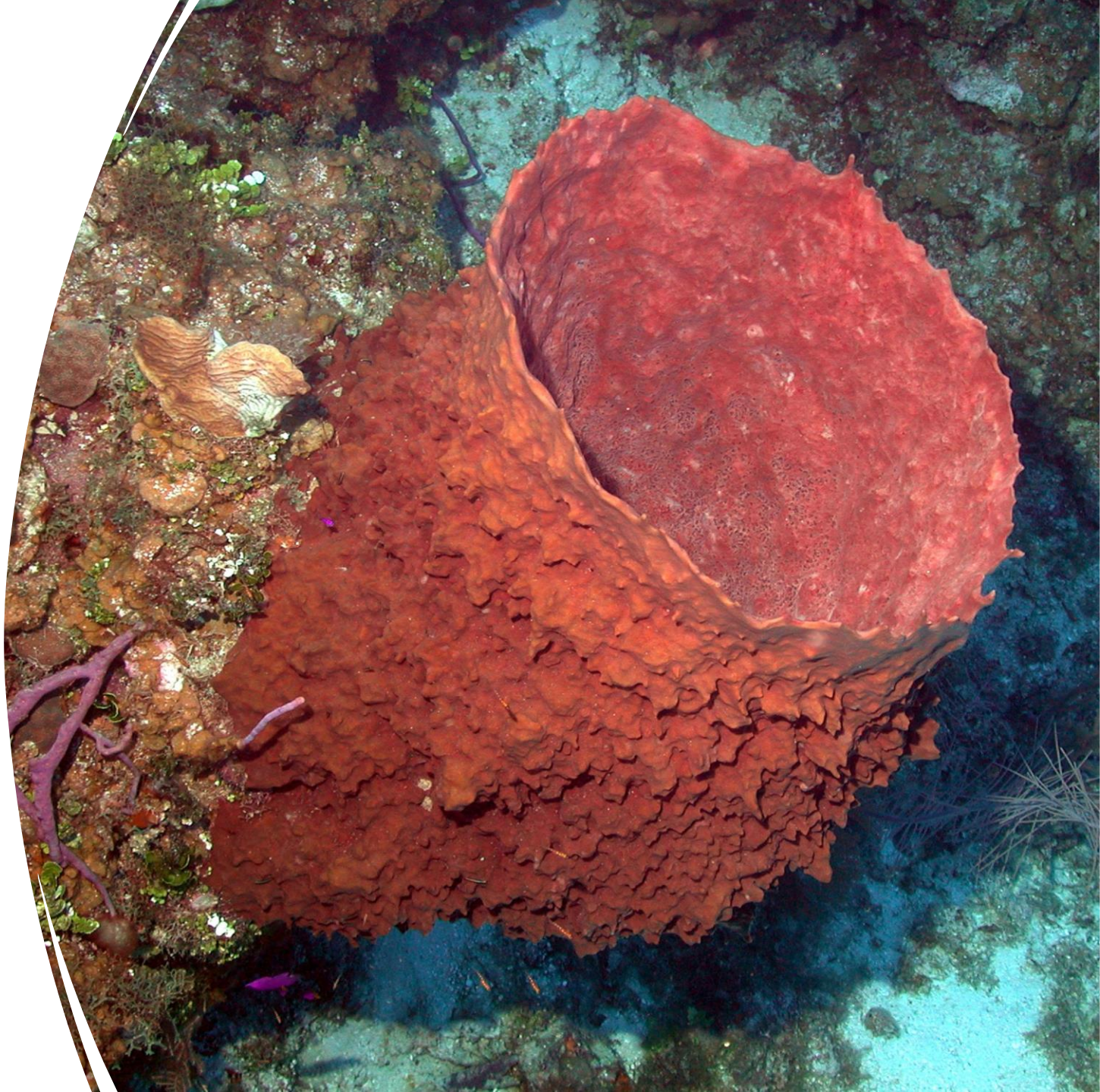


Fonti

- https://www.microbiologiaitalia.it/biologia-marina/medusa-immortale/
- Journal of Zoological Systematics and Evolutionary Research, vol. 45, n. 1, 2006, pp. 11-19
- P. Schuchert, Revision of the European athecate hydroids and their medusae (Hydrozoa, Cnidaria): families Oceanidae and Pachycordylidae, in Revue Suisse de Zoologie, vol. 111, n. 2, 2004, pp. 315-369
- S Piraino, F Boero, B Aeschbach, V Schmid. Reversing the Life Cycle: Medusae Transforming into Polyps and Cell Transdifferentiation in Turritopsis nutricula (Cnidaria, Hydrozoa). Biol Bull. 1996 Jun;190(3):302-312. doi: 10.2307/1543022. PMID: 29227703.

xestospongia muta

- Spugna gigante arriva a vivere 2200 anni



Anatomia

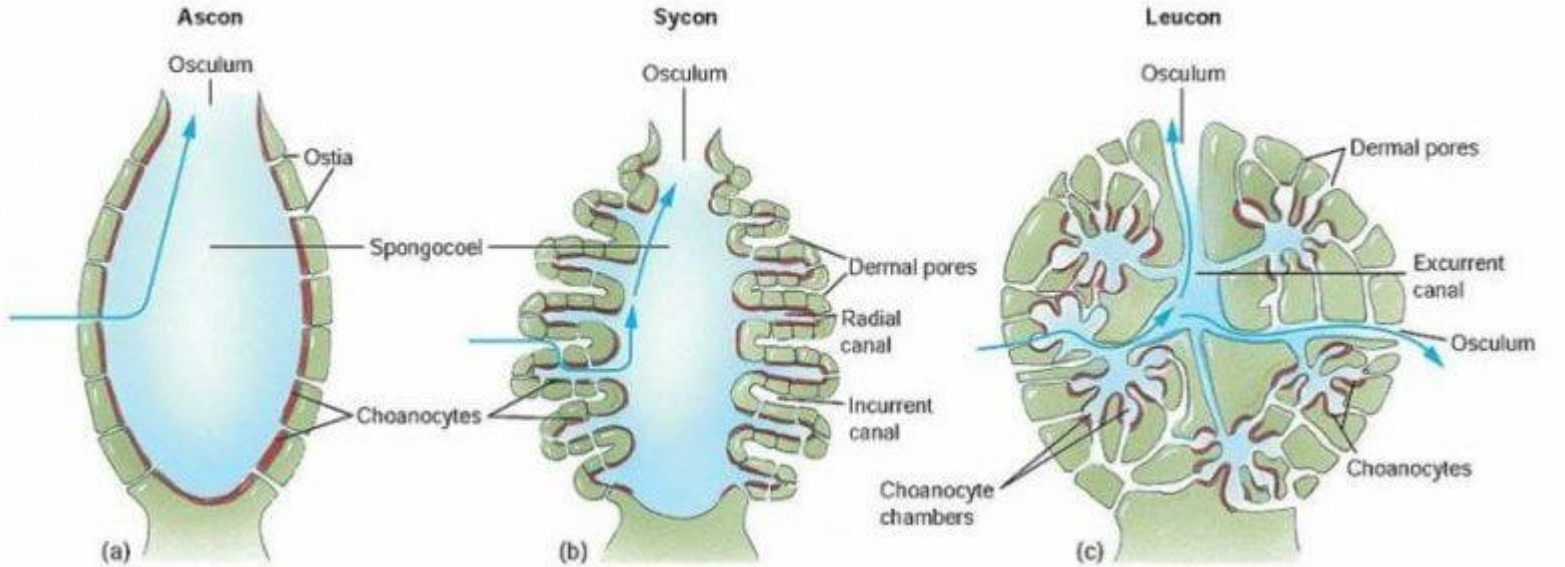
Le dimensioni delle spugne sono molto variabili, da pochi centimetri fino a 2 metri. Il corpo delle spugne è costituito fondamentalmente d un sacco con una cavità centrale principale, detta **spongocele,** attraversato da numerosi pori e che presenta un'apertura principale detta **osculo**. L'acqua fluisce dai pori verso la cavità centrale, per poi fuoriuscire dall'osculo. La morfologia di quest strutture rimane comunque molto variabile per quanto riguarda forn dimensione dello spongocele e il numero di osculi. Lo spongocele è organizzato secondo tre schemi fondamentali:

•**Ascon:** lo spongocele è costituito da un semplice sacco. E' presente solo in alcune spugne calcaree di dimensioni ridotte

•**Sycon:** lo spongocele è costituito da una camera principale da cui si diramano estensioni digitiformi.

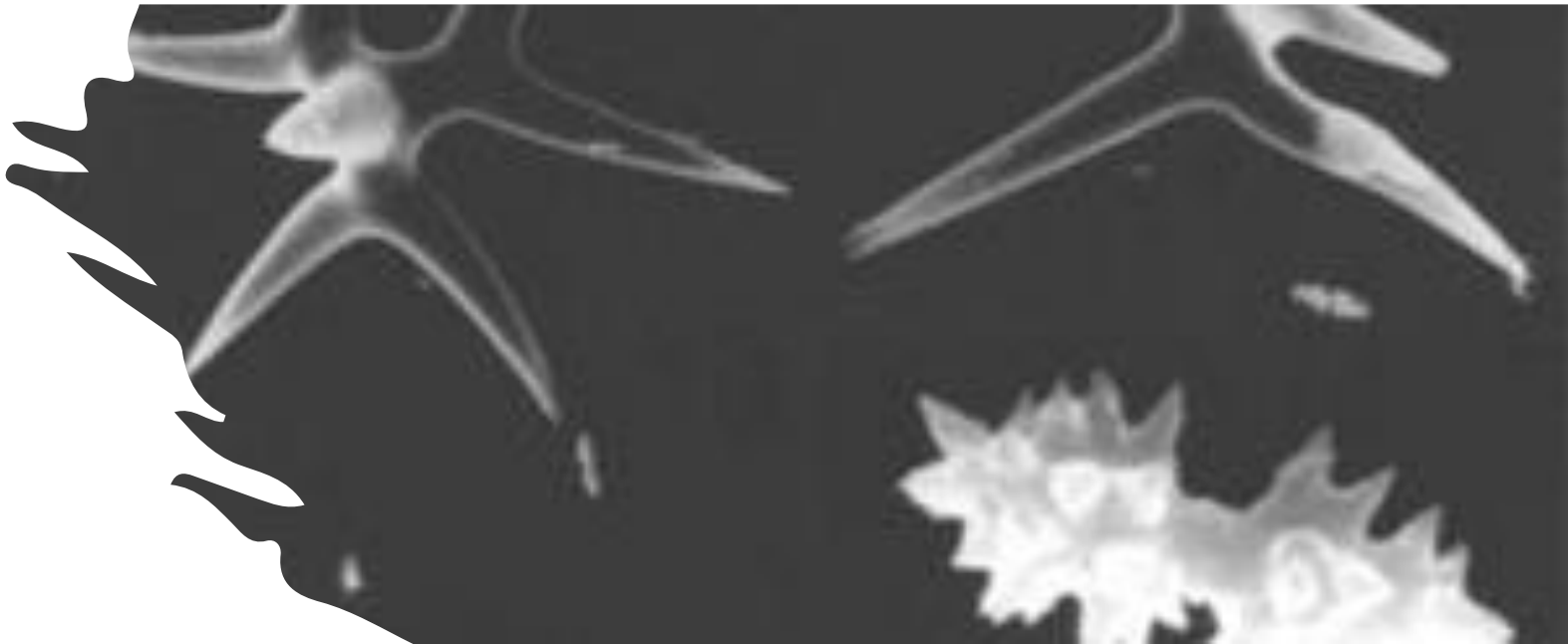
•**Leucon:** lo spongocele è formato da una sacca estremamente ramificata, con numerose concamerazioni.

Nonostante questi animali non esibiscano un'organizzazione in veri e propri tessuti, possiedono differenti tipi di cellule con diverse funzioi sono costituiti infatti da due strati cellulari, uno esterno, il **pinacoderma**, costituito da cellule epidermiche dette **pinacociti**, e uno interno, il **coanoderma**, costituito da cellule flagellate dette **coanociti**. Tra i due strati di cellule si sviluppa la **mesoila**, una matrice gelatinosa in cui sono alloggiati diversi tipi cellulari tra cui gli archeociti, ovvero cellule ameboidi che possono differenziarsi in diversi tipi cellulari.



Spicole

Immersi nella mesoila si trovano anche spongociti e sclerociti, questi ultimi secernono spicole, che possono essere formate da carbonato di calcio ($CaCO_3$) o di silice (SiO_2) e presentare diverse forme. Le spicole costituiscono sia l'impalcatura del corpo della spugna sia un efficiente protezione da eventuali predatori, frequentemente infatti, queste fuoriescono dal corpo della spugna facendola risultare spinosa. Alcune spugne inoltre producono terpenoidi o benzochinoni, composti repellenti o tossici per i predatori.



Alimentazione

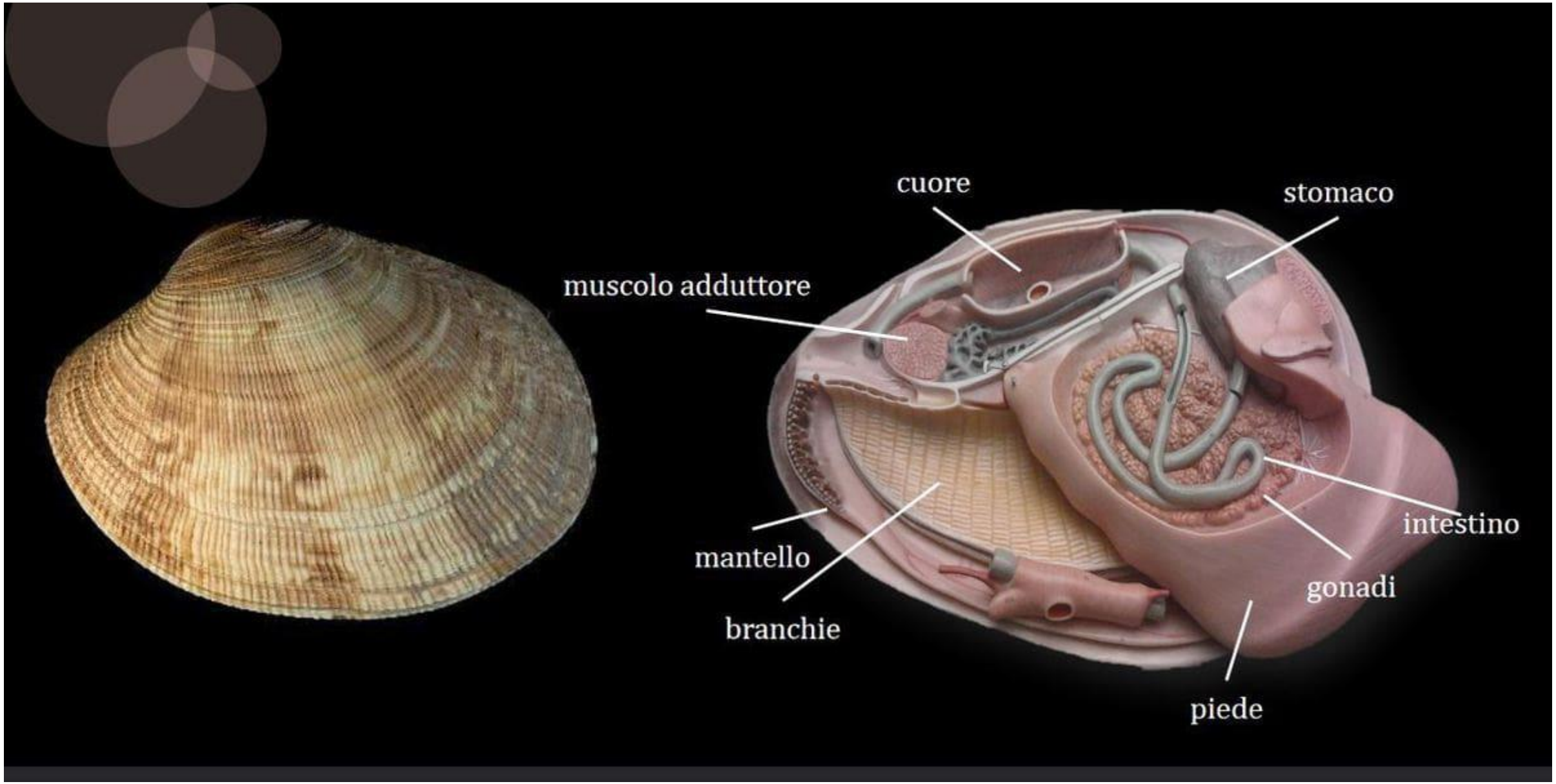
I poriferi sono animali tipicamente filtratori e si nutrono principalmente di batteri. I composti organici prodotti dalle spugne hanno infatti un effetto antibiotico che facilita l'uccisione e l'agglutinazione dei batteri.

Il processo di filtrazione avviene grazie ai coanociti, formati da tre componenti principali: il primo è un flagello che convoglia l'acqua con le sostanze nutritive attraverso la spugna; il secondo è un collaretto, posto attorno al flagello, formato da microvilli e microfilamenti, i quali costituiscono una rete che intrappola le particelle; il terzo componente è il corpo cellulare del coanocita che ingerisce le particelle intrappolate. I coanociti però, non digeriscono le particelle ingerite, le accumulano in vacuoli alimentari che migrano fino alla base della cellula e trasferiscono il loro contenuto agli amebociti della mesoila, dove viene svolta la digestione.

Una minima parte delle specie di poriferi è invece carnivora, e si nutre di piccoli animali. Un esempio è Asbestopluma hypogea, una Demospongia in grado di nutrirsi di piccoli crostacei della famiglia degli Artemiidae.

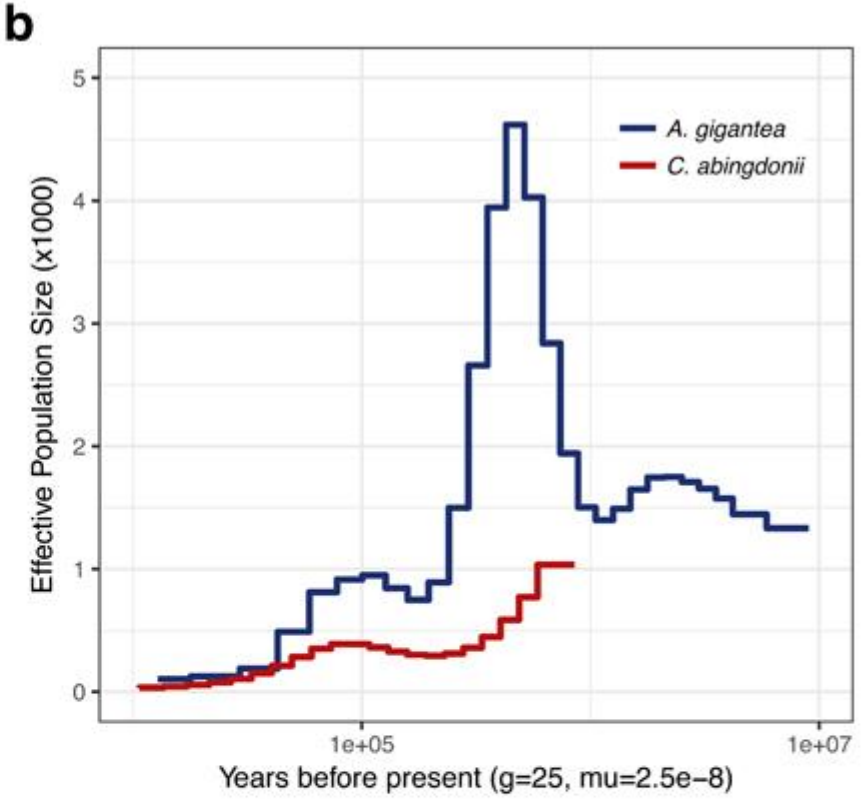
Questa cozza

vive 500 anni


cuore
stomaco
muscolo adduttore
intestino
mantello
gonadi
branchie
piede

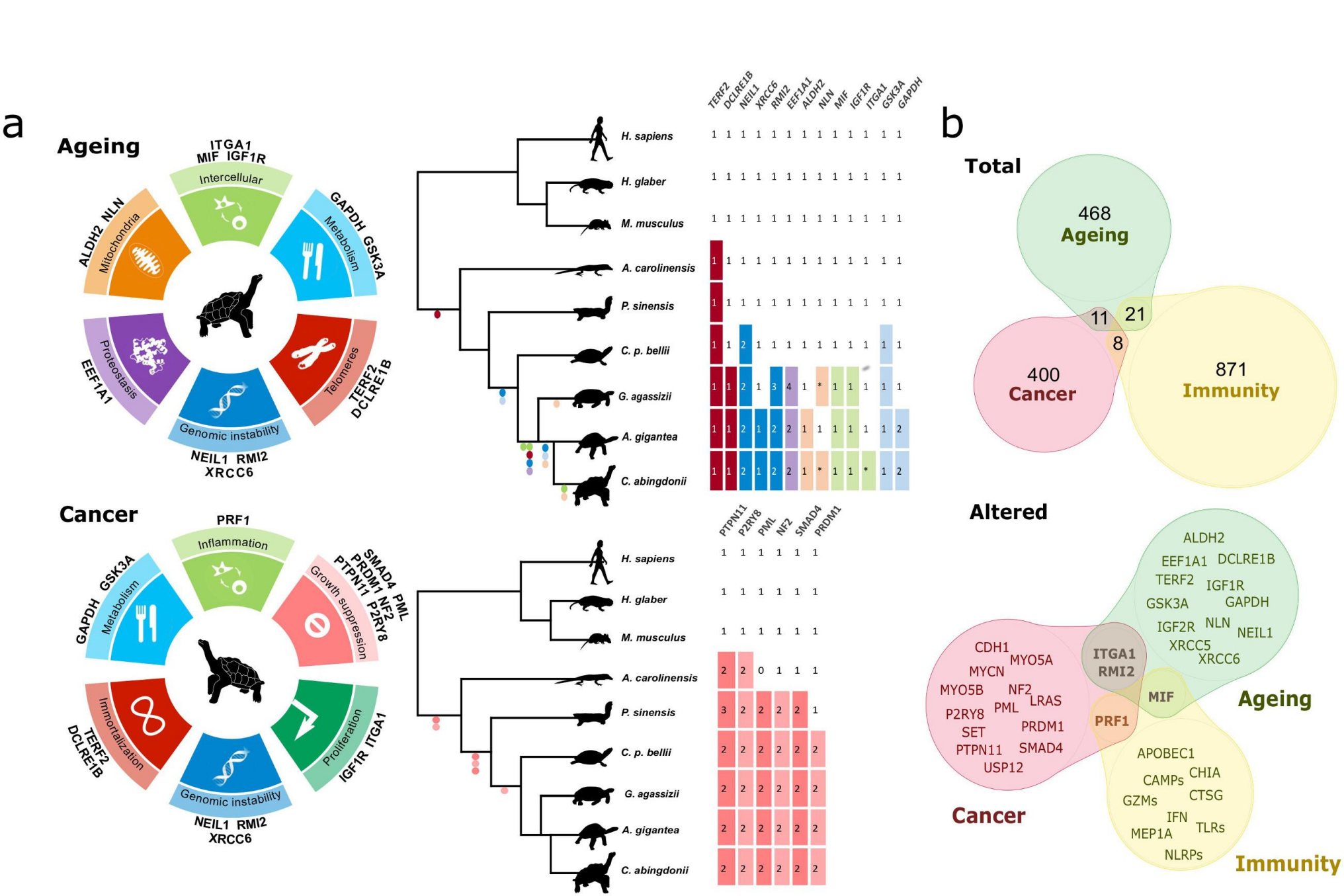
Gli animali più longevi sono
1.«sedentari»
2. vivono
in acqua meglio se fredda

Il primo animale Terrestre è la tartaruga gigante delle Galapagos che in mediua vive “solo” 177 anni



- E un animale «strano» per essere longevo perché è grande (arriva a 150 cm di luinghezza) pesa fino a 300 kg
- Più il corpo è sviluppato più è elevato il numero di cellule e conseguentemente la possibilità di sviluppare neoplasie
- Questa tartaruga ha un sistema estremamente efficiente di riparazione del DNA

Nat Ecol Evol. 2019 January ; 3(1): 87–95. doi:10.1038/s41559-018-0733-x.



Genomic basis of longevity and cancer in giant tortoises.

a, Genes potentially implicated in C. abingdonii and A. gigantea longevity extension and cancer resistance classified according to their putative role in the different hallmarks. Tables indicate copy-number variations and relevant variants of age-related genes and tumour suppressors found in C. abingdonii, A. gigantea and other species. In the tables, numbers indicate gene copy numbers, asterisks pseudogenization events and dots the presence/absence of the variant (in different colours, related to each hallmark). b, Venn diagrams showing the relationships between cancer-, ageing- and immunity-related genes, as classified before annotation. The top diagram represents all the genes related to each category that have been manually annotated, with the number of genes in each group. The bottom diagram shows those genes showing potentially interesting variations after annotation.

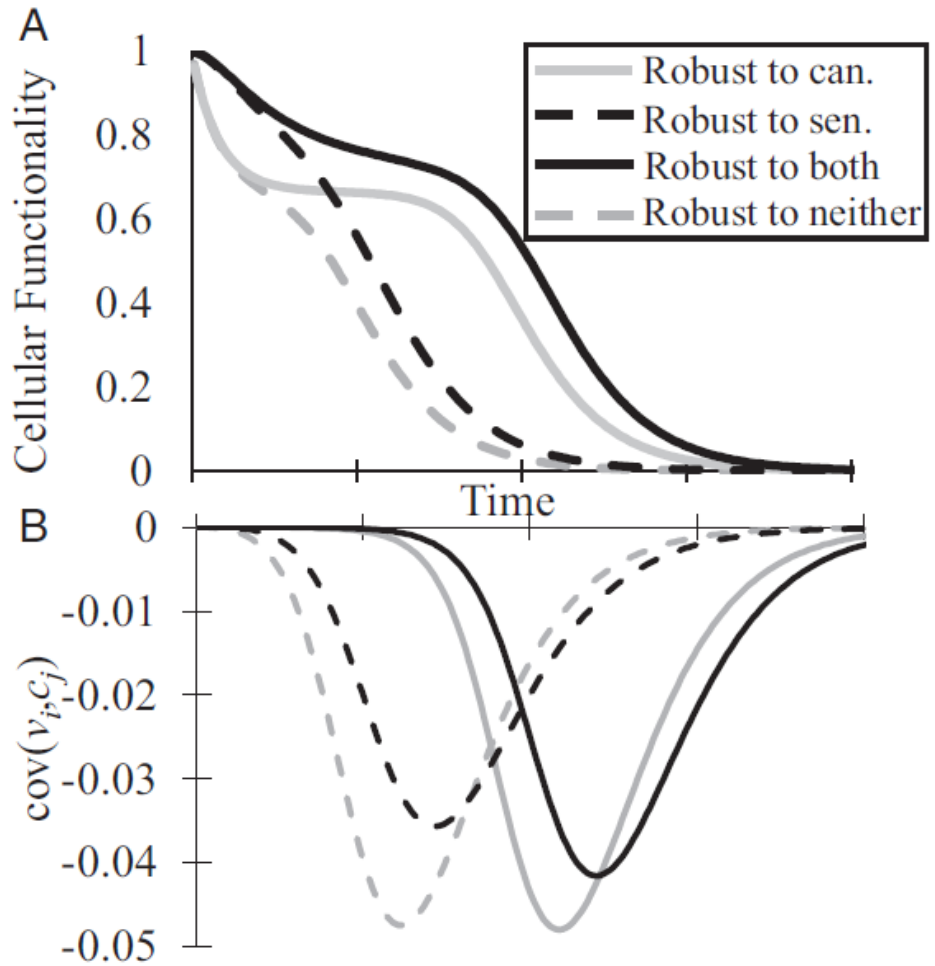


Fig. 3. (*A*) Robustness to somatic changes delays, but does not halt, loss of functional cells. (*B*) Failure to halt aging is a result of negative covariance between cellular cancer (can.) *c* and senescence (sen.) *v*, and is negative under all conditions. While the magnitude of negative covariance decreases later in life, this decrease is due to a depletion of total variance of cell types (most cells are either senescent or cancerous) and occurs long after a multicellular organism would have died (fraction of functional cells ~0.1). $\alpha = 0.002$ throughout.

Intercellular competition and the inevitability of multicellular aging

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Current theories attribute aging to a failure of selection, due to either pleiotropic constraints or declining strength of selection after the onset of reproduction. These theories implicitly leave open the possibility that if senescence-causing alleles could be identified, or if antagonistic pleiotropy could be broken, the effects of aging might be ameliorated or delayed indefinitely. These theories are built on models of selection between multicellular organisms, but a full understanding of aging also requires examining the role of somatic selection within an organism. Selection between somatic cells (i.e., intercellular competition) can delay aging by purging nonfunctioning cells. However, the fitness of a multicellular organism depends not just on how functional its individual cells are but also on how well cells work together. While intercellular competition weeds out nonfunctional cells, it may also select for cells that do not cooperate. Thus, intercellular competition creates an inescapable double bind that makes aging inevitable in multicellular organisms.

negligible senescence | cellular degradation | cellular robustness | cooperation | cancer

Biological aging is defined as a loss in organismal fecundity and/or increase in mortality with age (1). Mutations that increase mortality early in life will have profound fitness consequences and are likely to be purged by selection (1, 2). However, mutations that affect mortality later in life, after reproduction, fall under an ever-darkening "selection shadow" (i.e., progressively relaxed selection) that allows them to fix in a population due to drift (3, 4). Additionally, antagonistic pleiotropy, in which genes that increase fitness components early in life also decrease fitness components later in life, can result in aging as a side effect of selection for early reproduction (5, 6). Both mutation accumulation and antagonistic pleiotropy contain an implicitly optimistic message regarding the potential to ameliorate aging: There exist "longevity genes" for which aging and nonaging alleles are possible. Eliminating aging, according to these two theories, is therefore a practical challenge rather than a fundamental impossibility.

Whereas mutation accumulation and antagonistic pleiotropy theory address the role of organismal selection in aging, we ask here whether aging is a fundamental and intrinsic feature of multicellular life. For an organism to avoid aging, it must overcome or mitigate the consequences of mitotically heritable changes in somatic cells, the vast majority of which are deleterious, and hence best thought of as "damage." Heritable cellular degradation is a product not just of somatic mutations (7) but also of other changes, such as epigenetic drift (8) and the accumulation of misfolded proteins (9). In unicellular organisms, competition between cells can weed out deleterious heritable changes, allowing a population to exist indefinitely despite individual degradation (10). Just as competition between individuals can eliminate deleterious alleles from a unicellular population, competition between cells within a multicellular organism can weed out malfunctioning, slower growing cells within an organism (11–15). Therefore, intercellular competition seems to hold the potential for immortality; by continually eliminating damaged cells, a multicellular organism might persist in perpetuity (16) if only selection to do so were somehow strong enough.

Aging in multicellular organisms occurs at both the cellular and intercellular levels (17). Multicellular organisms, by definition, require a high degree of intercellular cooperation to maintain homeostasis. Often, cellular traits required for producing a viable multicellular phenotype come at a steep cost to individual cells (14, 18, 19). Conversely, many mutant cells that do not invest in holistic organismal fitness have a selective advantage over cells that do. If intercellular competition occurs, such "cheater" or "defector" cells may proliferate and displace "cooperating" cells, with detrimental consequences for the multicellular organism (20, 21). Cancer, a leading cause of death in humans at rates that increase with age, is one obvious manifestation of cheater proliferation (22–24).

The role of intercellular competition in the proliferation of cheater cells is illustrated by organisms that have different levels of intercellular competition in different tissues. Cells of the nematode *Caenorhabditis elegans* are terminally differentiated at birth, precluding intercellular competition, except for germ-line cells. Consequently, cancers in *C. elegans* are limited to the indeterminately dividing germ-line cells, and somatic tissues remain cancer-free (25). Similarly, cells in *Drosophila melanogaster* do not divide after a fly reaches adulthood, save for the gut and germ-line cells. As expected, while larval *D. melanogaster* can develop cancers in several tissues, cancers in adults are relegated to the gut and absent from tissues where cell turnover is limited or nonexistent (26, 27).

Thus, intercellular competition proves to be a double-edged sword; competition can remove damaged cells, but competition can also allow cheating cells to prosper (14). Here, we derive a general model of the effect of somatic evolution on aging and examine the behavior of a related model of discrete genotypes in simple numerical cases. Aging is characterized by the dual, but seemingly contradictory, features of loss of cellular vigor and uncontrolled cell growth (17), and we model the evolution of two

Significance

We lay out the first general model of the interplay between intercellular competition, aging, and cancer. Our model shows that aging is a fundamental feature of multicellular life. Current understanding of the evolution of aging holds that aging is due to the weakness of selection to remove alleles that increase mortality only late in life. Our model, while fully compatible with current theory, makes a stronger statement: Multicellular organisms would age even if selection were perfect. These results inform how we think about the evolution of aging and the role of intercellular competition in senescence and cancer.

Author contributions: P.N. and J.M. designed research; P.N. performed research; P.N. analyzed data; and P.N. and J.M. wrote the paper.

The authors declare no conflict of interest.

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See Commentary on page 12851.

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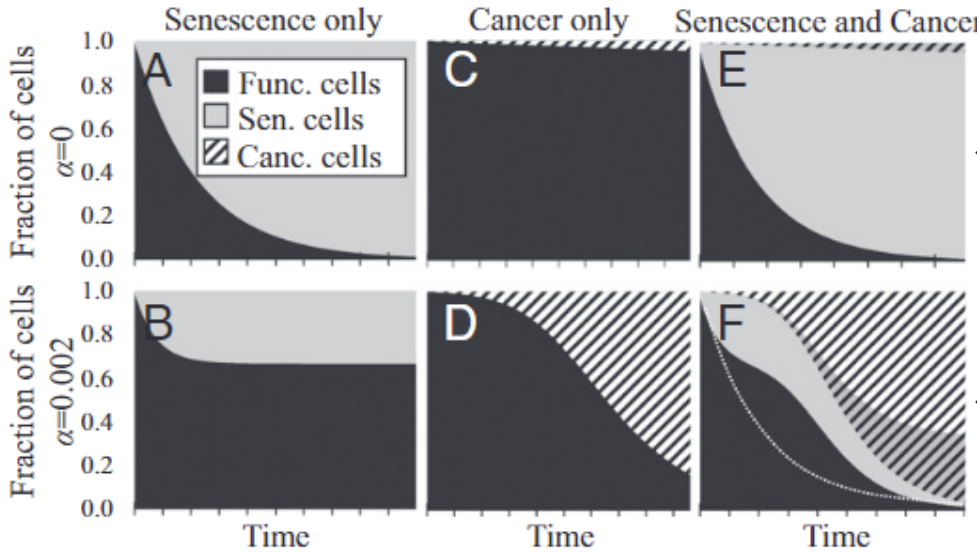
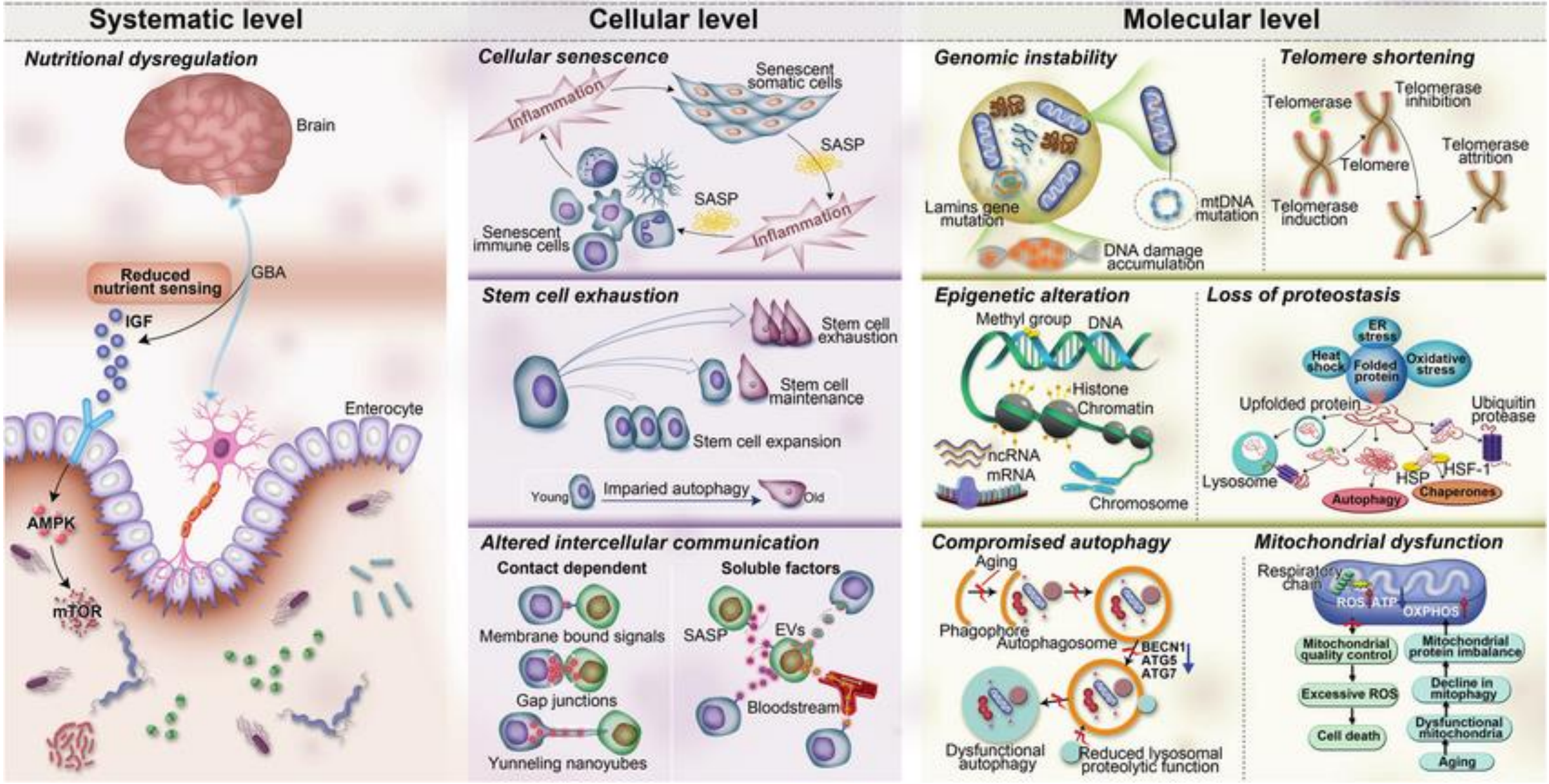


Without cellular competition

With cellular competition

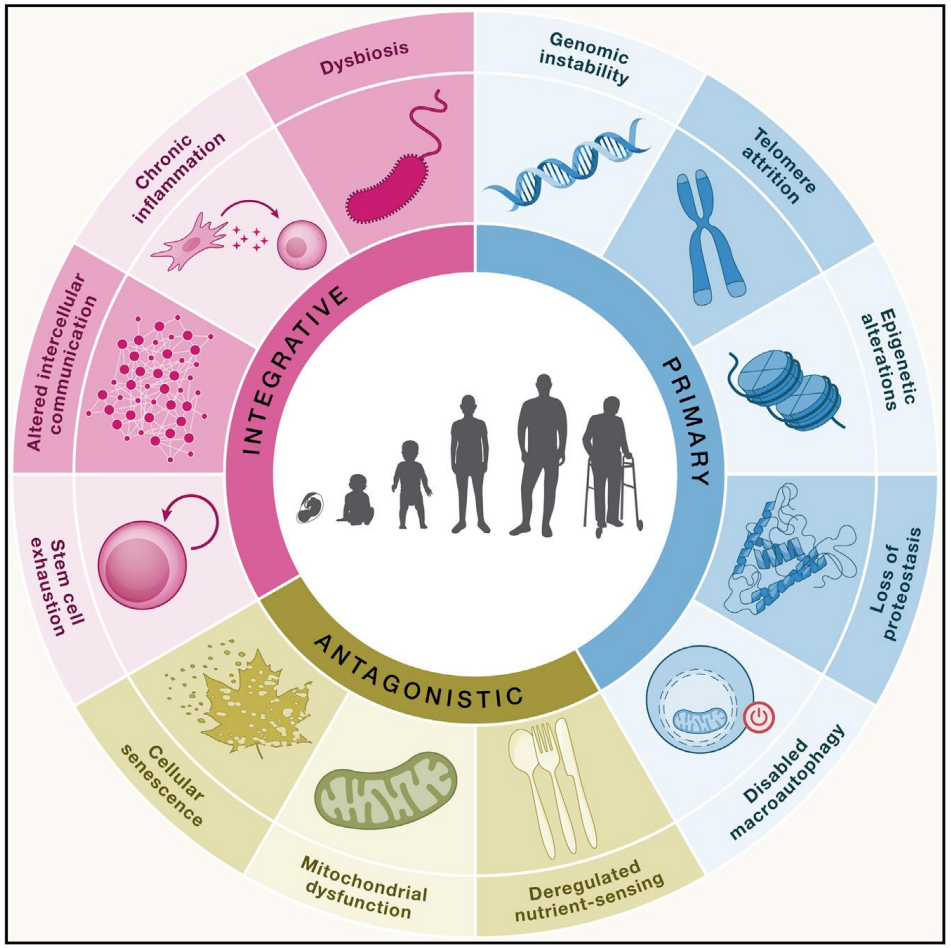
Fig. 2. Intercellular competition prevents accumulation of senescent cells at the cost of allowing cancerous cells to proliferate. (*A* and *B*) Cellular changes causing senescence ($\mu_v = 10^{-3}$, $\mu_c = 0$) cause senescent cells (gray) to accumulate without intercellular competition ($\alpha = 0$, top row), depleting functional cells (black), but are purged when cells compete ($\alpha = 0.002$, bottom row). Cellular changes causing cancer ($\mu_v = 0$, $\mu_c = 10^{-5}$) lead to a small population of cancerous cells (black diagonal stripes) that are prevented from proliferating without intercellular competition (*C*) but can spread when cells compete (*D*). When cells are subject to both senescence- and cancer-causing changes, senescent cells accumulate without intercellular competition (*E*) and cancerous cells proliferate when cells compete (*F*). In *F*, a portion of cancerous cells acquire senescent changes, resulting in a class of cells that are both cancerous and senescent (gray with diagonal stripes). The white dashed line in *F* indicates functional cells from *E* to illustrate the extent to which intercellular competition delays (but does not prevent) the loss of functional cells.


Systematic level
Cellular level
Molecular level
Nutritional dysregulation
Brain
Reduced nutrient sensing
GBA
IGF
Enterocyte
AMPK
mTOR
Cellular senescence
Inflammation
Senescent somatic cells
SASP
SASP
Senescent immune cells
Inflammation
Stem cell exhaustion
Stem cell exhaustion
Stem cell maintenance
Stem cell expansion
Young
Imparied autophagy
Old
Altered intercellular communication
Contact dependent
Soluble factors
Membrane bound signals
Gap junctions
Yunneling nanoyubes
SASP
EVs
Bloodstream
Genomic instability
Lamins gene mutation
mtDNA mutation
DNA damage accumulation
Telomere shortening
Telomerase
Telomerase inhibition
Telomere
Telomerase attrition
Telomerase induction
Epigenetic alteration
Methyl group
DNA
Histone
Chromatin
ncRNA
mRNA
Chromosome
Loss of proteostasis
ER stress
Heat shock
Folded protein
Oxidative stress
Upfolded protein
Ubiquitin protease
Lysosome
HSP
HSF-1
Autophagy
Chaperones
Compromised autophagy
Aging
Phagophore
Autophagosome
BECN1
ATG5
ATG7
Dysfunctional autophagy
Reduced lysosomal proteolytic function
Mitochondrial dysfunction
Respiratory chain
ROS
ATP
OXPHOS
Mitochondrial quality control
Mitochondrial protein imbalance
Excessive ROS
Decline in mitophagy
Cell death
Dysfunctional mitochondria
Aging

The ten hallmarks of aging are subdivided into three categories:
molecular hallmarks (genomic instability, telomere dysfunction, epigenetic alterations, loss of proteostasis, compromise of autophagy, and mitochondrial dysfunction),
cellular hallmarks (cellular senescence, stem cell exhaustion, and altered intercellular communication),
and systemic alterations (deregulated nutrient sensing).

AMPK protein kinase
AMP-activated catalytic subunit alpha 1,
ATG5: autophagy-related 5,
ATG-7 autophagy-related 7, ATP adenosine triphosphate,
BECN1 Beclin 1,
ER endoplasmic reticulum stress,
EVs extracellular vesicles,
GBA gut-brain axis,
HSF-1 heat shock factor-1,
HSP heat shock protein,

IGF insulinlike growth factor-1,
mtDNA mitochondrial DNA,
mRNA messenger RNA,
mTOR mechanistic target of rapamycin kinase,
ncRNA noncoding RNA,
OXPHOS oxidative phosphorylation,
Rb retinoblastoma,
ROS, reactive oxygen species,
SASP senescence-associated secretory phenotype



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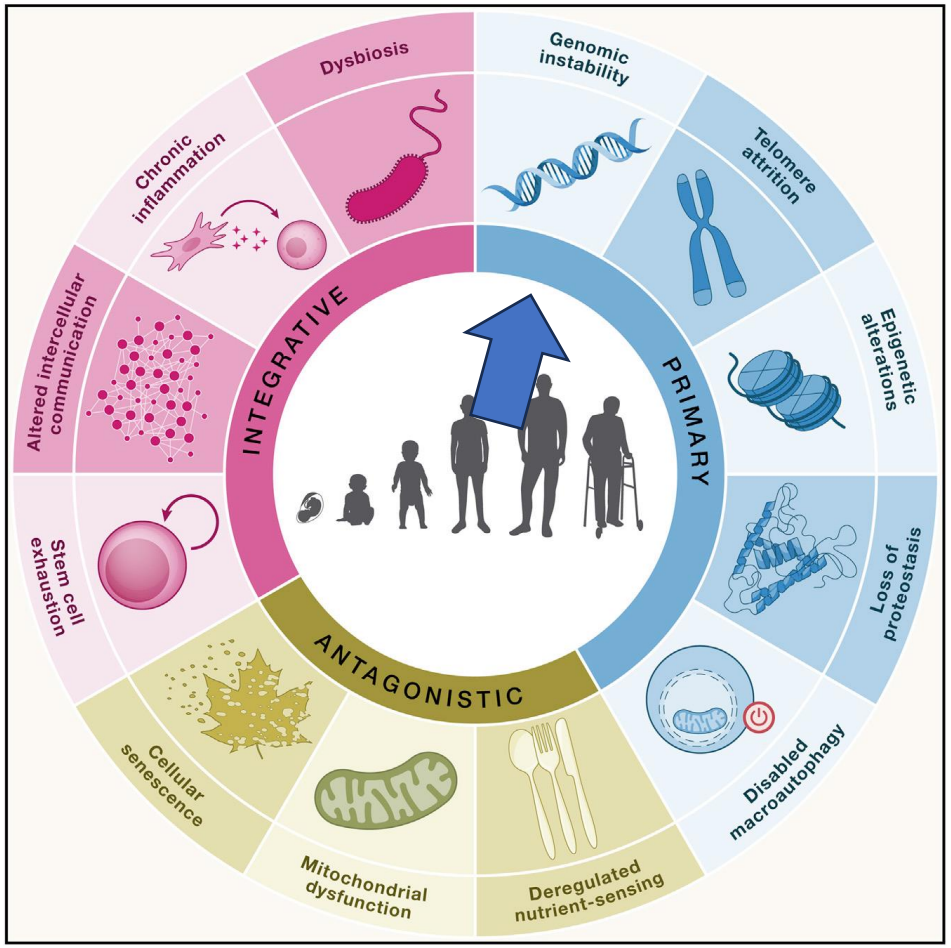

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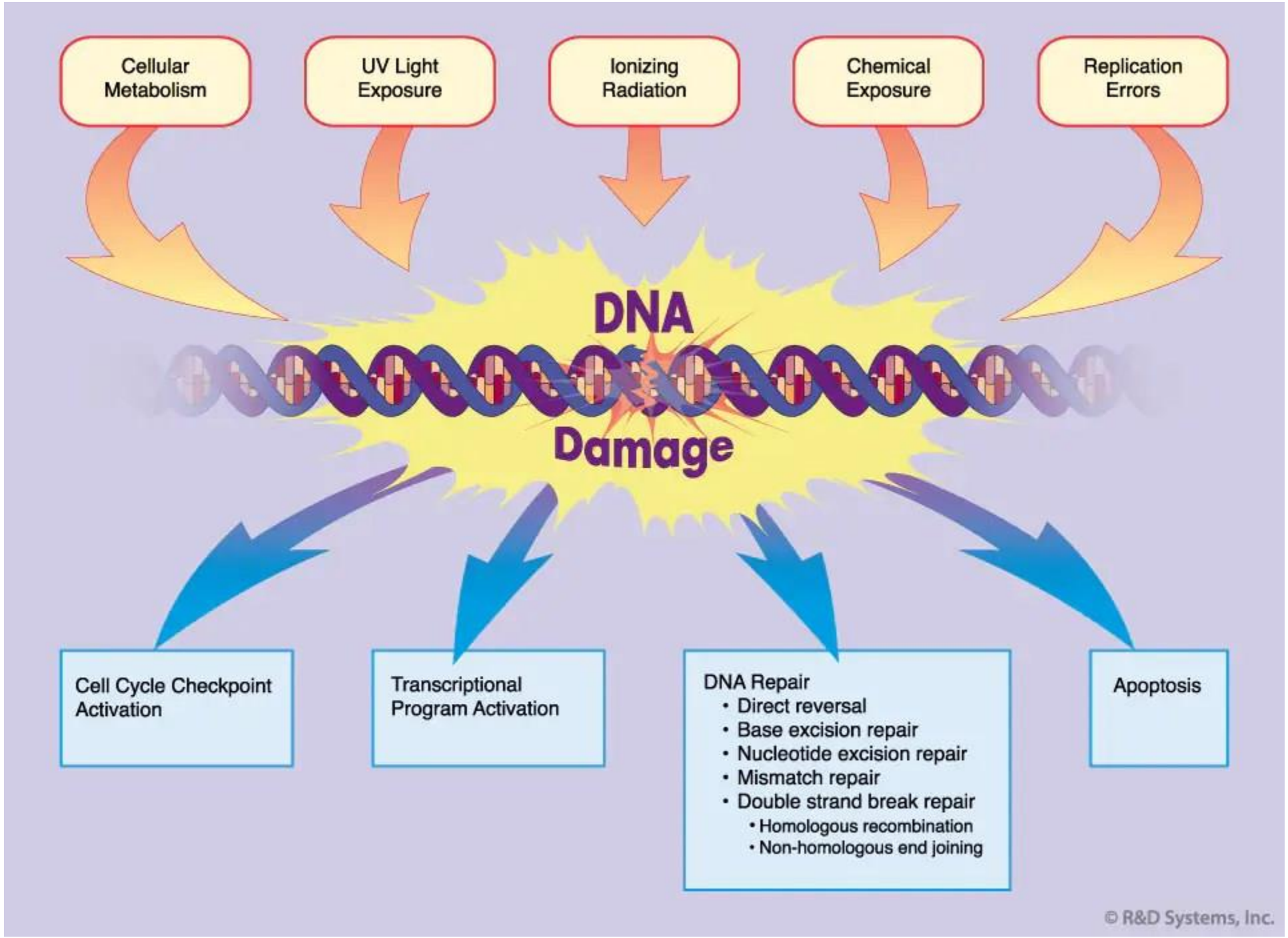
Cellular Metabolism
UV Light Exposure
Ionizing Radiation
Chemical Exposure
Replication Errors
DNA
Damage
Cell Cycle Checkpoint Activation
Transcriptional Program Activation
DNA Repair
• Direct reversal
• Base excision repair
• Nucleotide excision repair
• Mismatch repair
• Double strand break repair
• Homologous recombination
• Non-homologous end joining
Apoptosis
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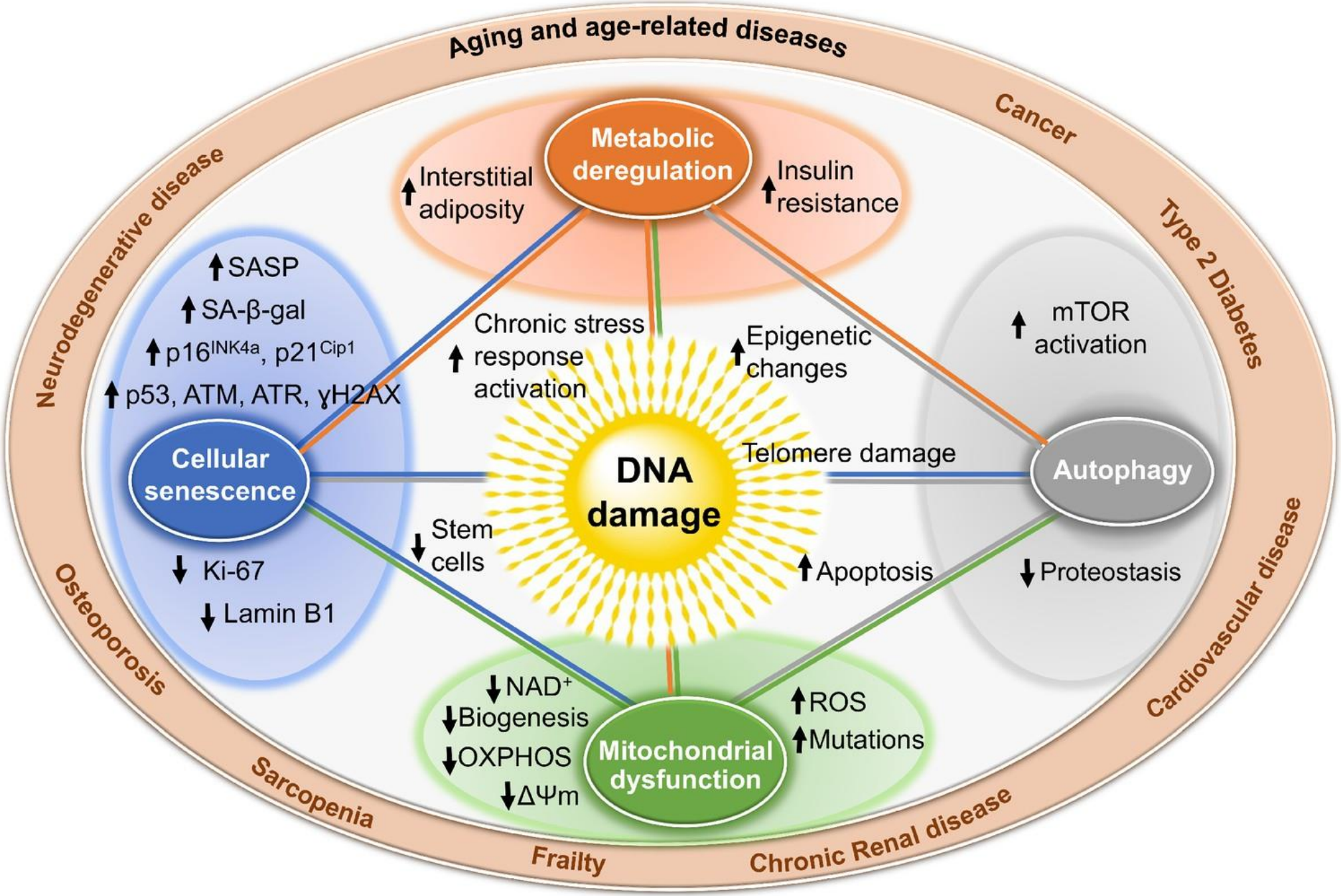
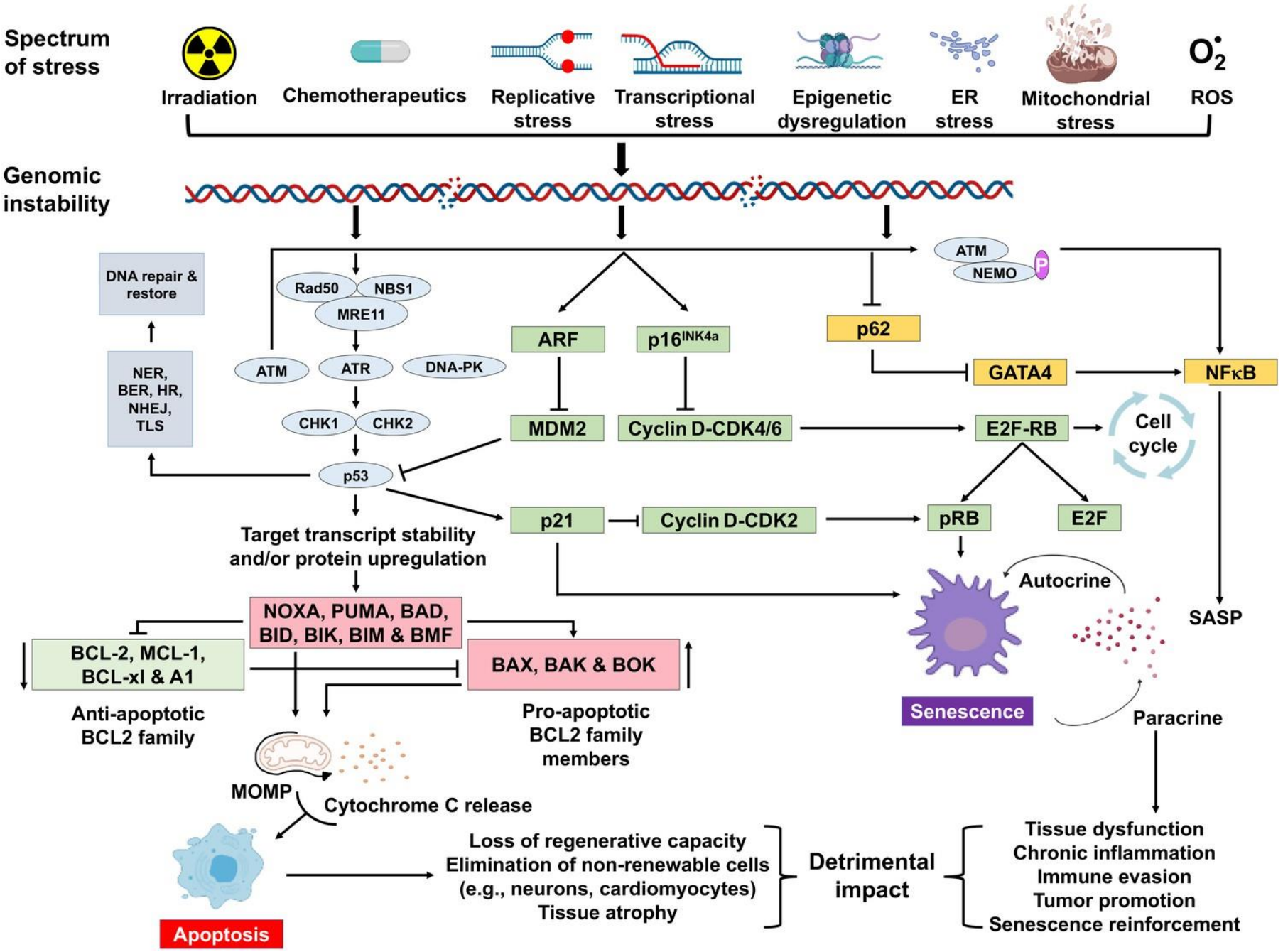


https://doi.org/10.7554/eLife.62852



Schematic representation of signaling events within a cell that enable DNA damage to promote aging.
Depicted are various stressors that can lead to genome instability and activation of the DNA damage response (DDR). The DDR (light blue) leads to cell cycle arrest (green). If signaling persists, apoptosis or senescence ensues. Senescence can affect neighboring, undamaged cells.

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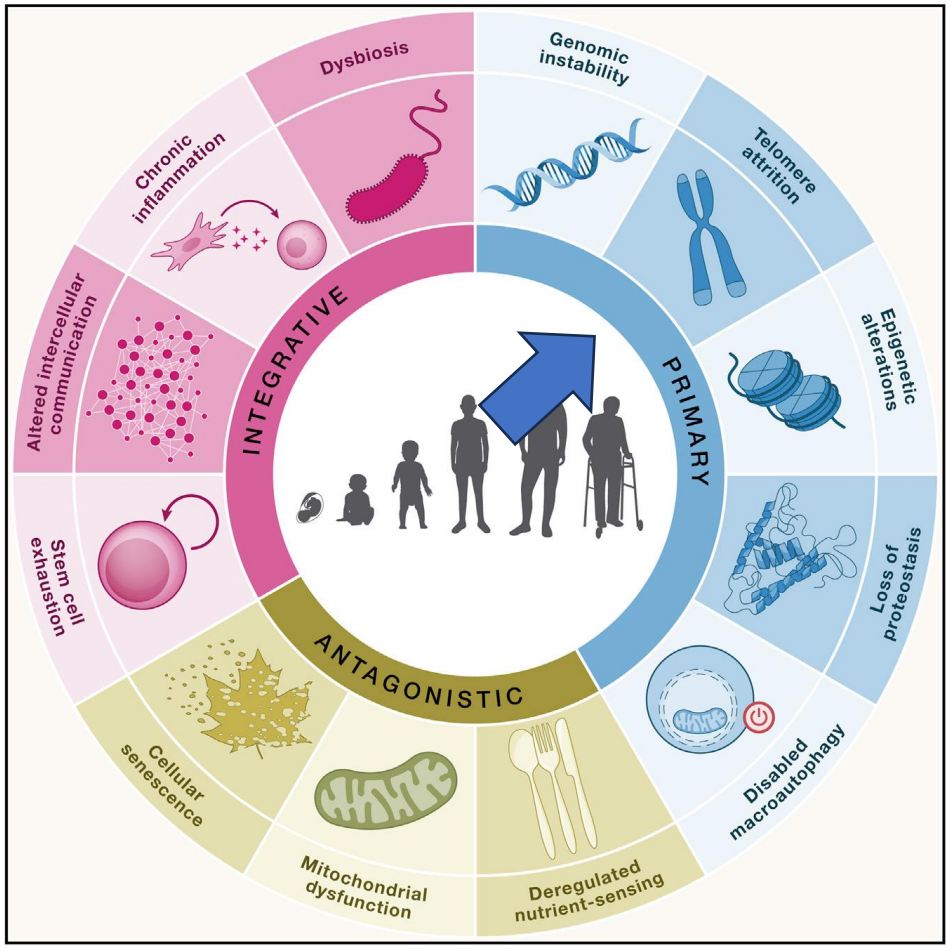

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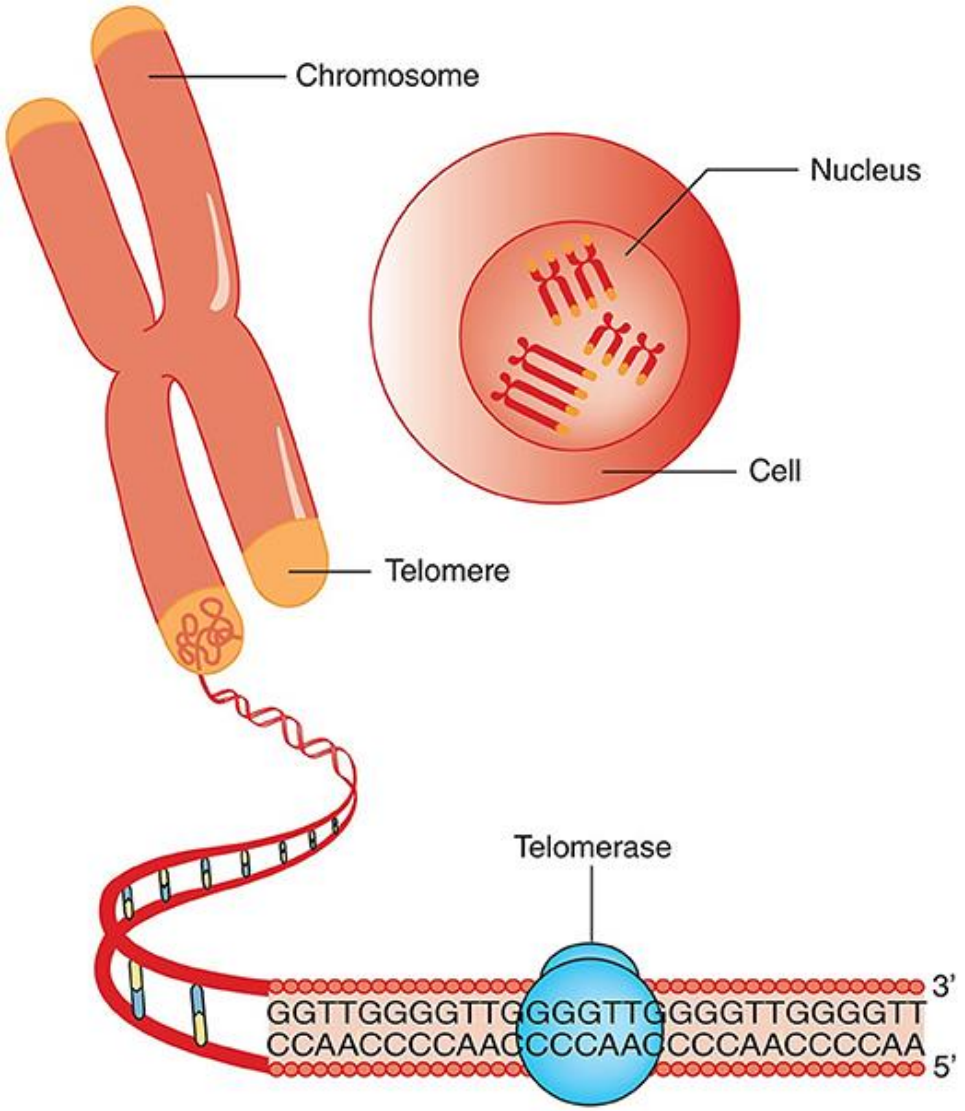
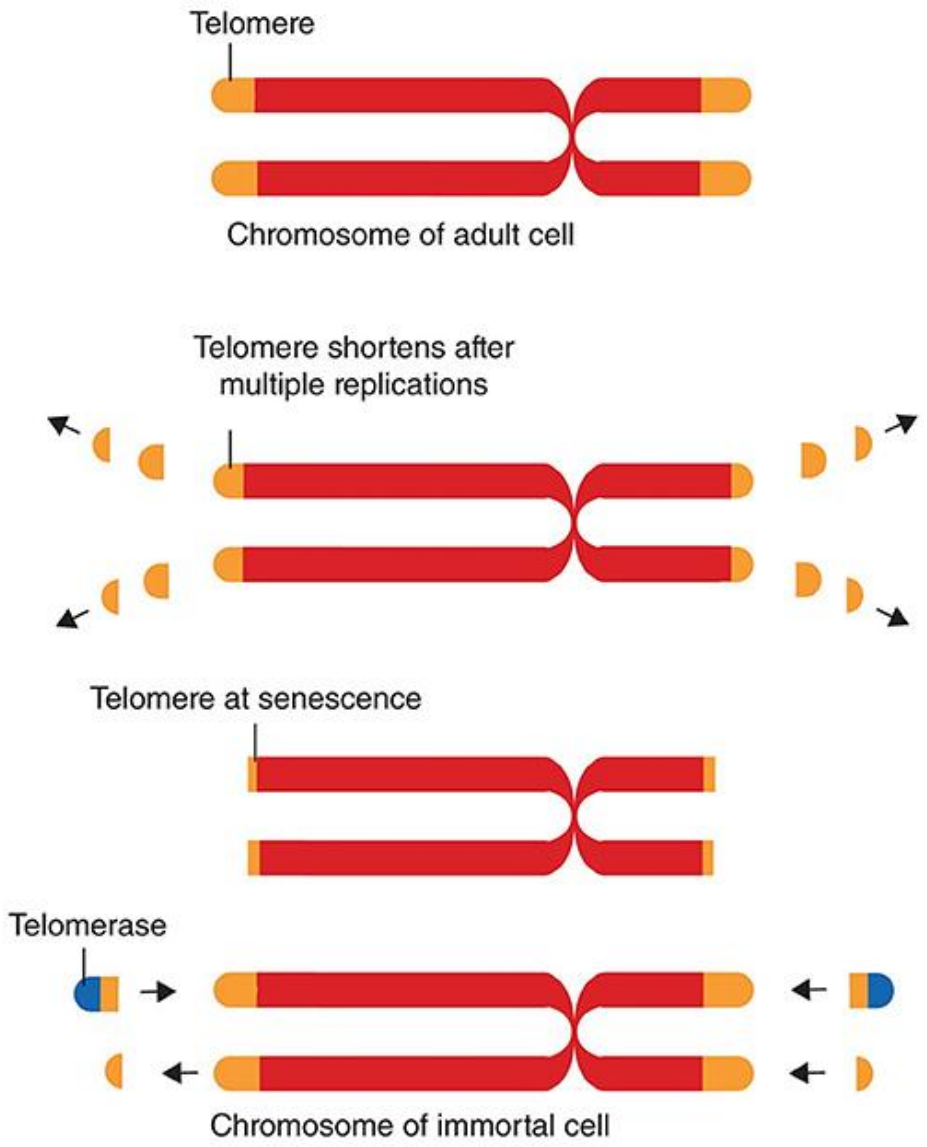
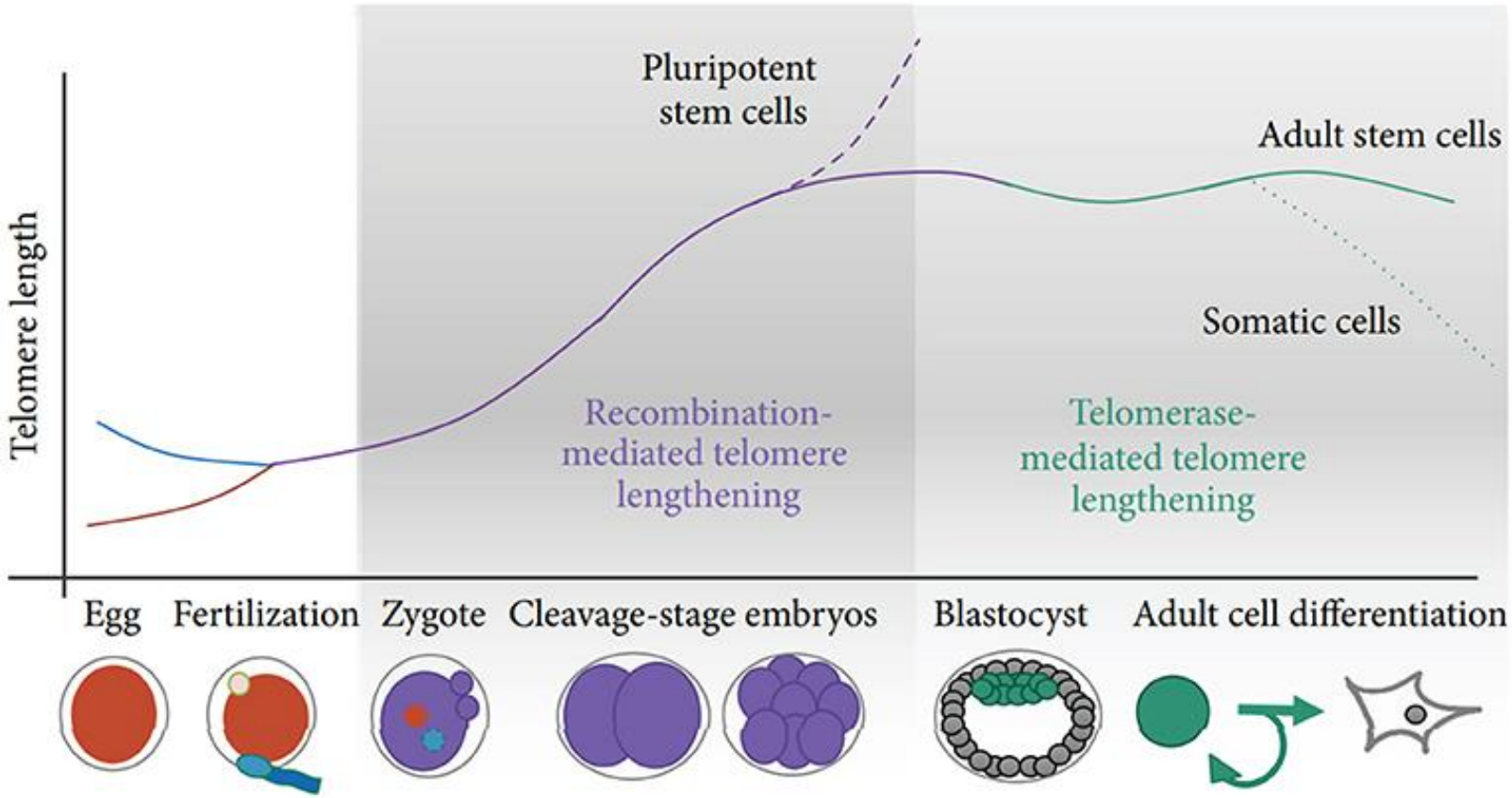




Telomere attrition, telomere length and telomerase. Chromosomes have repeated base segments called telomeres that shorten with each replication cycle (cell division). The enzyme telomerase has the capability to extend the telomere ends, thus prolonging cell life and potentially inducing immortality (which is a cancer cell hallmark).



Schematic of telomere length reprogramming in mammalian embryonic development. The greatest telomere lengthening takes place during the earliest stages of preimplantation development, the cleavage-stage embryo, which may coincide with zygote genome activation. Recombination-mediated telomere lengthening (ALT) is also purportedly responsible for reprogramming in pluripotent stem cells, including ESCs, ntESCs, and iPSCs. Later, in development and adult life, telomerase becomes the dominant telomere maintenance mechanism for the inner cell mass and in tissue-specific telomere replenishment in stem cell niches.

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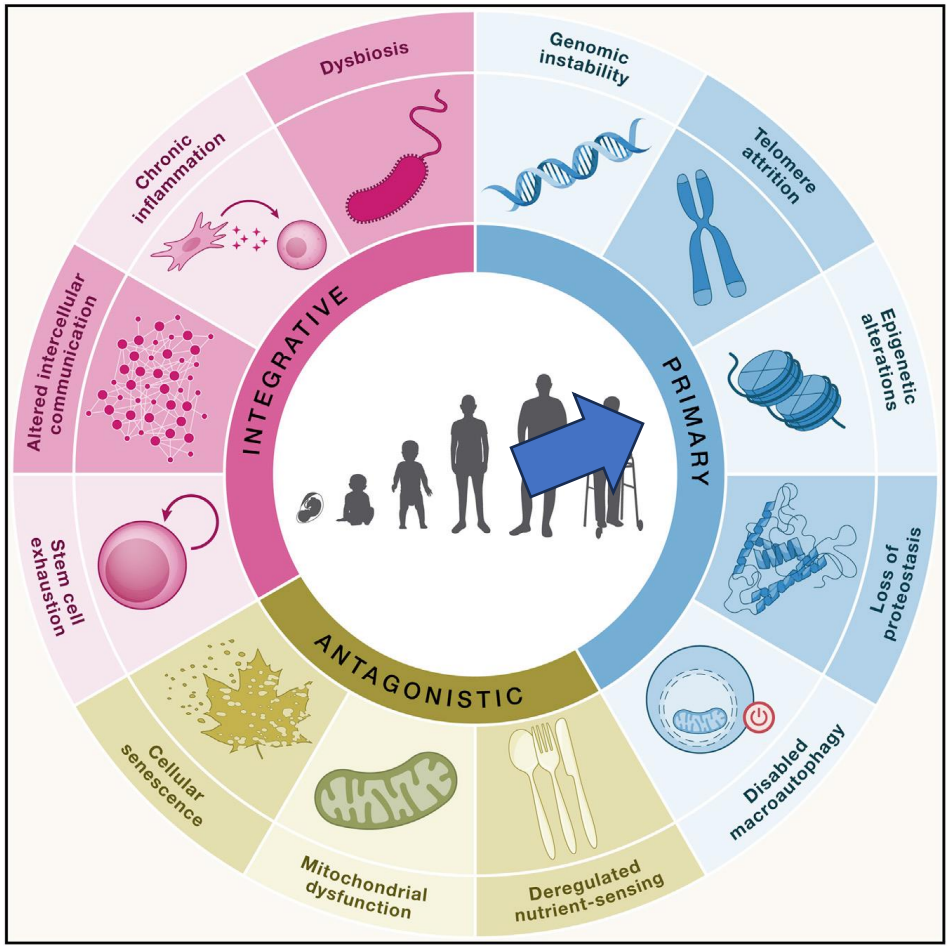

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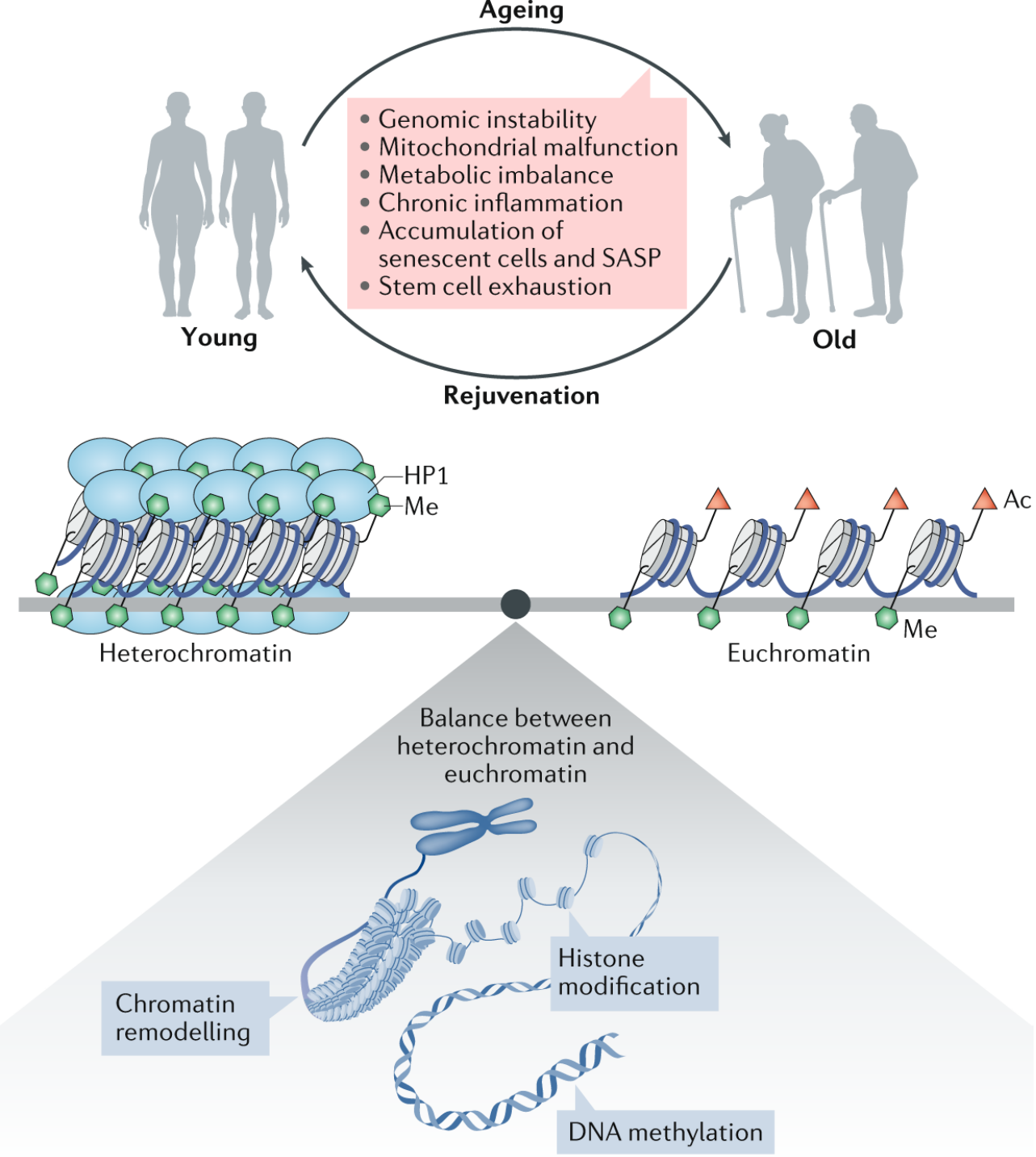
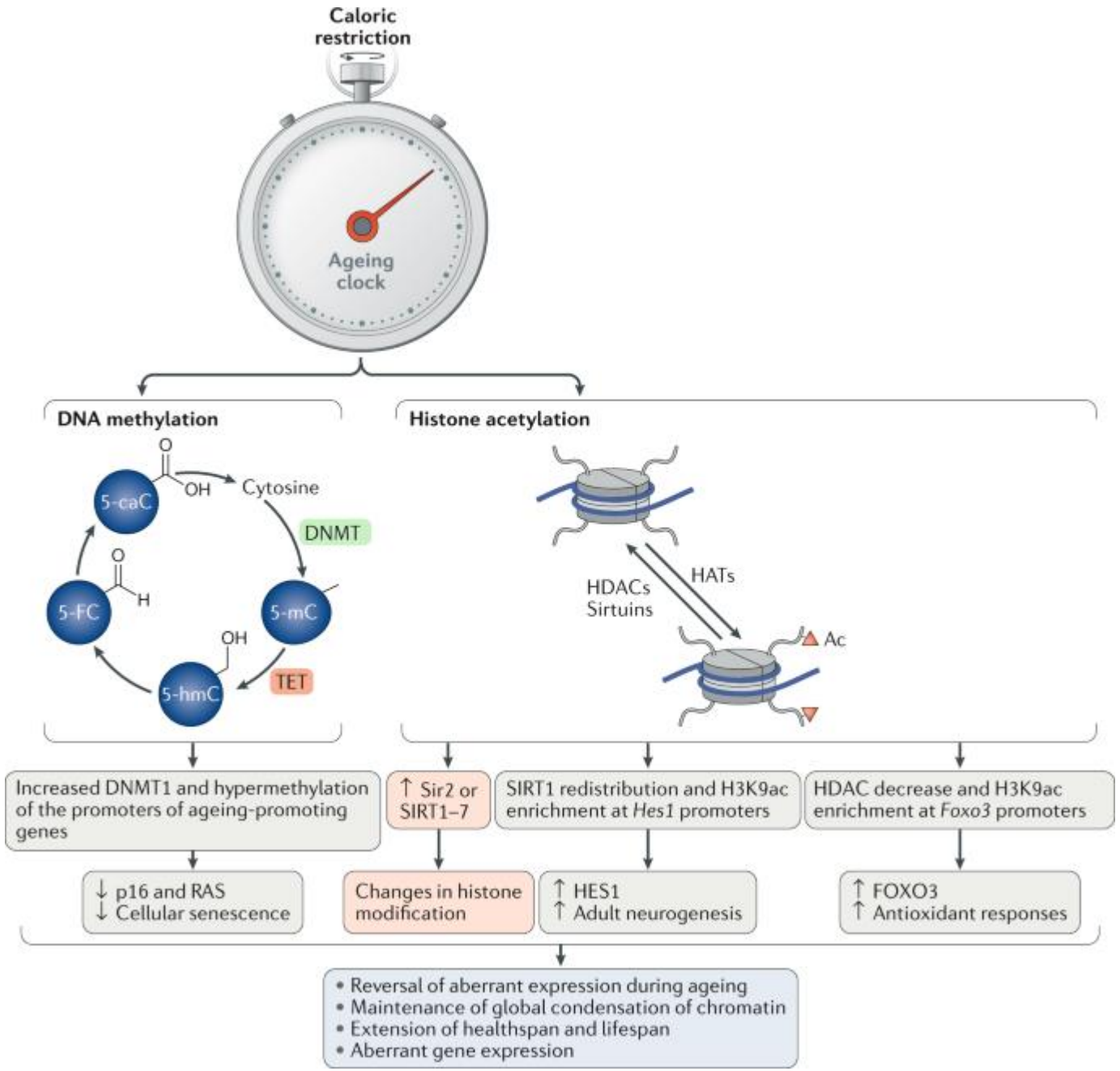


Ageing-associated epigenetic changes include DNA methylation, histone modifications and chromatin remodelling, which together contribute to a general loss of heterochromatin in aged cells. Maintaining the balance between heterochromatin and euchromatin can prevent cellular defects that accumulate during ageing, including genomic instability, mitochondrial malfunction, metabolic imbalance, chronic inflammation, senescence-associated secretory phenotype (SASP), stem cell exhaustion and senescent cell accumulation. Together, lifespan-intervention strategies work through different layers of epigenetic regulation to maintain a healthier state in cells, tissues and organisms. Ac, histone acetylation; HP1, heterochromatin protein 1 (HP1 family members are HP1α, HP1β anad HP1γ); Me, H3K9me3.

https://doi.org/10.1038/s41580-019-0204-5



Caloric restriction (CR) is a powerful rejuvenation strategy to turn back the clock of ageing. CR influences epigenetic processes via two representative mechanisms: DNA methylation and histone modification. For example, CR activates DNA methyltransferases (DNMTs) to hypermethylate the promoter regions of ageing-promoting genes (such as those encoding p16 and RAS, the activation of which induces cellular senescence), ceasing the expression of these genes. CR also modulates ten–eleven translocations (TETs) to change the global DNA methylation landscape. At the histone level, CR is widely reported to be able to activate *Sir2* or the seven homologues of SIR2 in mammals (SIRT1–SIRT7). On the other hand, CR causes redistribution of SIRT1 on chromatin, causes enrichment of Lys9-acetylated histone H3 (H3K9ac) at the promoters of *Hes1*(a basic helix–loop–helix transcriptional regulator) and promotes adult neurogenesis. Other histone deacetylases (HDACs) may be inhibited by CR, leading to higher levels of H3K9ac at the promoter of the transcription factor *Foxo3*, and induce antioxidant responses. Together, CR-induced epigenetic changes result in the maintenance of global condensation of chromatin, a reversal of aberrant gene expression and eventual extension of healthspan and lifespan. Ac, histone acetylation; 5-caC, 5-carboxycytosine; 5-FC, 5-formylcytosine; HATs, histone acetyltransferases; 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine.

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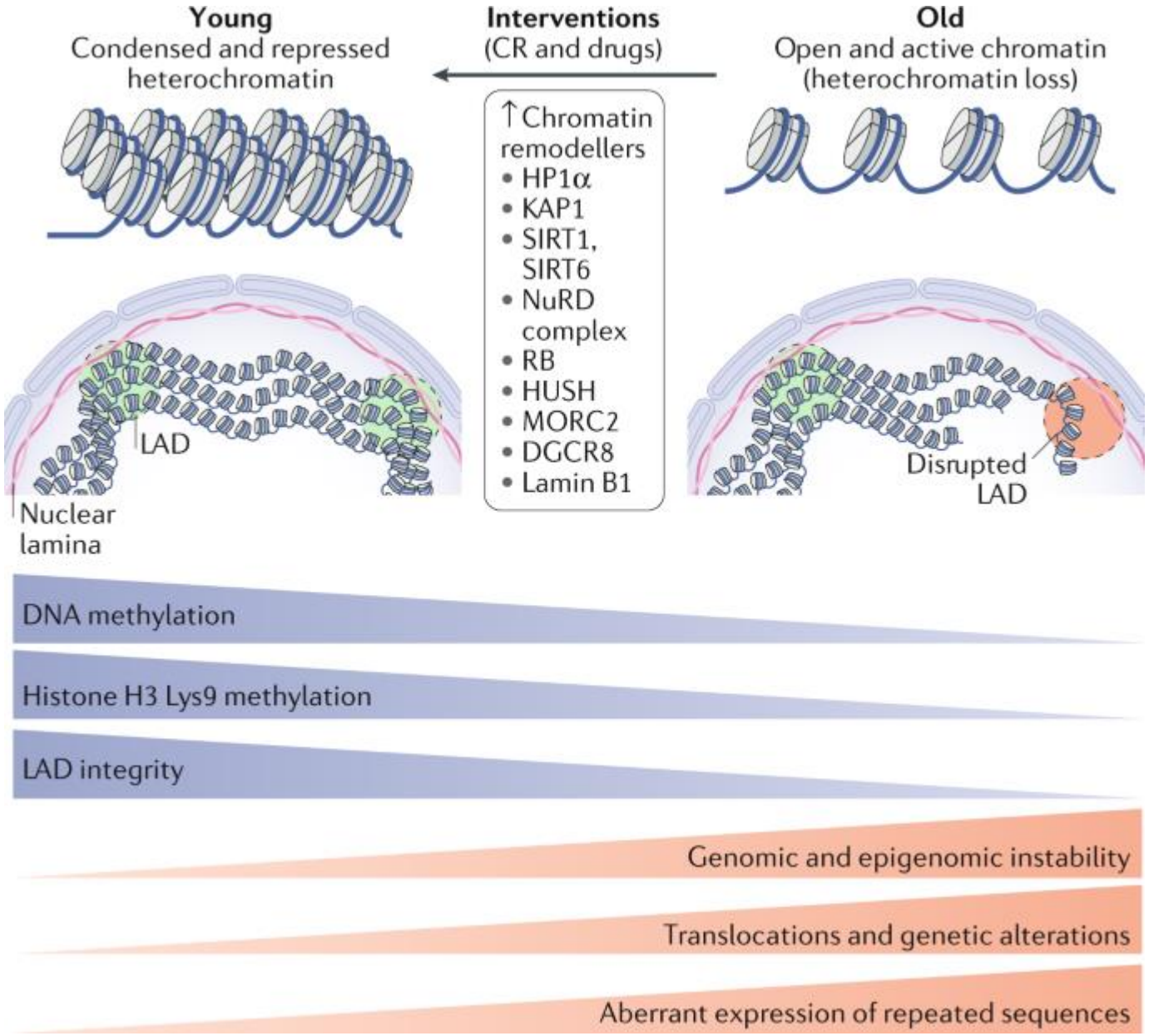
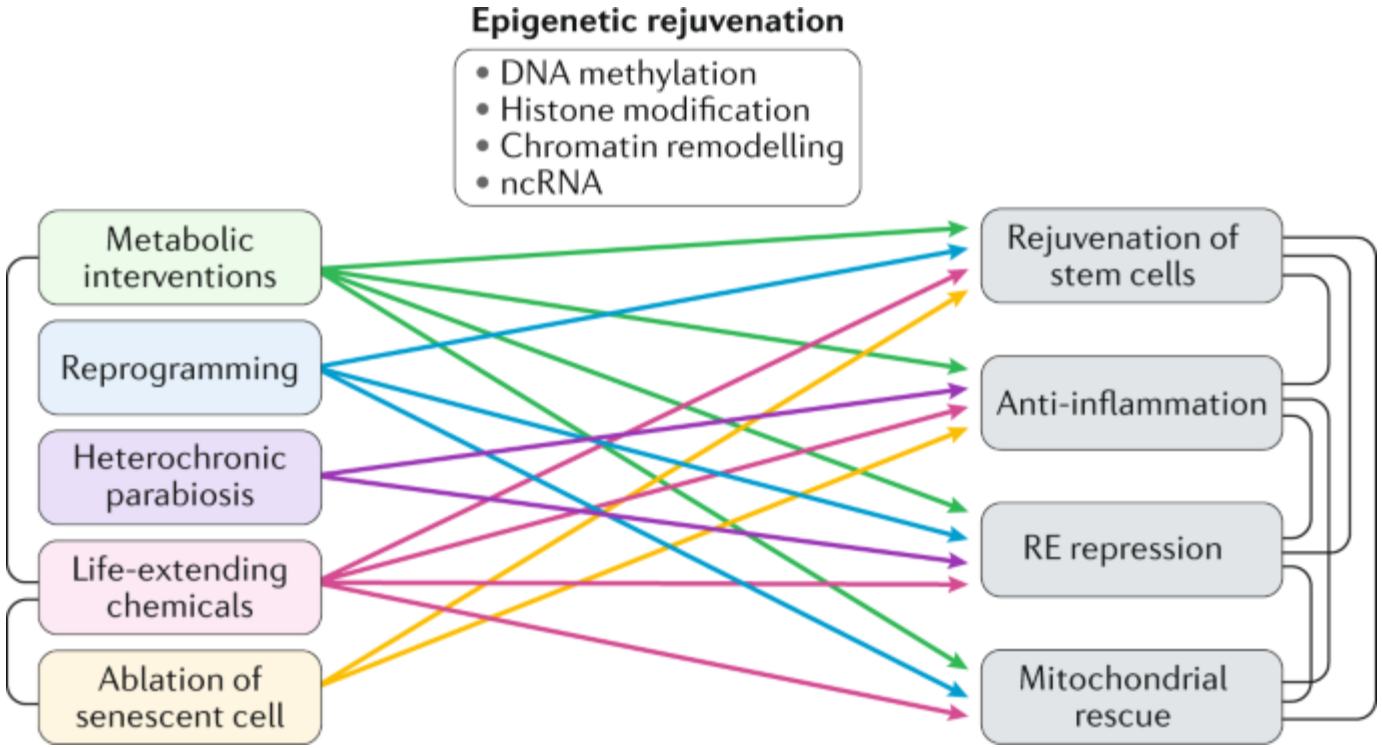


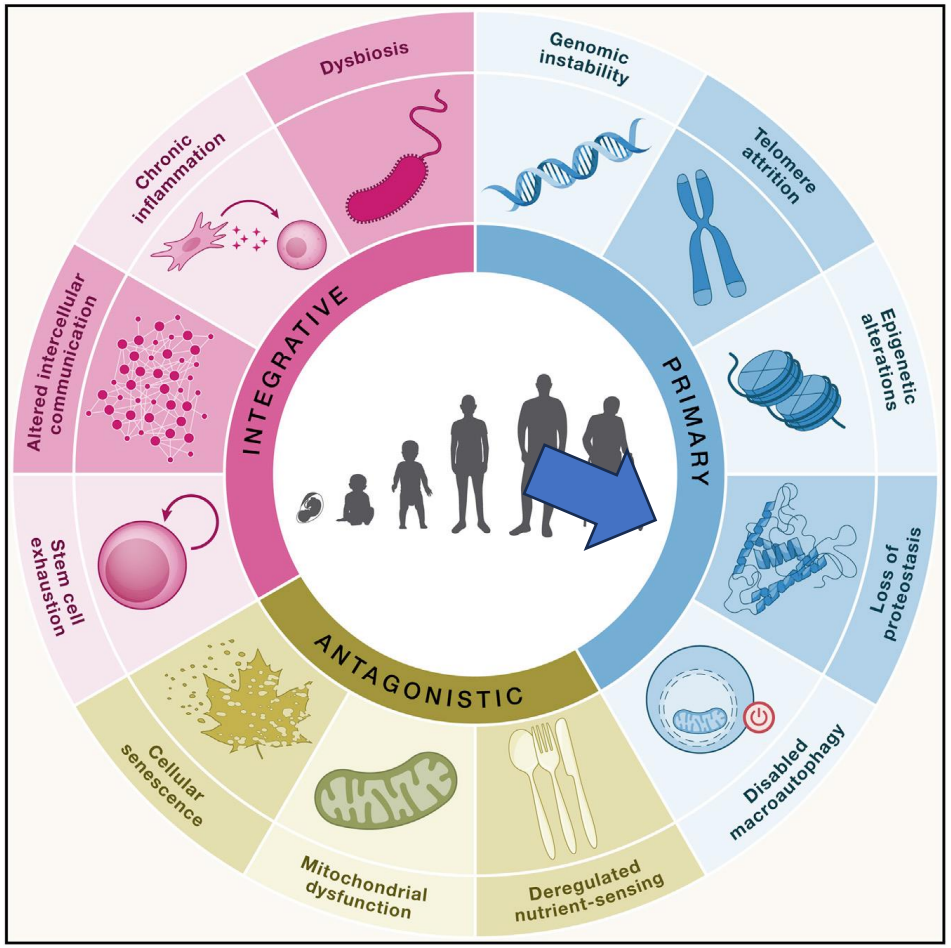
In young cells, repeating sequences are highly DNA methylated and condensed into heterochromatin; some of these repeating sequences are attached to the nuclear membrane, forming a nuclear territory at the periphery of the nucleus known as 'lamina-associated domains' (LADs; indicated by green circles). In old cells, repeating sequences lose their methylation coating and become open and accessible to transcription factors. The structures of LADs are also detached from the nuclear membrane and disrupted (indicated by the orange circle). These process lead to reactivation of repeating sequences, increasing genomic and epigenomic instability with increasing numbers of translocations and genetic alterations, and aberrant transcription of repeating sequences. Overexpression of some chromatin modifiers or binding proteins facilitates stabilization of the chromatin structure in repeating sequence regions. Caloric restriction (CR) and drugs may help to keep condensed and repressed heterochromatin in aged cells, which may contribute to their life-extending functions. HUSH, human silencing hub; NuRD, nucleosome remodeller and deacetylase.

https://doi.org/10.1038/s41580-019-0204-5



Metabolic manipulation, epigenetic reprogramming, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation constitute five possible health- and life-extending strategies. These interventions induce epigenetic reprogramming to alter gene expression and reprogramme aged cells to a younger state. Stem cell rejuvenation is a common feature of all these rejuvenation interventions. In addition, the epigenetic programme interacts with important molecular pathways, such as those associated with maintenance of mitochondrial homeostasis, suppression of retrotransposon elements and amelioration of inflammation to counteract ageing. The connecting lines indicate a reported relationship between intervention and effect. The lines between interventions (left-hand side) indicate that some life-extending chemicals mimic the effect of caloric restriction to exert their function, while senolytic drugs could eliminate senescent cells. The lines between effects (right-hand side) mean these effects may influence each other. ncRNA non-coding RNA; RE, Repetitive elements.

https://doi.org/10.1038/s41580-019-0204-5



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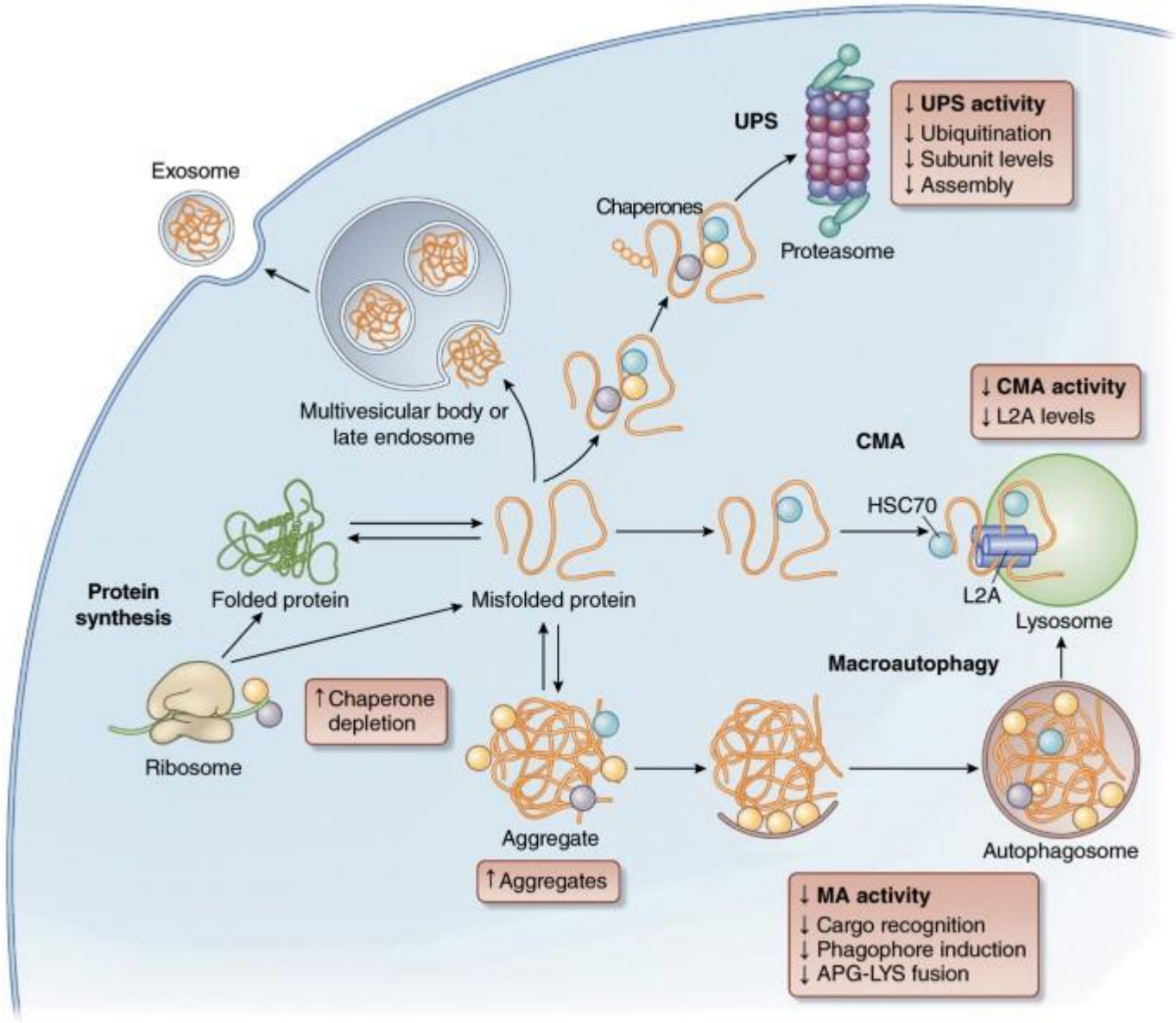
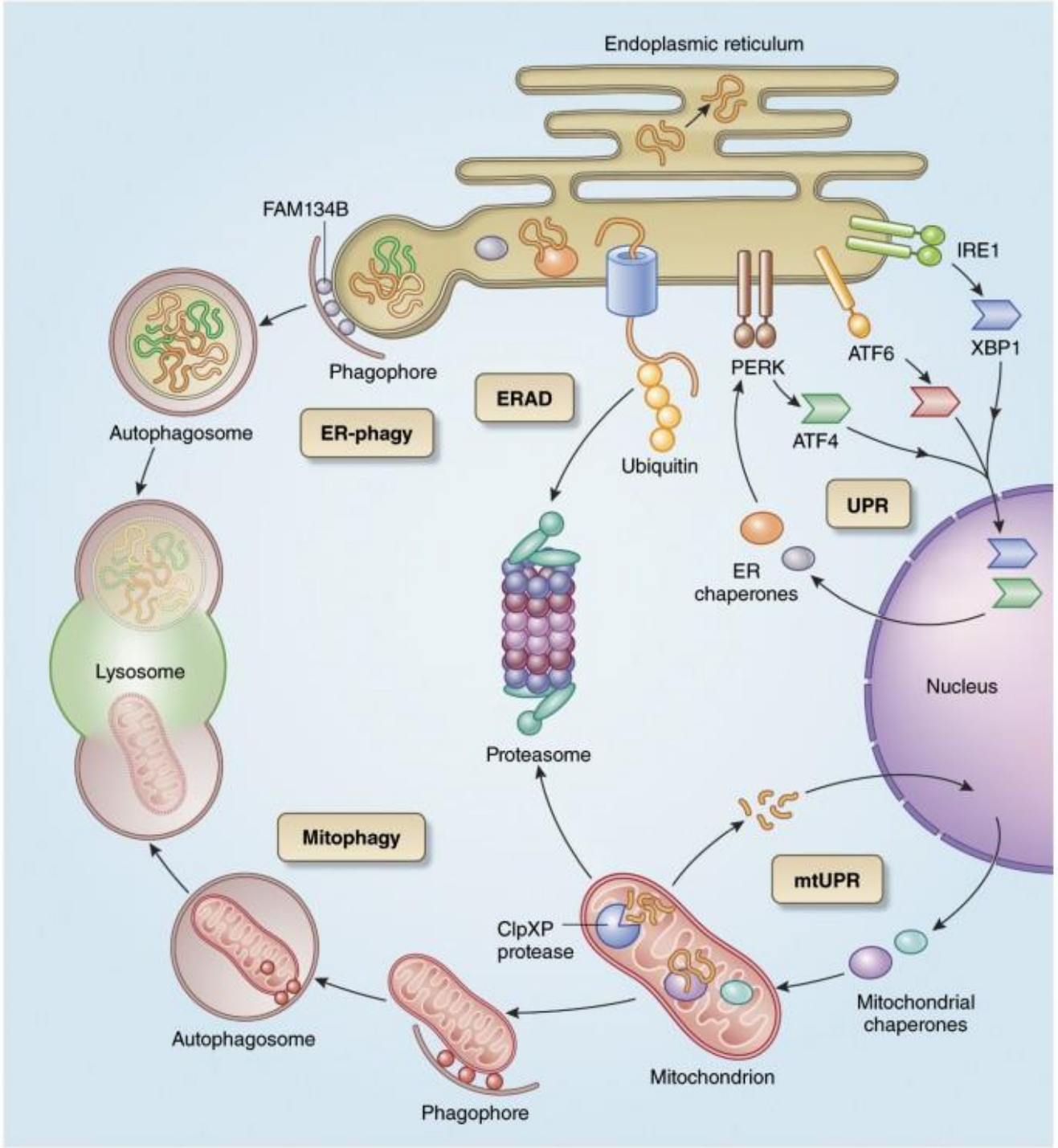


Chaperones and two proteolytic systems, the ubiquitin proteasome system (UPS) and autophagy, take care of maintenance of intracellular proteostasis. Chaperones (blue, yellow and gray circles) assist *de novo* synthesized proteins and unfolded proteins to reach their folded stable status. If folding is not possible, chaperones target the unfolded protein for degradation by the proteasome (often after ubiquitination) or in lysosomes. Single soluble proteins can reach the lysosomal lumen through a membrane transporter in chaperone-mediated autophagy (CMA). Once misfolded proteins organize into oligomers or insoluble aggregates, the only options for their elimination from the cytosol are either by degradation in lysosomes through macroautophagy (MA) or expulsion outside the cell by means of small vesicles (exosomes). Red boxes indicate changes with age in different steps or components of the intracellular proteostasis networks. APG-LYS, autophagosome-lysosome; HSC70, heat-shock cognate protein of 70kDa; L2A, lysosome-associated membrane protein type 2A

https://doi.org/10.1038/nm.4001



Schematic of the mechanisms that preserve proteostasis in the endoplasmic reticulum (ER) and in mitochondria. The ER and mitochondria can undergo degradation as a whole organelle through specialized forms of autophagy, ER-phagy (assisted by the recently identified FAM134B protein) and mitophagy, respectively. In addition, these organelles have their own proteostasis systems that are activated by the presence of unfolded proteins. In the ER, these unfolded proteins activate the unfolded protein response (UPR) that has three arms (mediated by PERK and ATF4, IRE1 and XBP1, and by ATF6). Activation of the UPR attenuates protein translation and enhances the expression of ER chaperones. If this response is not sufficient, unfolded proteins are retrotranslocated for degradation in the cytoplasm by the proteasome (ERAD). The mitochondrial UPR (mtUPR) is similarly activated in response to proteotoxic stress to enhance chaperone content in mitochondria and to attenuate translation. Unfolded mitochondrial proteins are cleaved by the ClpXP protease into small peptides that upon translocation into the cytosol activate the mtUPR.

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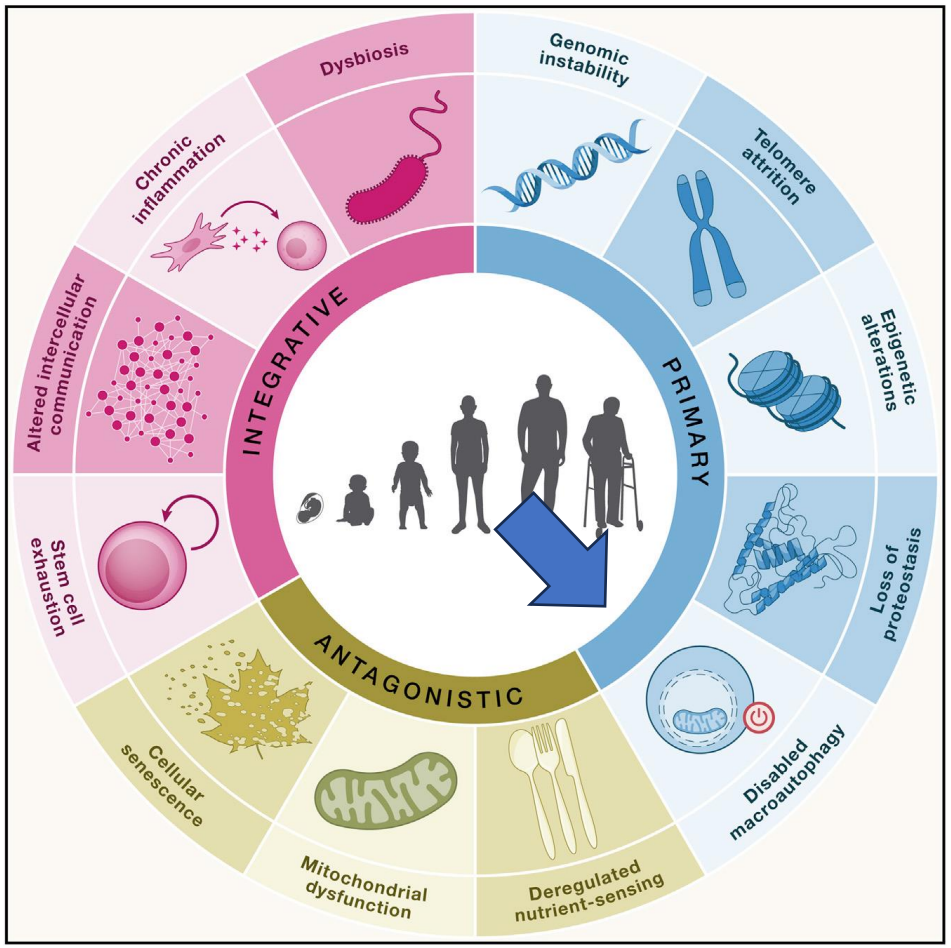

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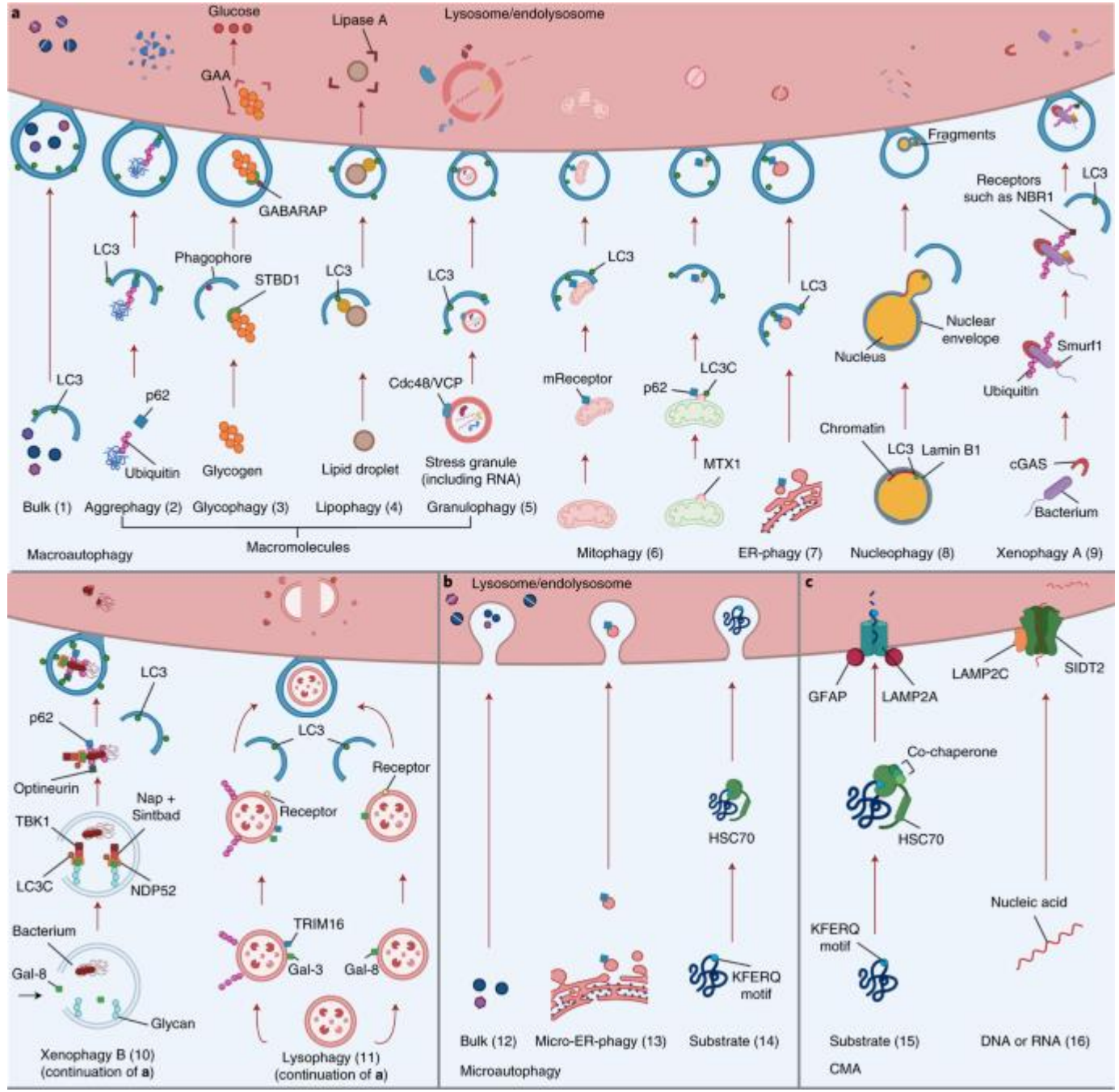
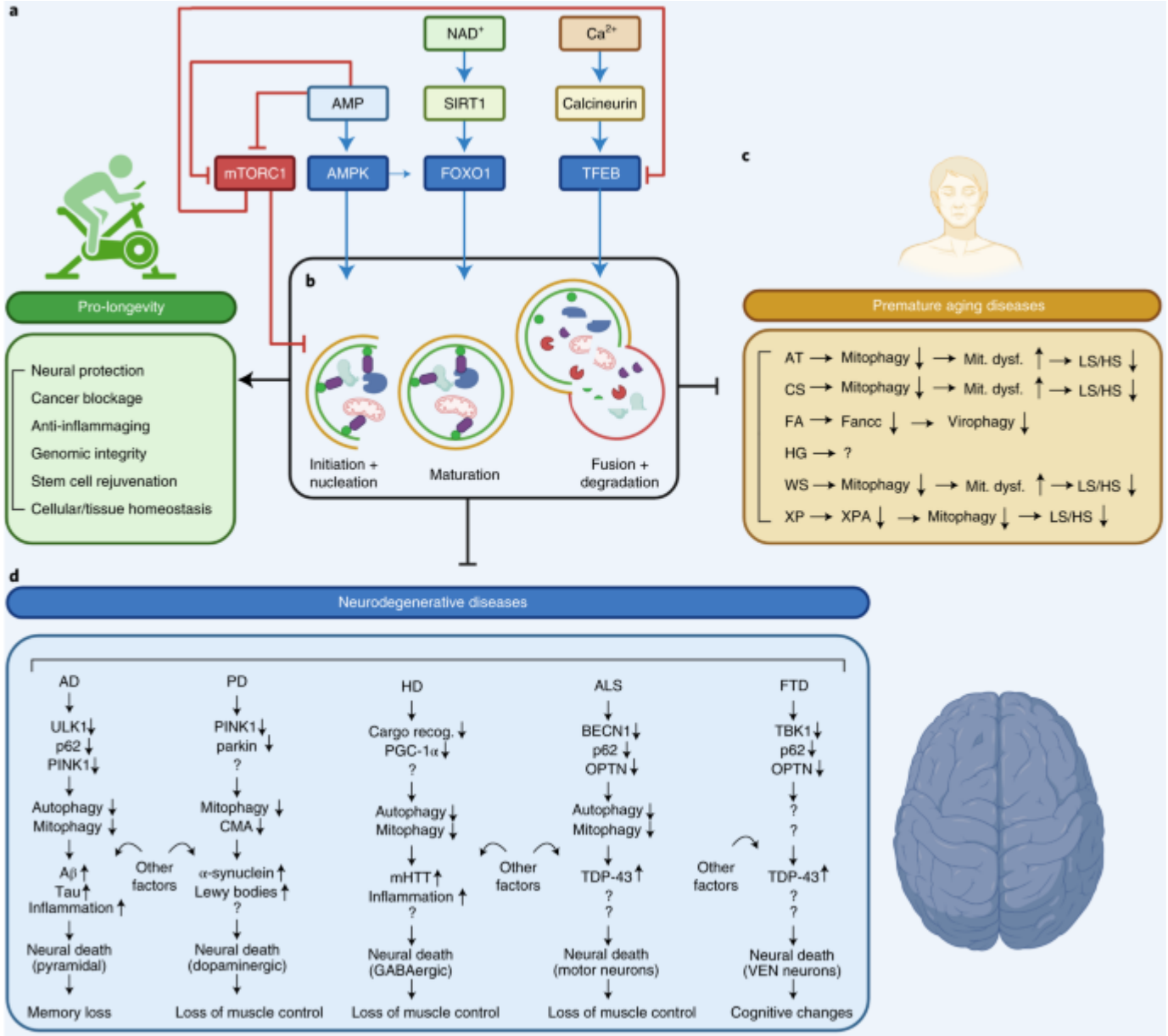
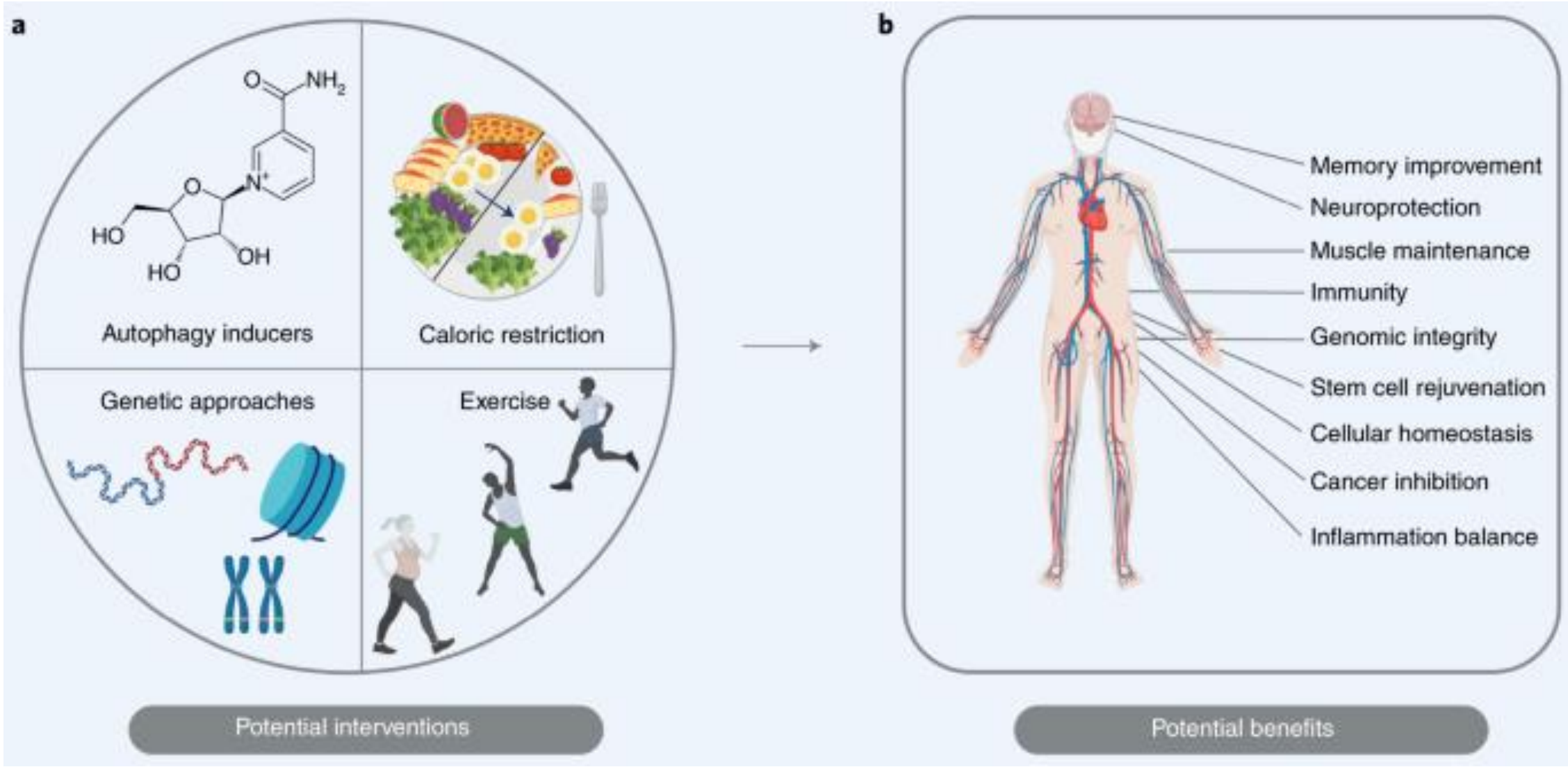

a
Glucose
GAA
Lipase A
Lysosome/endolysosome
GABARAP
LC3
Phagophore
STBD1
LC3
LC3
LC3
mReceptor
LC3
LC3
Fragments
Receptors such as NBR1
LC3
Nuclear envelope
Nucleus
Smurf1
Ubiquitin
LC3
p62
Ubiquitin
Glycogen
Lipid droplet
Cdc48/VCP
Stress granule (including RNA)
p62
LC3C
MTX1
Chromatin
LC3
Lamin B1
cGAS
Bacterium
Bulk (1)
Aggrephagy (2)
Glycophagy (3)
Lipophagy (4)
Granulophagy (5)
Macroautophagy
Macromolecules
Mitophagy (6)
ER-phagy (7)
Nucleophagy (8)
Xenophagy A (9)
b
Lysosome/endolysosome
c
LC3
p62
Optineurin
TBK1
Nap + Sintbad
LC3C
NDP52
Bacterium
Gal-8
Glycan
LC3
Receptor
LC3
Receptor
TRIM16
Gal-3
Gal-8
HSC70
KFERQ motif
GFAP
LAMP2A
LAMP2C
SIDT2
Co-chaperone
HSC70
KFERQ motif
Nucleic acid
Xenophagy B (10)
(continuation of a)
Lysophagy (11)
(continuation of a)
Bulk (12)
Micro-ER-phagy (13)
Substrate (14)
Microautophagy
Substrate (15)
CMA
DNA or RNA (16)



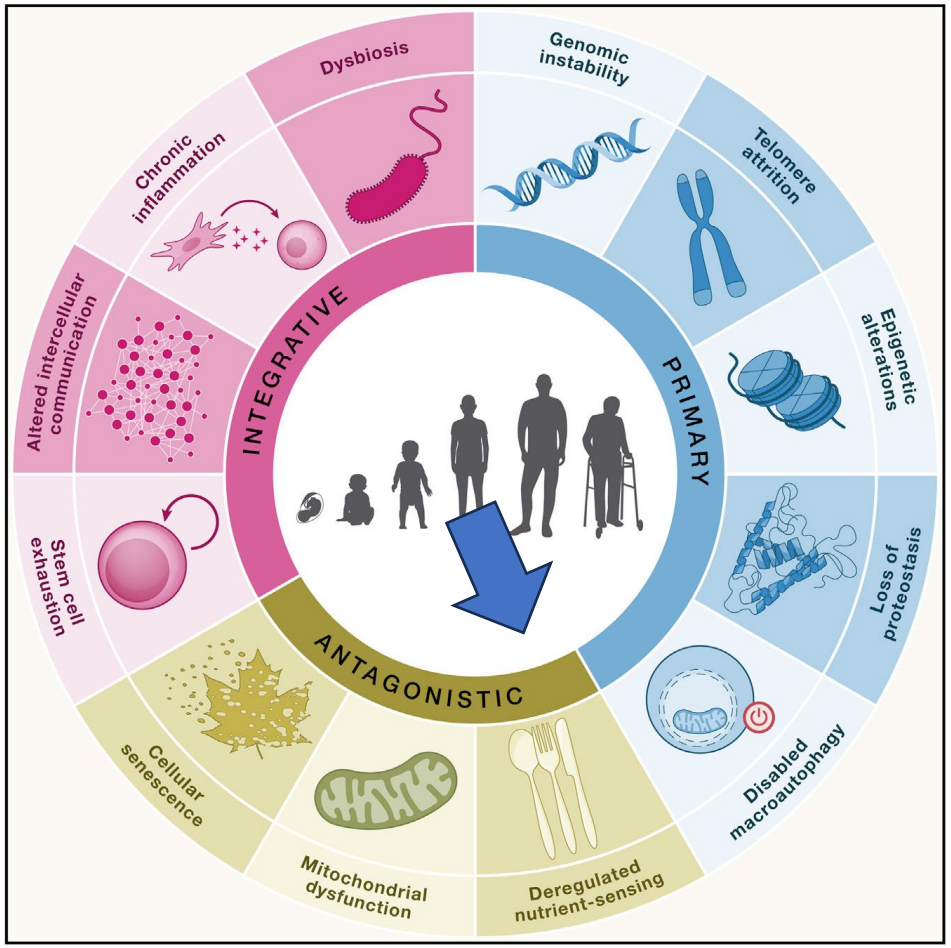
a, Autophagy participates in multiple processes that are essential for longevity. **b**, A brief summary of some of the major known mechanisms that regulate autophagy in multiple organisms and their influence on the process. **c**, A list summarizing premature aging diseases with impaired mitophagy as a cause of mitochondrial dysfunction, which contributes to short lifespan (LS) and healthspan (HS). These premature aging diseases are ataxia telangiectasia (AT), Cockayne syndrome (CS), Fanconi anemia (FA), Hutchinson–Gilford syndrome (HG), Werner syndrome (WS) and xeroderma pigmentosum (XP; especially group A). Changes in autophagy and mitophagy in Hutchinson–Gilford syndrome are elusive. **d**, Autophagy (including subtypes of selective autophagy, such as mitophagy) is impaired in broad neurodegenerative diseases, where impairment may drive or exacerbate disease progression. These diseases include AD, Parkinson's disease (PD), Huntington's disease, ALS and frontotemporal dementia (FTD). We emphasize that these are not the only drivers of the diseases and other processes may have roles leading to pathology and symptomatology.

https://doi.org/10.1038/s43587-021-00098-4



a, Potential interventions to stimulate autophagy: autophagy inducers, dietary restriction, exercise and genetic approaches. **b**, Autophagy induction could positively impact human health.

https://doi.org/10.1038/s43587-021-00098-4

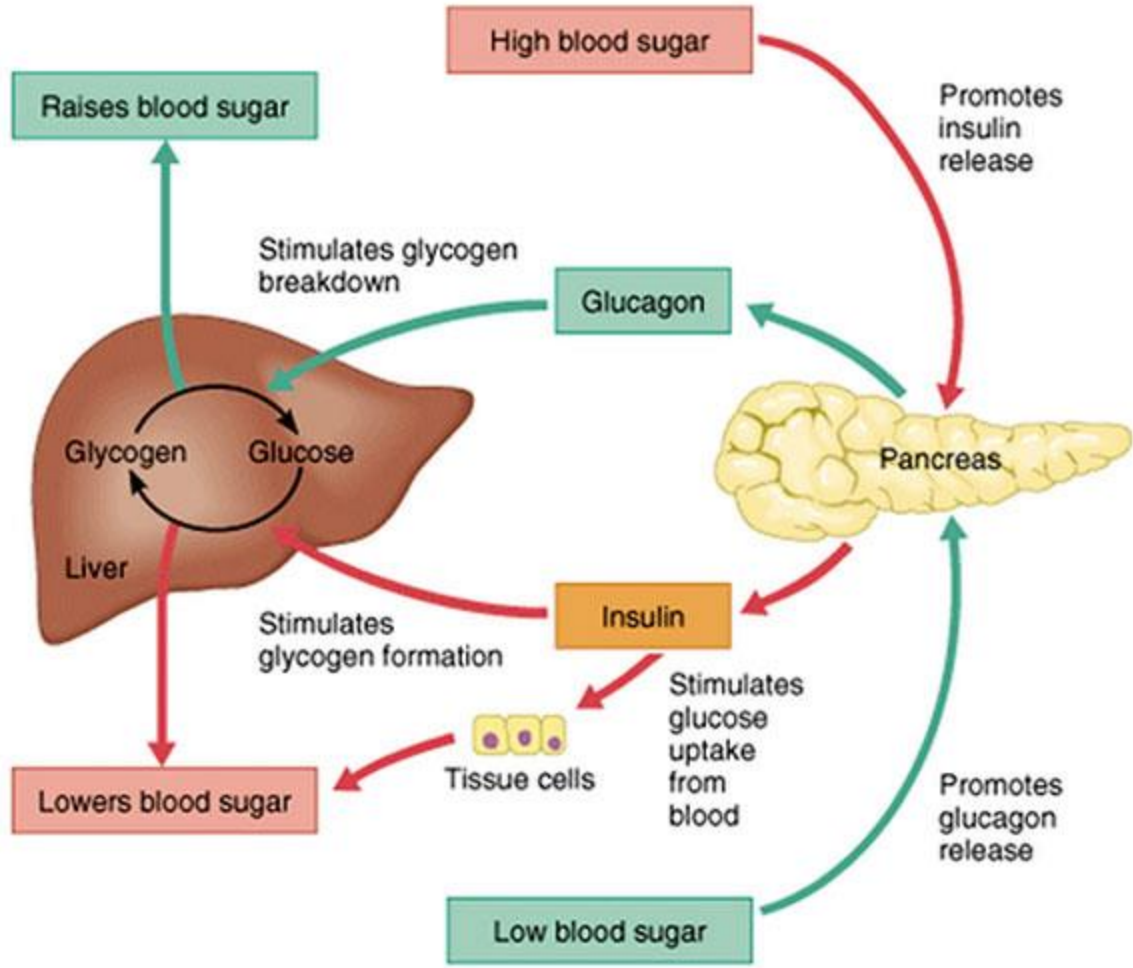


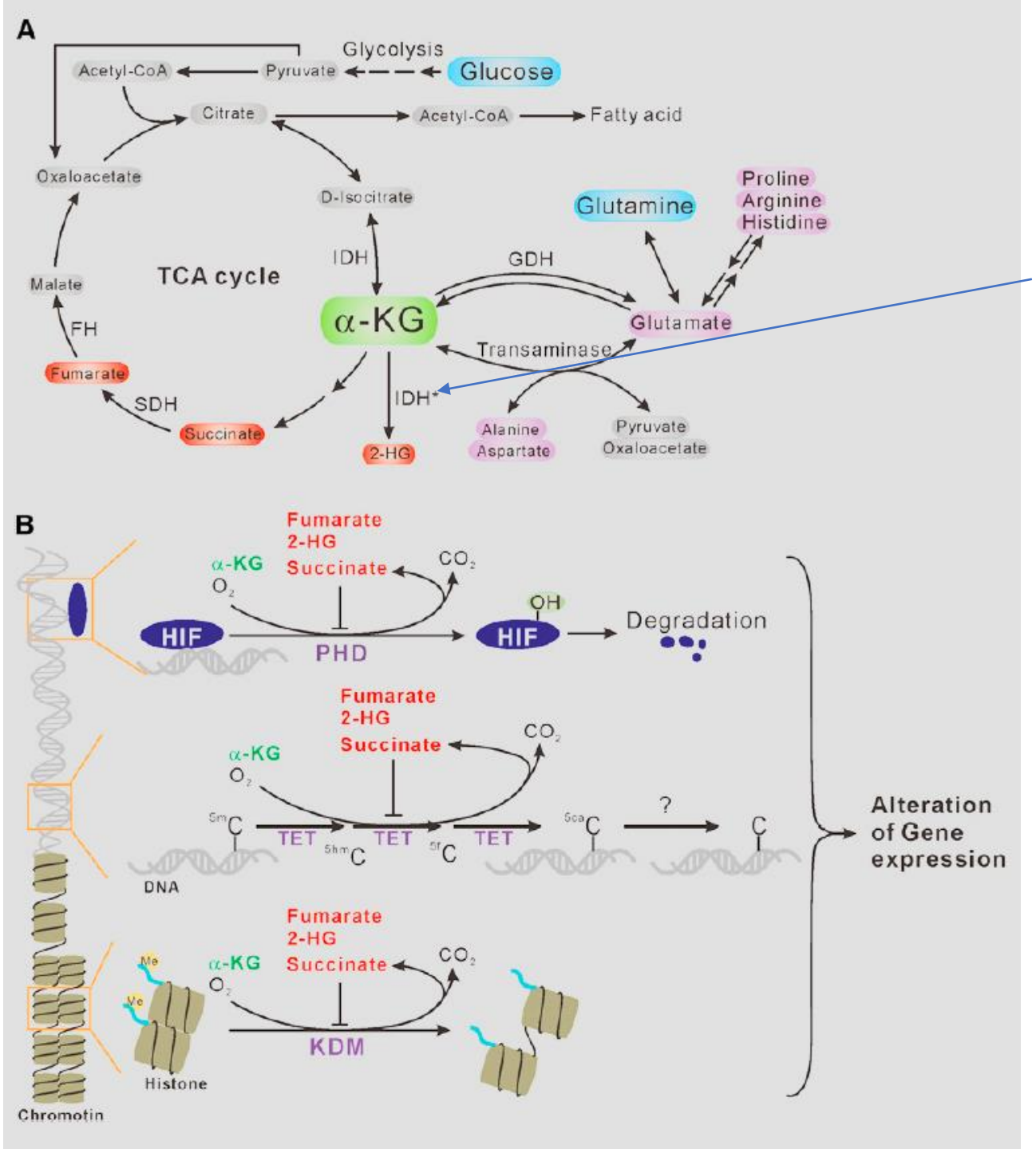
https://doi.org/10.1016/j.cell.2022.11.001

What Is Nutrient Sensing?

Cells throughout our body require a constant supply of nutrients to provide the energy they need to function, yet our nutrient intake is not constant.

Cells must therefore be able to store nutrients when they are abundant and access these stores when nutrients are scarce. Furthermore, nutrient levels in our bloodstream need to stay within certain safe ranges. For example, if blood sugar levels become too low (hypoglycaemia), an individual risks impaired thinking, unconsciousness and even coma and death. If blood sugar levels become too high (hyperglycaemia), organs can be damaged, and various key bodily functions can be disturbed, resulting in a coma and potentially death. Cells must therefore be able to sense nutrient levels in order to respond appropriately, absorbing, metabolising, storing and converting nutrients from one form to another, depending on the circumstances. To this end, a wide range of nutrient signalling mechanisms have evolved that allow the body to keep track of the nutrient balances.


High blood sugar
Promotes insulin release
Raises blood sugar
Stimulates glycogen breakdown
Glucagon
Glycogen
Glucose
Liver
Pancreas
Insulin
Stimulates glycogen formation
Stimulates glucose uptake from blood
Tissue cells
Lowers blood sugar
Promotes glucagon release
Low blood sugar



Dioxygenases in Sensing Metabolic Intermediates and Epigenetic Regulation

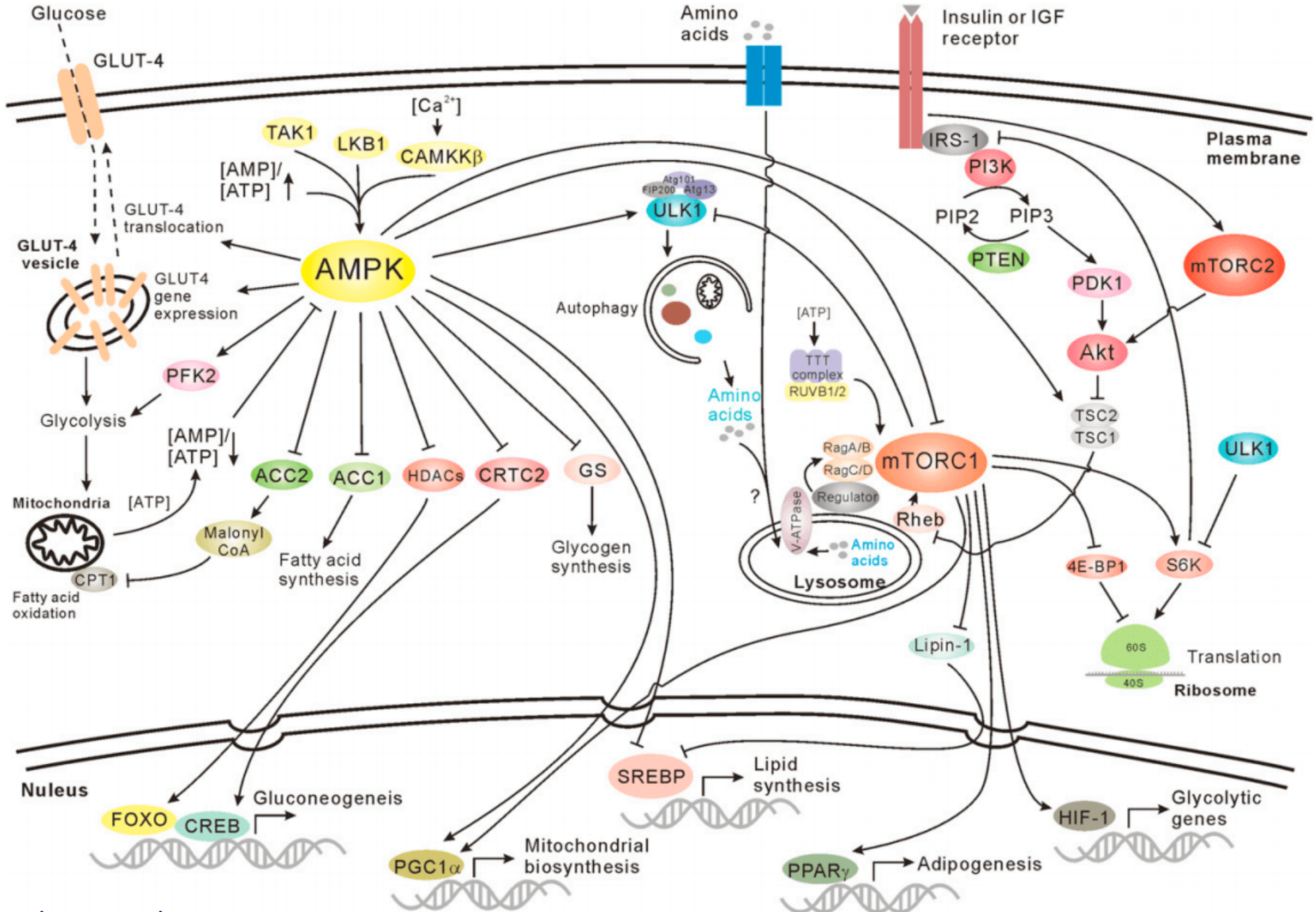
(A) Schematics of a-KG metabolism and TCA cycle. The mutant isocitrate dehydrogenase (IDH) (indicated with a star) may decrease a-KG and generate a new oncometabolite 2-hydroxylglutarat (2-HG).

(B) A proposed role of dioxygenases in metabolite sensing and epigenetic modifications. Using a-KG as a key substrate, dioxygenases is involved in HIFa hydroxylation, DNA demethylation, and histone demethylation. All processes are inhibited by normal metabolites, such as succinate and fumarate, as well as oncometabolite 2-HG.

Abbreviations are as follows:

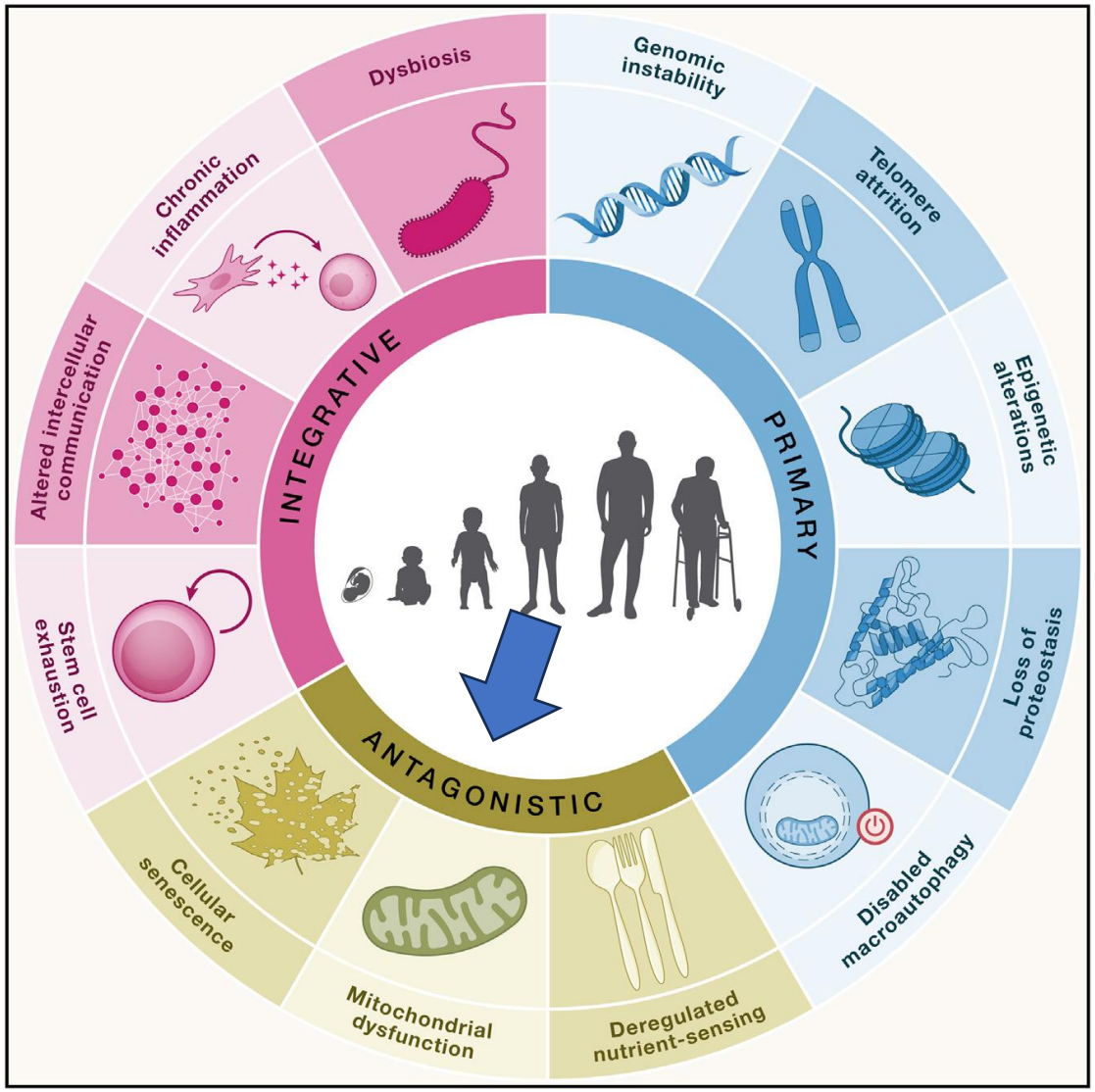
a-KG, a-ketoglutarate;
GDH, glutamate dehydrogenase;
SDH, succinate dehydrogenase;
FH, fumarase;
TET,ten-eleven translocation;
KDM, lysine demethylase;
PHD, prolyl hydroxylase domain protein.

http://dx.doi.org/10.1016/j.molcel.2013.01.019

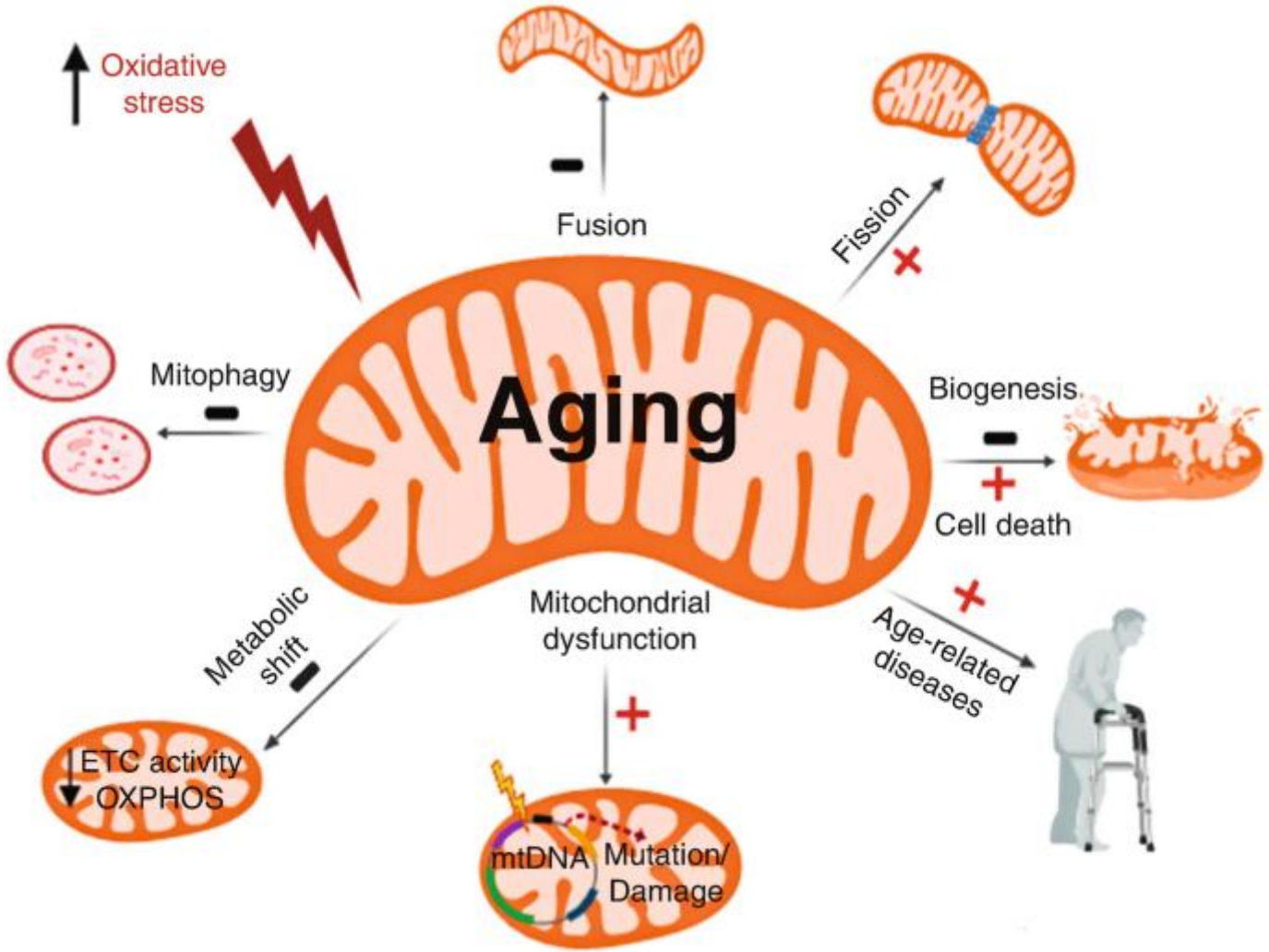


http://dx.doi.org/10.1016/j.molcel.2013.01.019

	Lifespan increase		Beneficial health effects	
	Dietary restriction	Mutations/ drugs	Dietary restriction	Mutations/ drugs
 Yeast	3 fold	10 fold	Extended reproductive period	Extended reproductive period, decreased DNA damage/mutations
 Worms	2-3 fold	10 fold	Resistance to misexpressed toxic proteins	Extended motility Resistance to mis-expressed toxic proteins and germ-line cancer
 Flies	2 fold	60-70%	None reported	Resistance to bacterial infection, extended ability to fly
 Mice	30-50%	30-50% (~100% in combination with DR)	Protection against cancer, diabetes, atherosclerosis,cardio-myopathy, autoimmune, kidney and respiratory diseases, reduced neurogeneration	Reduced tumor incidence, protection against age-dependent cognitive decline, cardio-myopathy, fatty liver and renal lesions. Extended insulin sensitivity
 Monkeys	Trend noted	Not tested	Prevention of obesity, protection against diabetes, cancer and cardiovascular disease	Not tested
 Humans	Not determined	Not determined (GHR deficient subjects reach old age)	Prevention of obesity, diabetes, hypertension Reduced risk factors for cancer and cardiovascular disease	Possible reduction in cancer and diabetes



https://doi.org/10.1016/j.cell.2022.11.001



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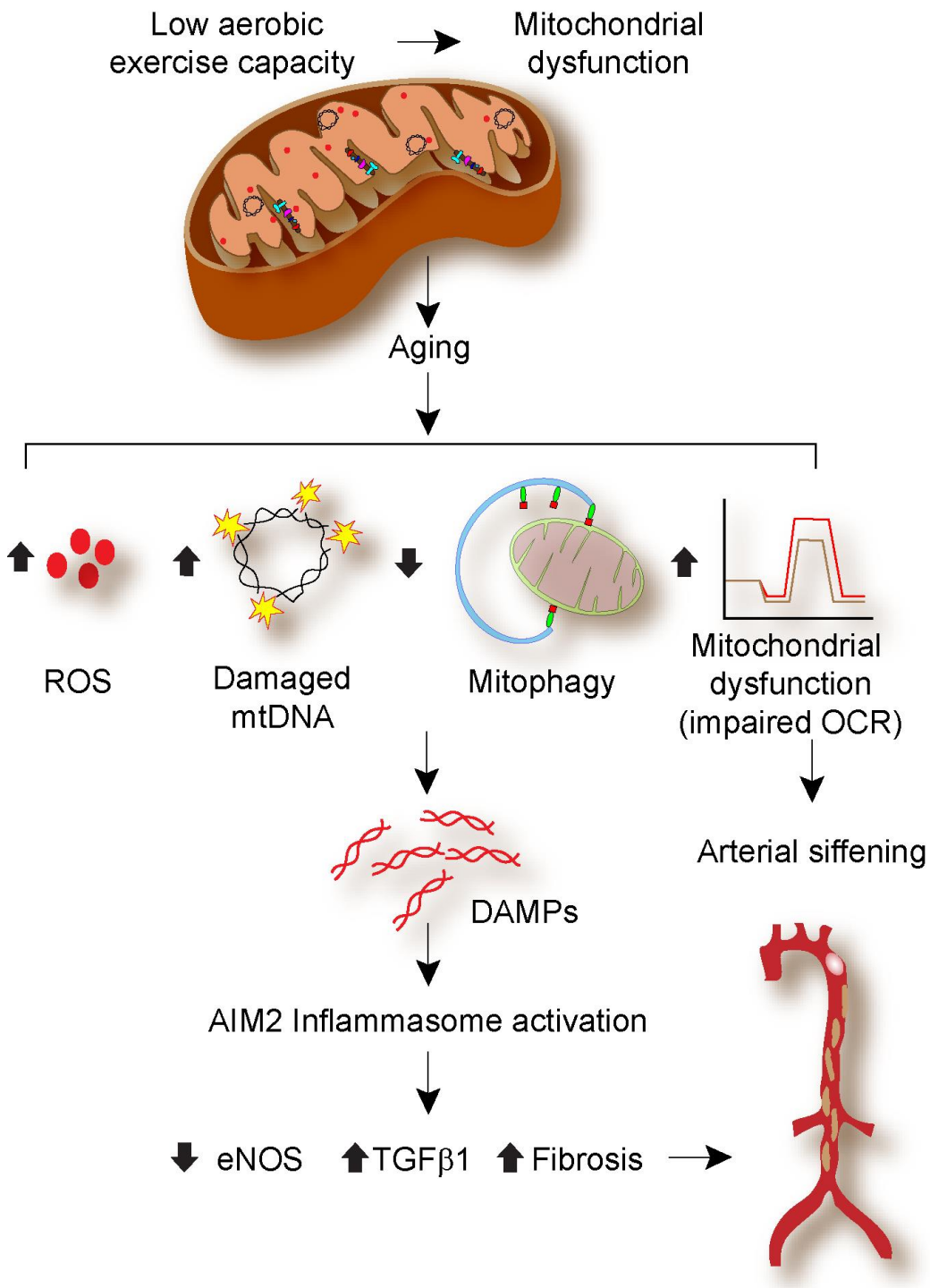
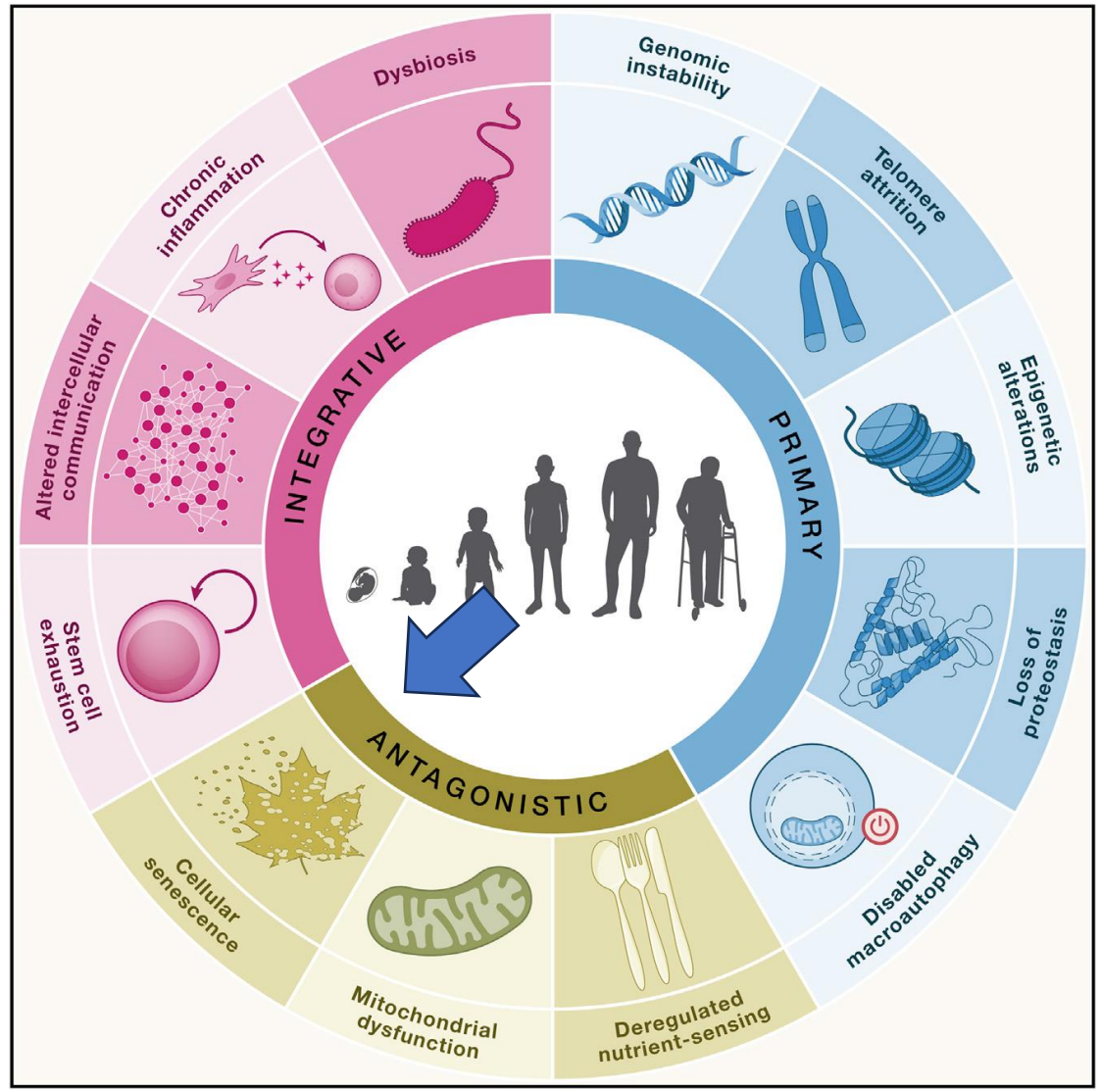


10.20517/jca.2022.35



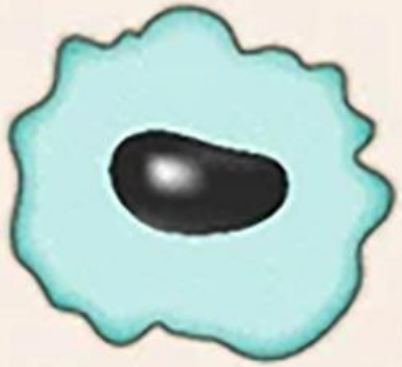
https://doi.org/10.1016/j.cell.2022.11.001

Triggers

- Telomere dysfunction
- Activated oncogenes (Hras^{V12})
- DNA-replication stress
- Oxidative Stress (O_2^-)
- Cell-cell fusion

Biological Consequences

Short-term

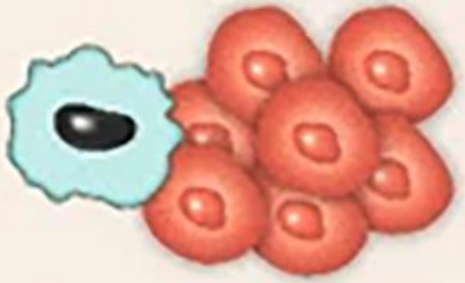


Tumor suppression

Limits tissue damage

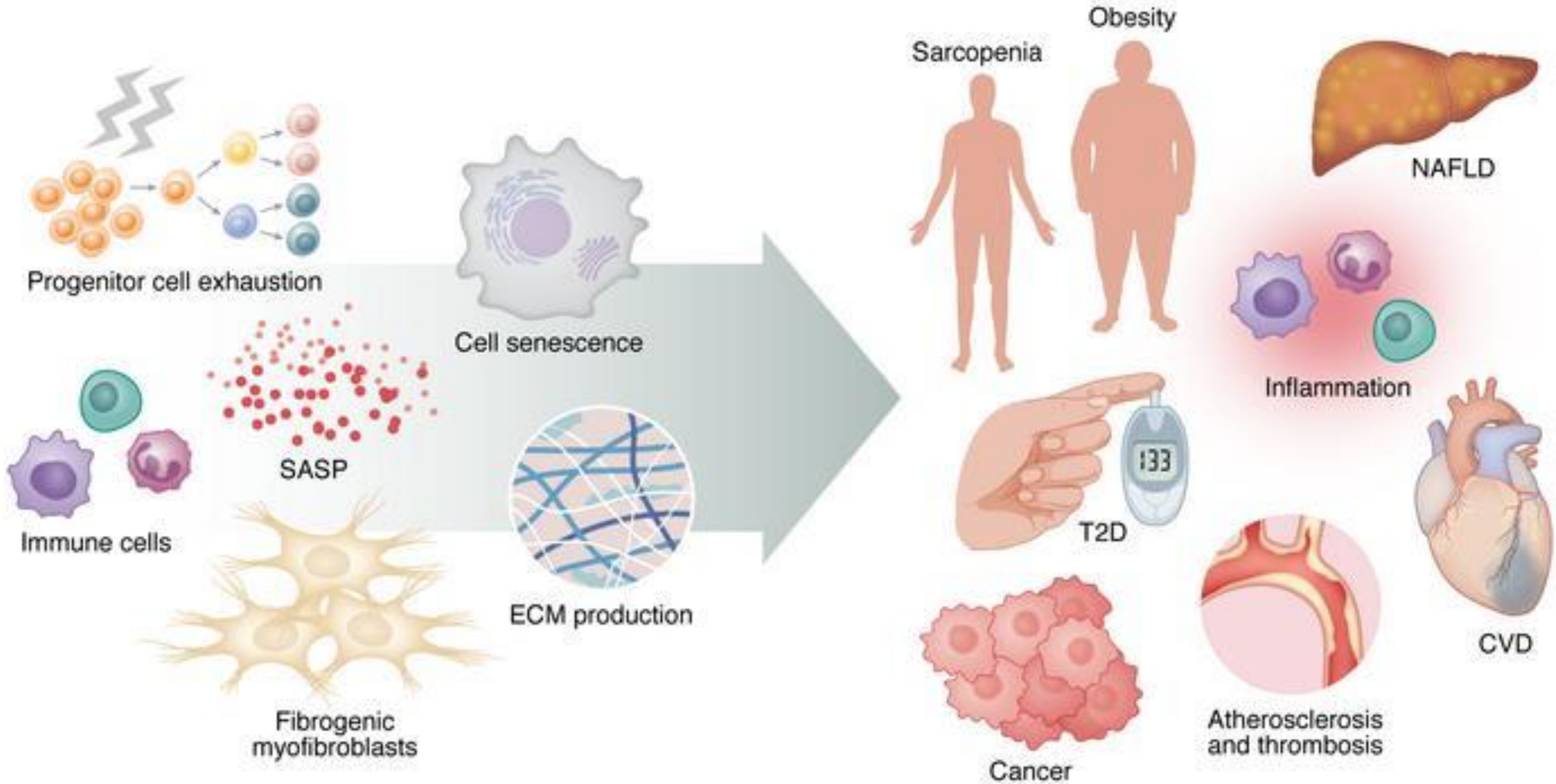
Embryonic development

Long-term



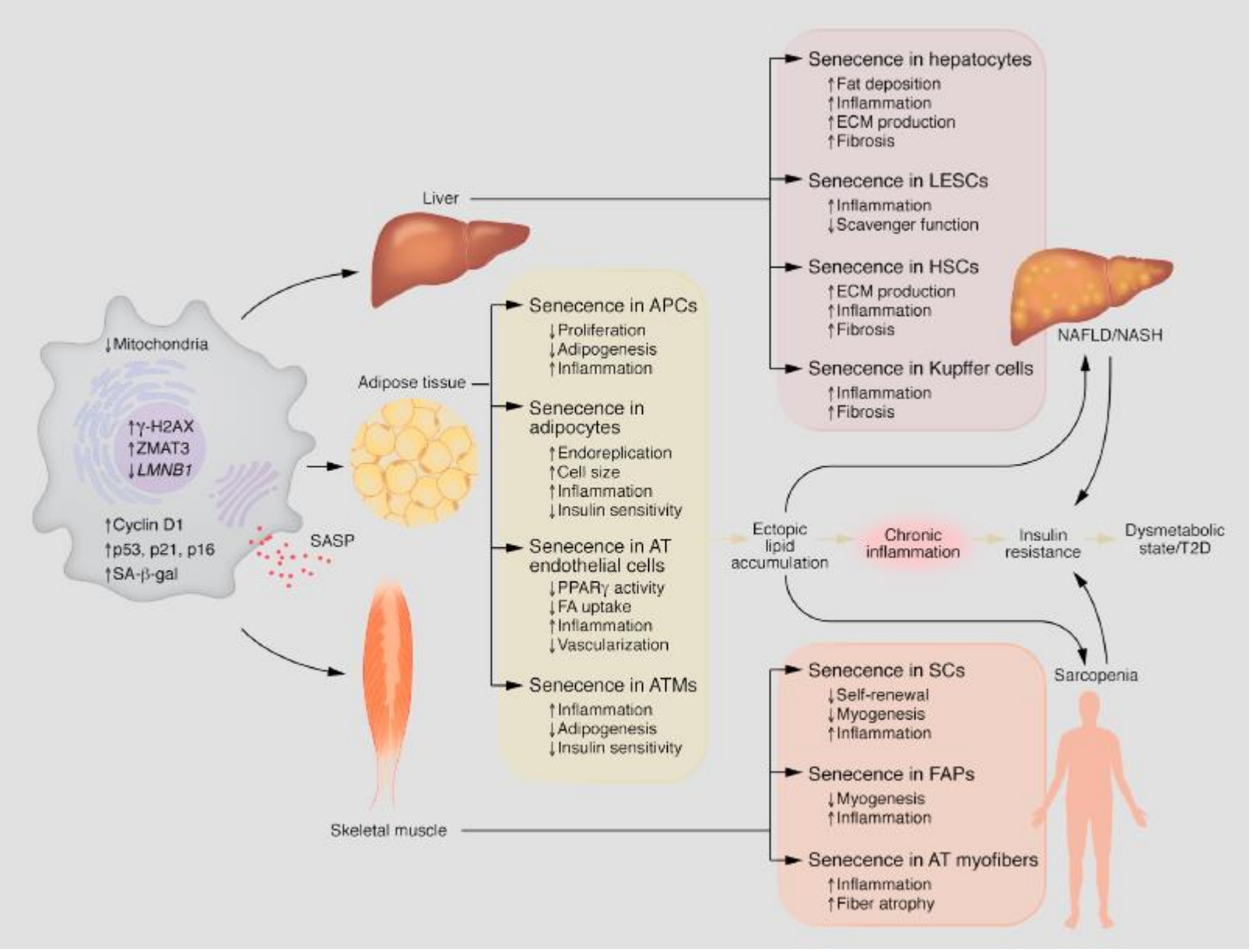
Tumorigenesis

Tissue ageing

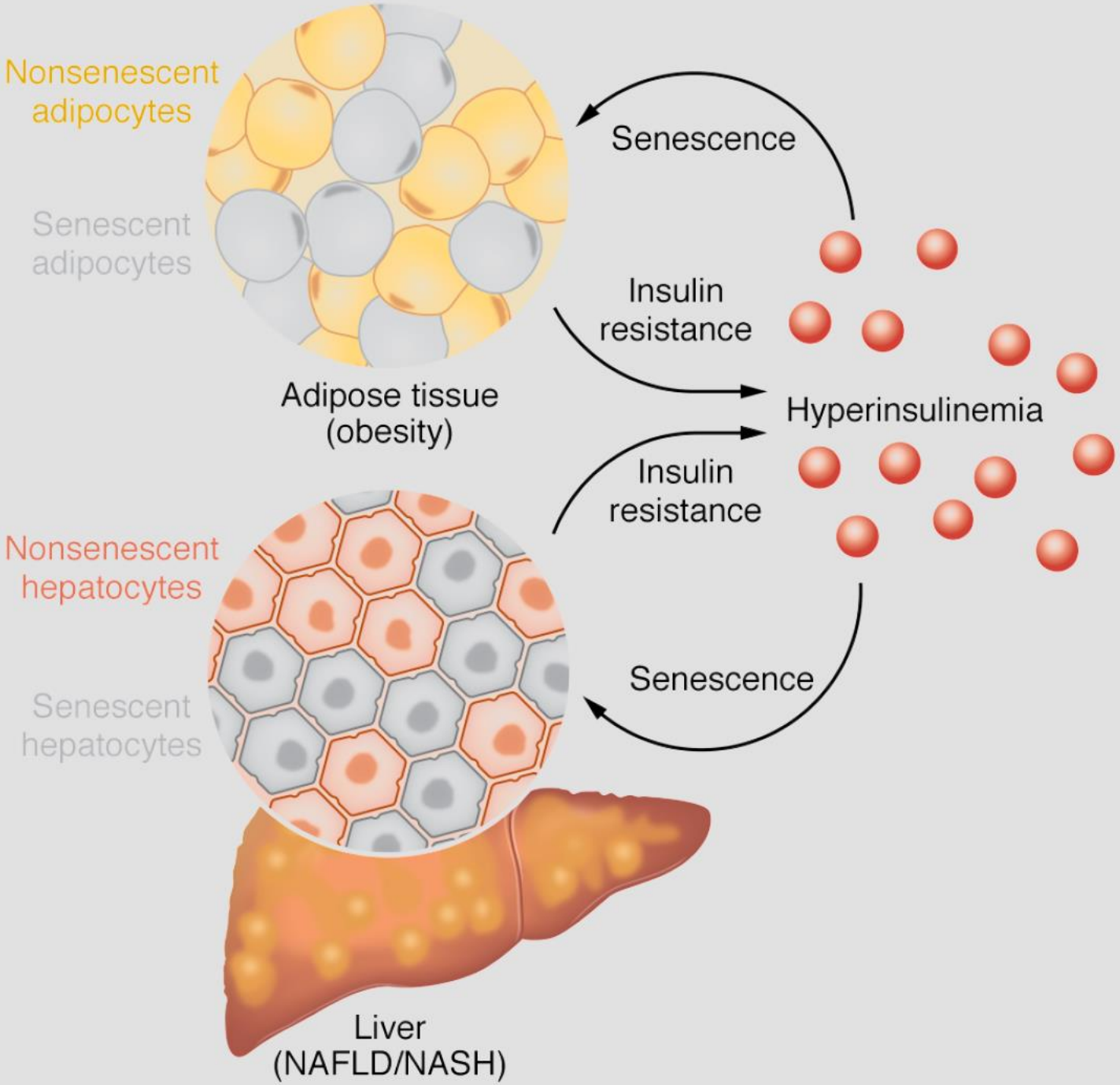


https://doi.org/10.1172/JCI169922.

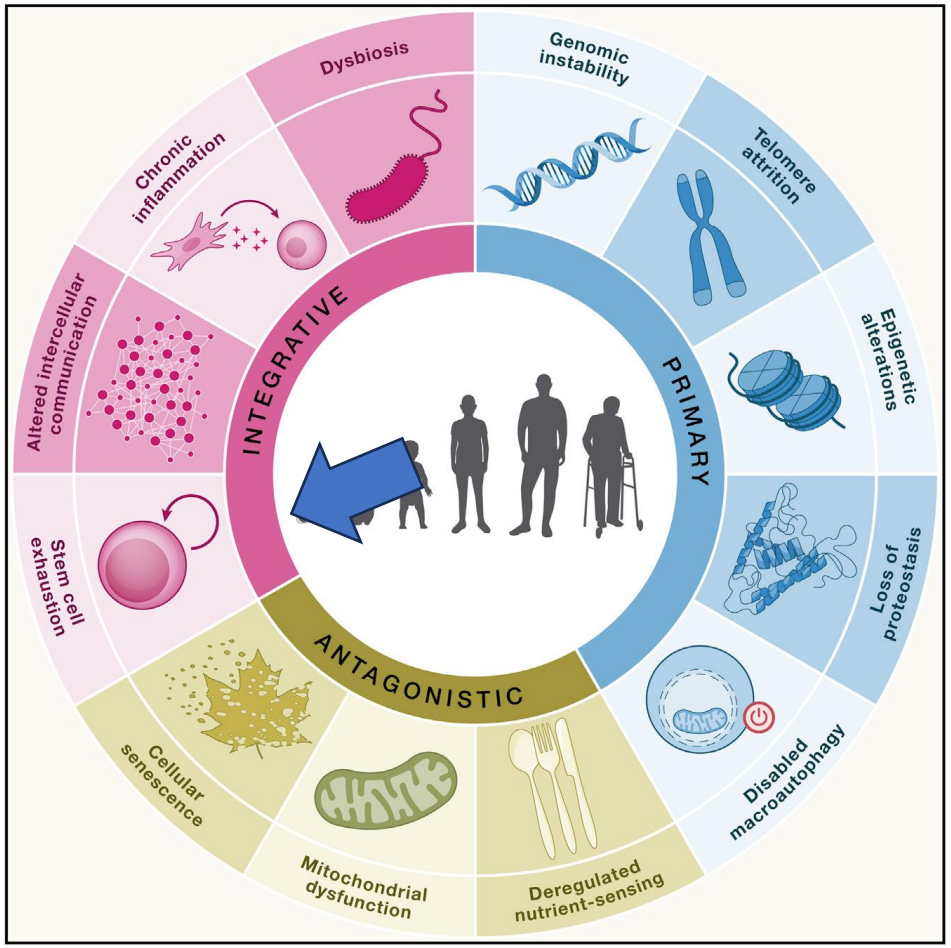
senescence-associated secretory phenotype (SASP).



Pathological role of senescent cells in tissue dysfunction and chronic metabolic disease. Cell senescence is a state of cell cycle arrest with senescent cells displaying characteristics such as being enlarged, flattened, and of irregular shape, elevated expression of p53, p21, p16, cyclin D1, and ZMAT3 proteins, increased lysosomal SA-β-gal activity, enhanced γ-H2AX phosphorylation, decreased mitochondrial content, decreased *LMNB1* expression, and SASP acquisition. Increased accumulation of senescent cells in key metabolic tissues (liver, adipose tissue, skeletal muscle) promotes local tissue dysfunction and systemic deleterious effects with IR and the development of common age-related diseases such as T2D, NAFLD/NASH, and sarcopenia. FA, fatty acid.



Cell senescence (CS) as likely mediator of the bidirectional relationship between IR and hyperinsulinemia. Senescent cells accumulate in multiple tissues in obesity, T2D, and NAFLD/NASH, including AT (adipose tissue)and the liver. Increased CS in those tissues may cause IR, which, in turn, leads to hyperinsulinemia. Hyperinsulinemia, on the other hand, may induce senescence in both adipocytes and liver cells, contributing to an increase in CS burden in the AT and liver. Thus, CS may enable and fuel a vicious cycle between IR and hyperinsulinemia, which plays a considerable role in the development of several metabolic diseases and their consequences.



https://doi.org/10.1016/j.cell.2022.11.001

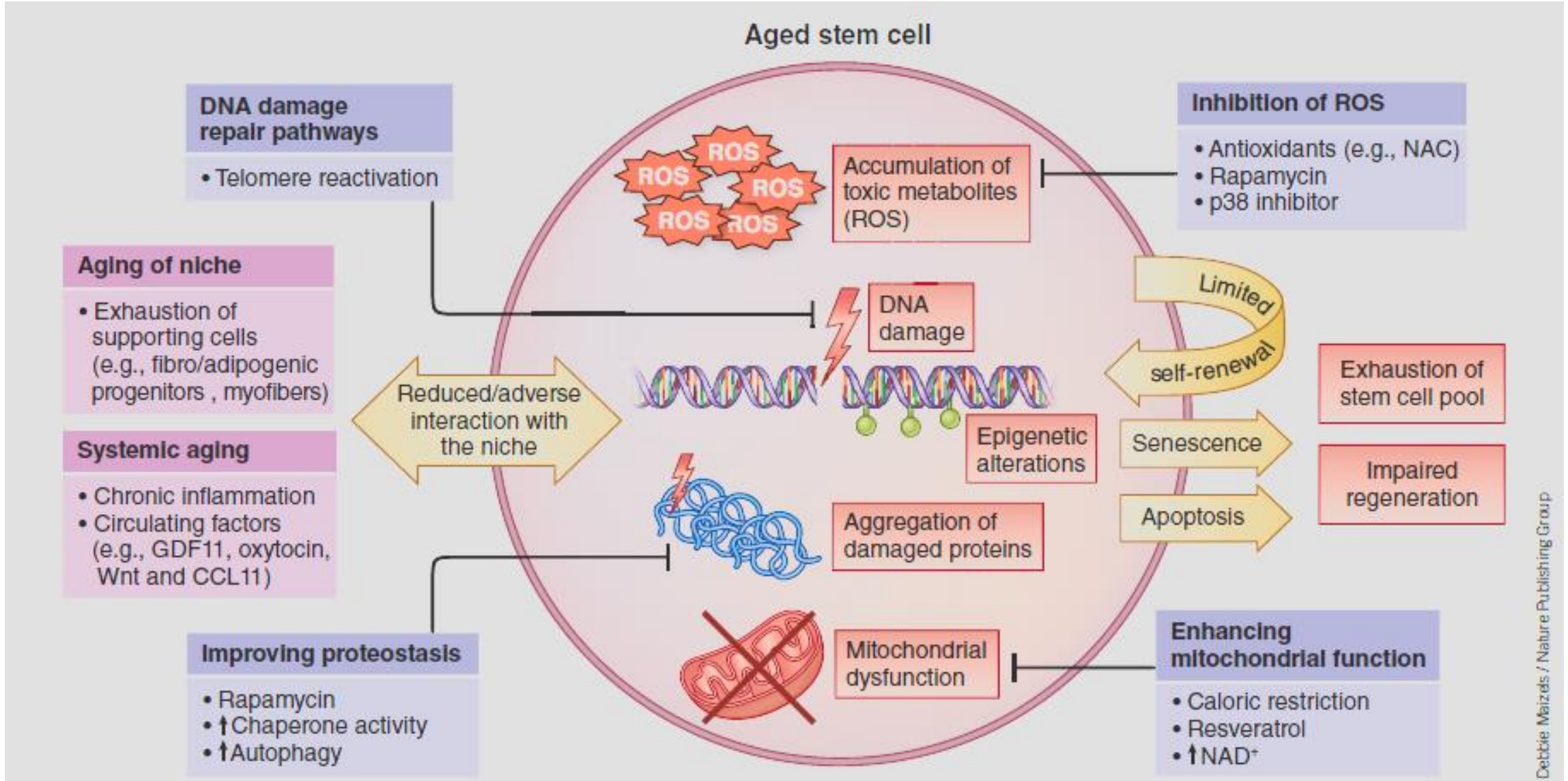


Figure 1 Common pathways contributing to stem cell loss and dysfunction in the aging process. Common aging phenotypes within the stem cell are shown in red, in the niche in pink, and the strategies by which to target and hopefully reverse these mechanisms in purple.

doi:10.1038/ nm.365

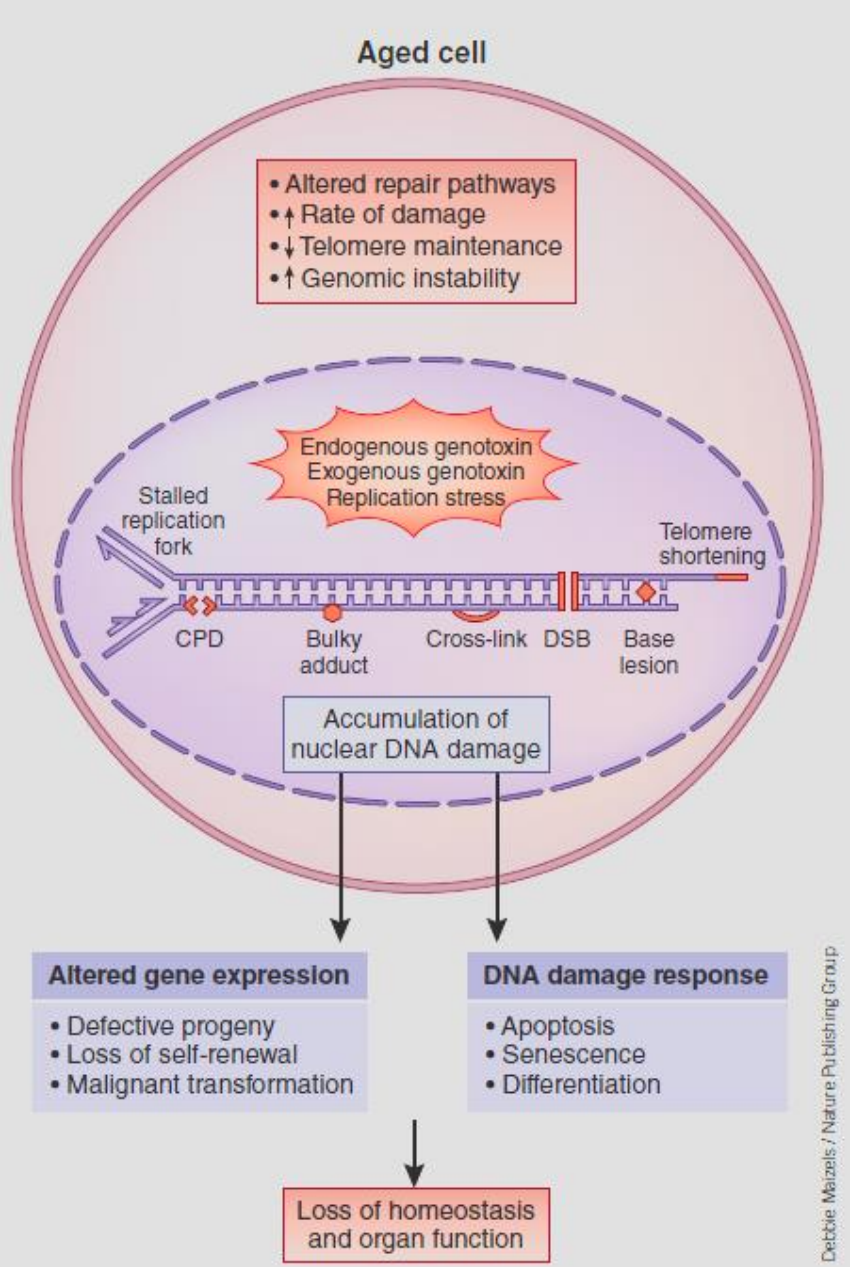


Figure 2 The effects of DNA damage in the aging genome that may affect stem cell function. Products of and effectors of DNA damage known to increase and accumulate during aging are shown, along with their effects on stem cell aging. CPD, cyclobutane pyrimidine dimer; DSB, double-strand break.

doi:10.1038/ nm.365

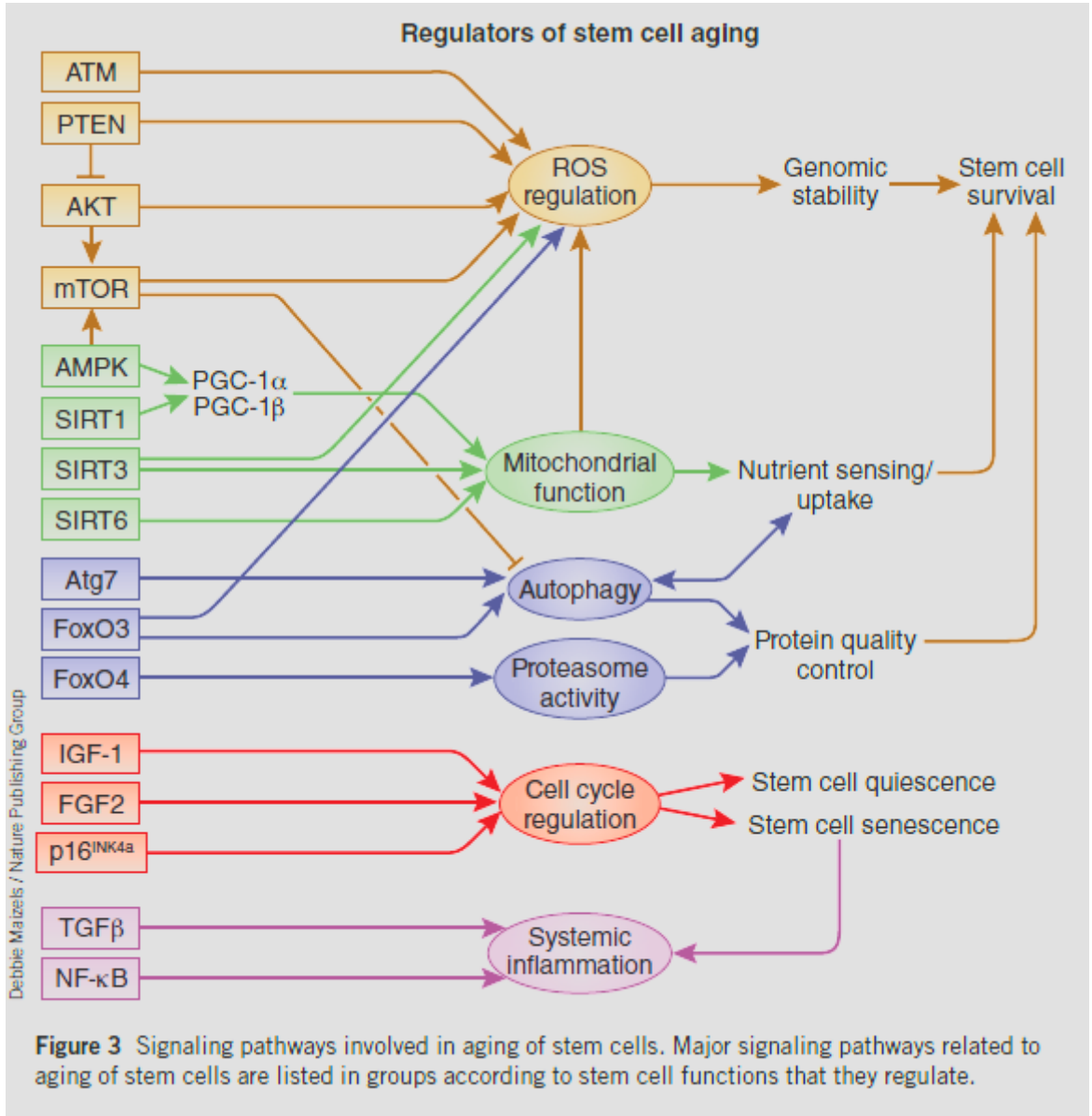
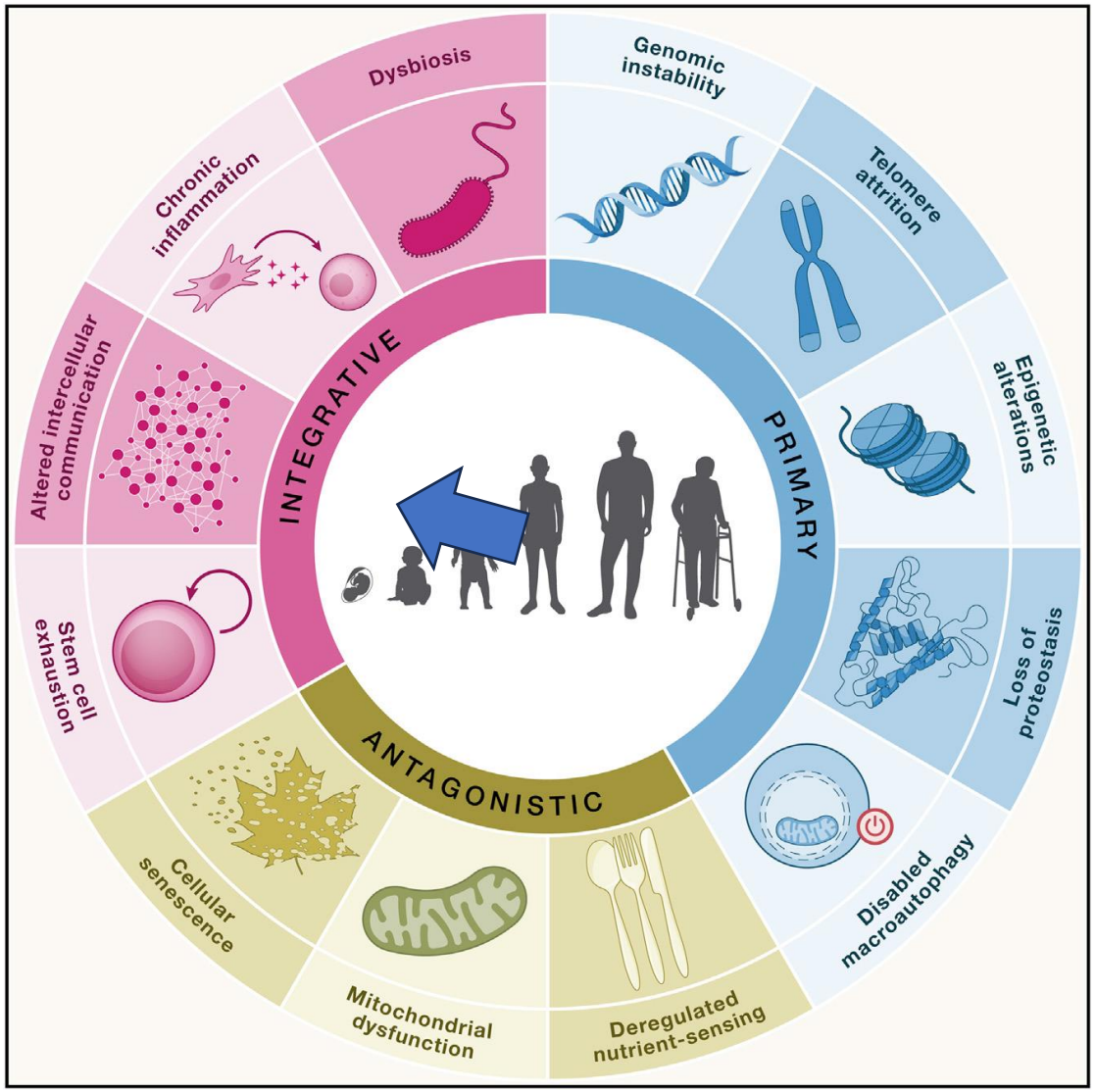


Figure 3 Signaling pathways involved in aging of stem cells. Major signaling pathways related to aging of stem cells are listed in groups according to stem cell functions that they regulate.

doi:10.1038/ nm.365



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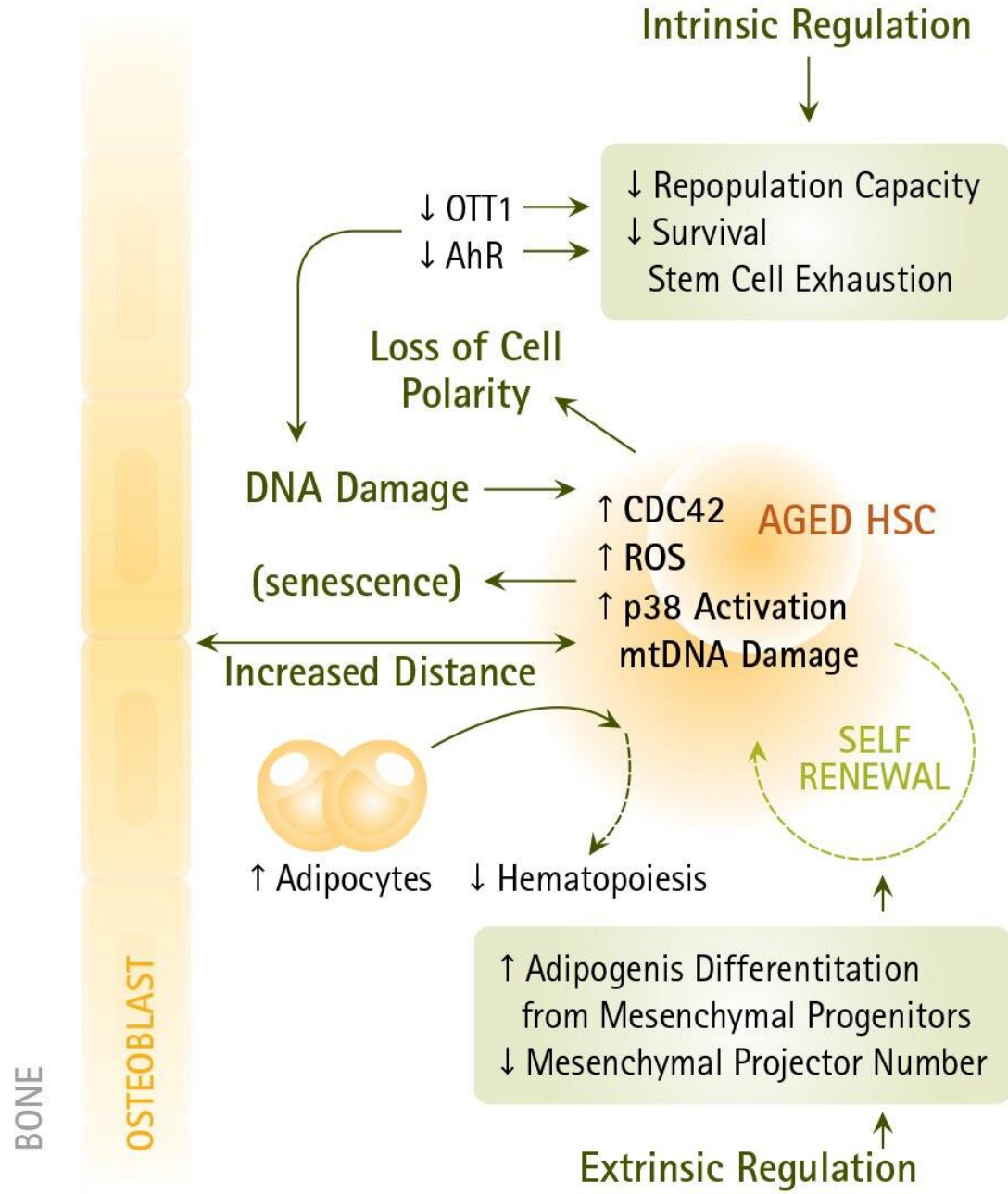
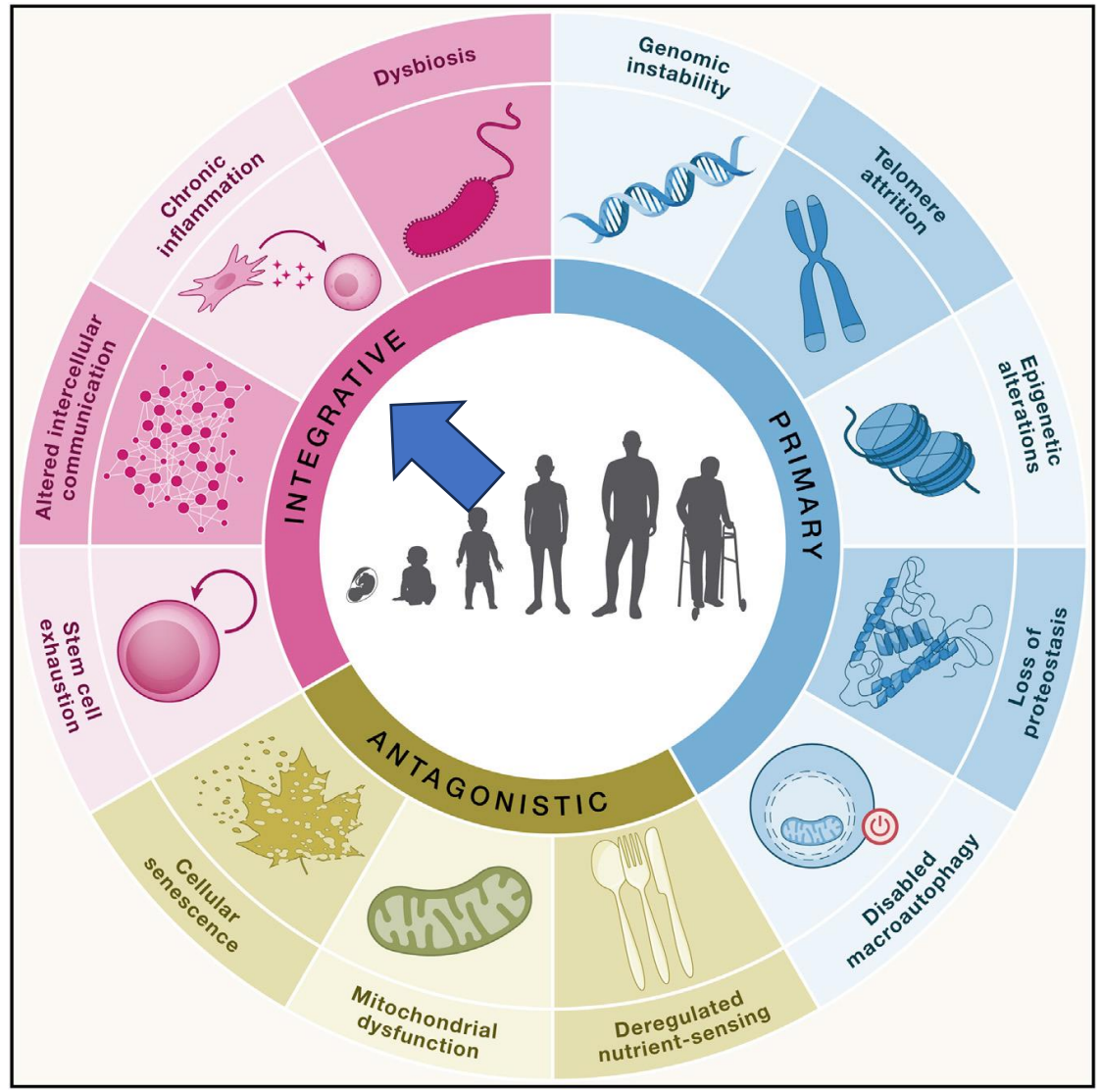

Intrinsic Regulation
↓ OTT1
↓ AhR
↓ Repopulation Capacity
↓ Survival
Stem Cell Exhaustion
Loss of Cell Polarity
DNA Damage
↑ CDC42
↑ ROS
↑ p38 Activation
mtDNA Damage
AGED HSC
(senescence)
Increased Distance
SELF RENEWAL
↑ Adipocytes
↓ Hematopoiesis
↑ Adipogenis Differentitation from Mesenchymal Progenitors
↓ Mesenchymal Projector Number
Extrinsic Regulation
BONE
OSTEOBLAST



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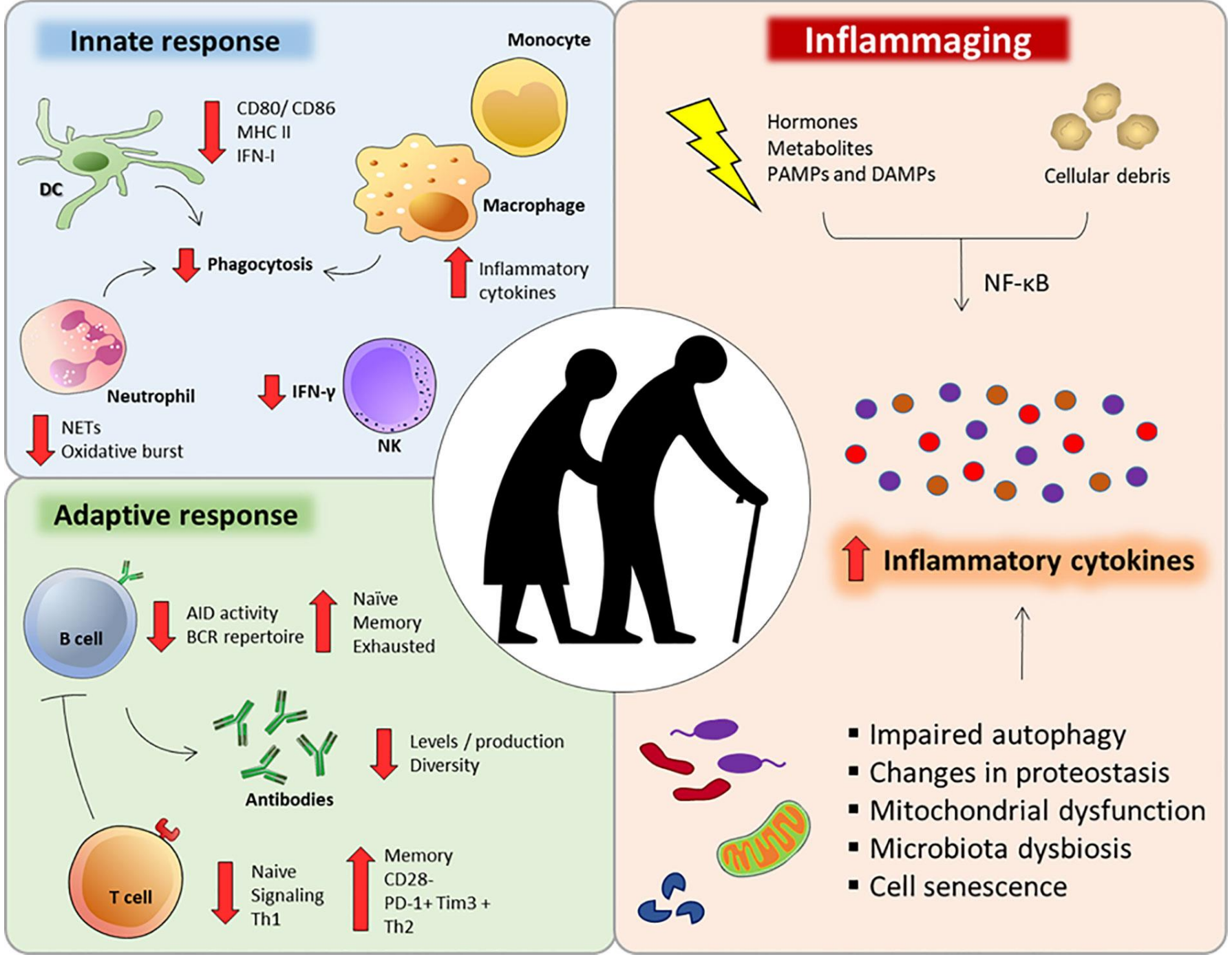

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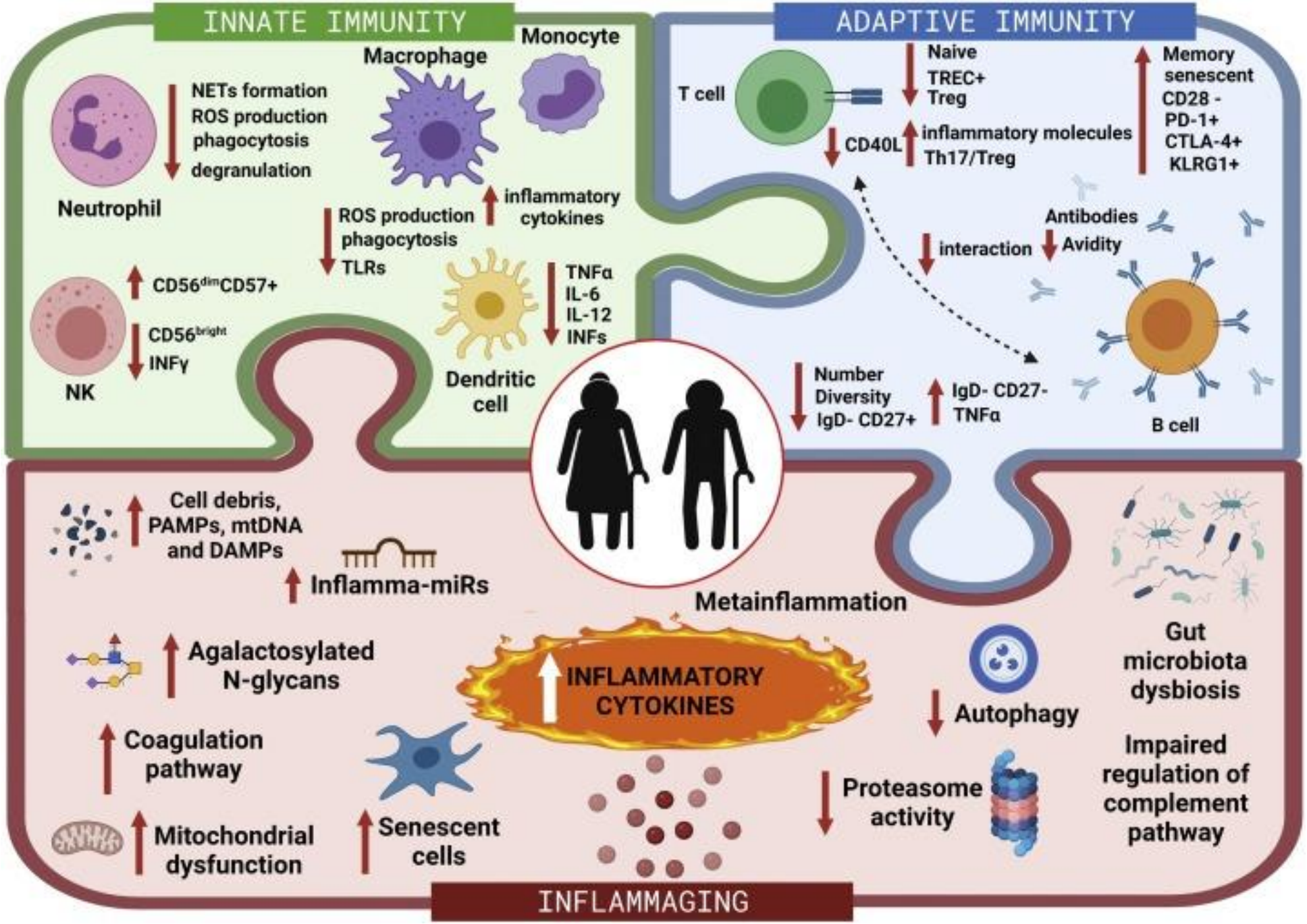

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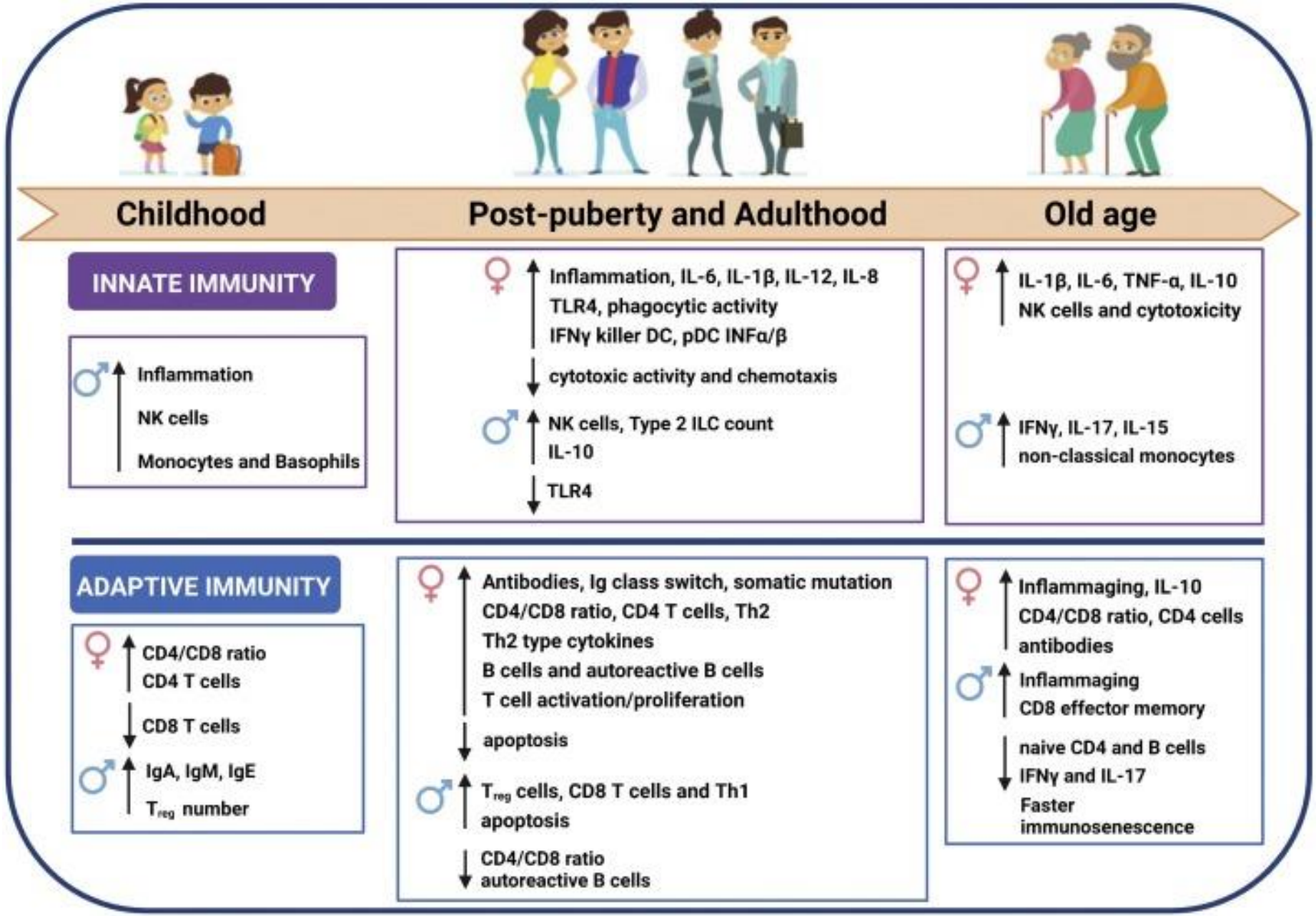

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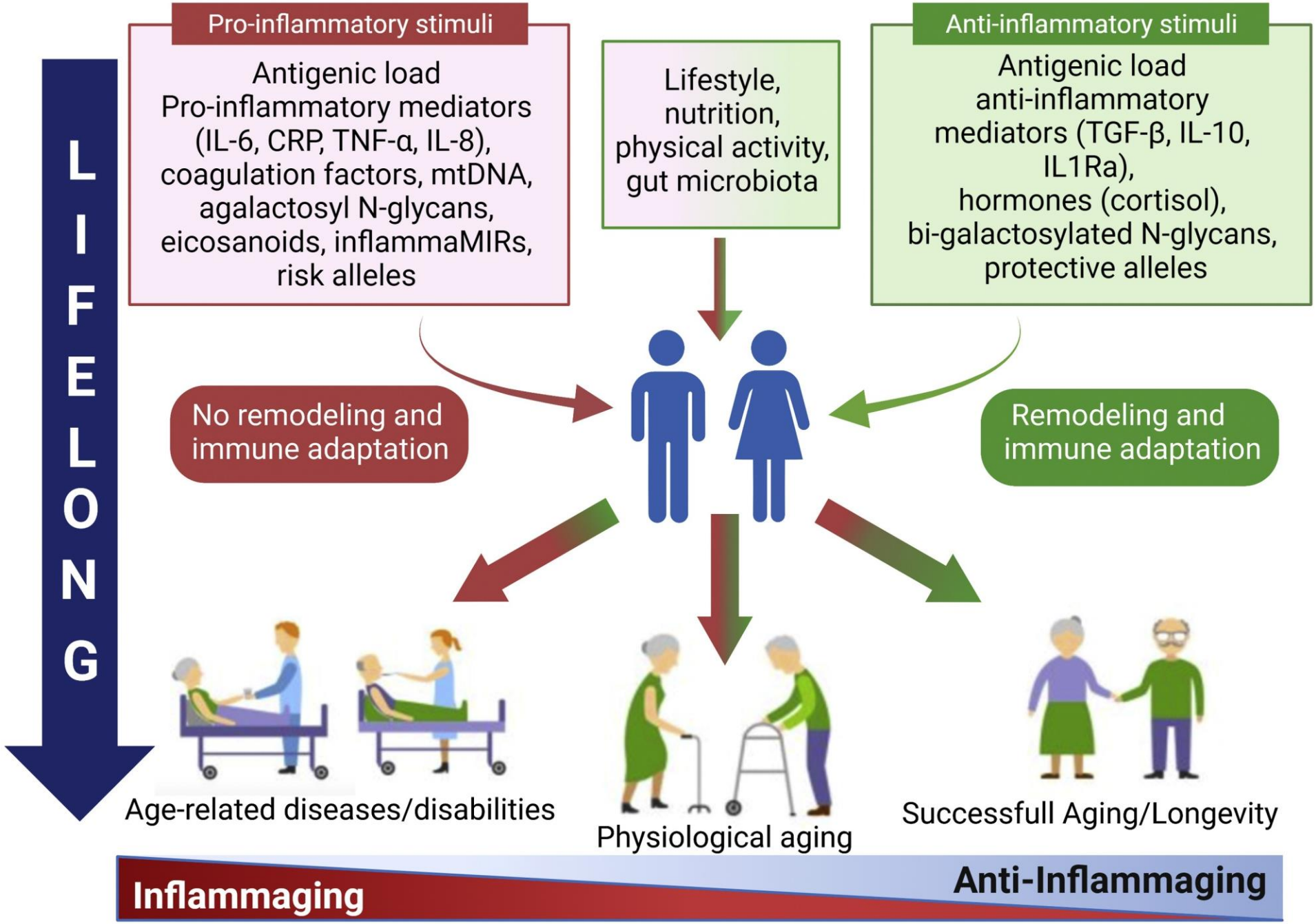

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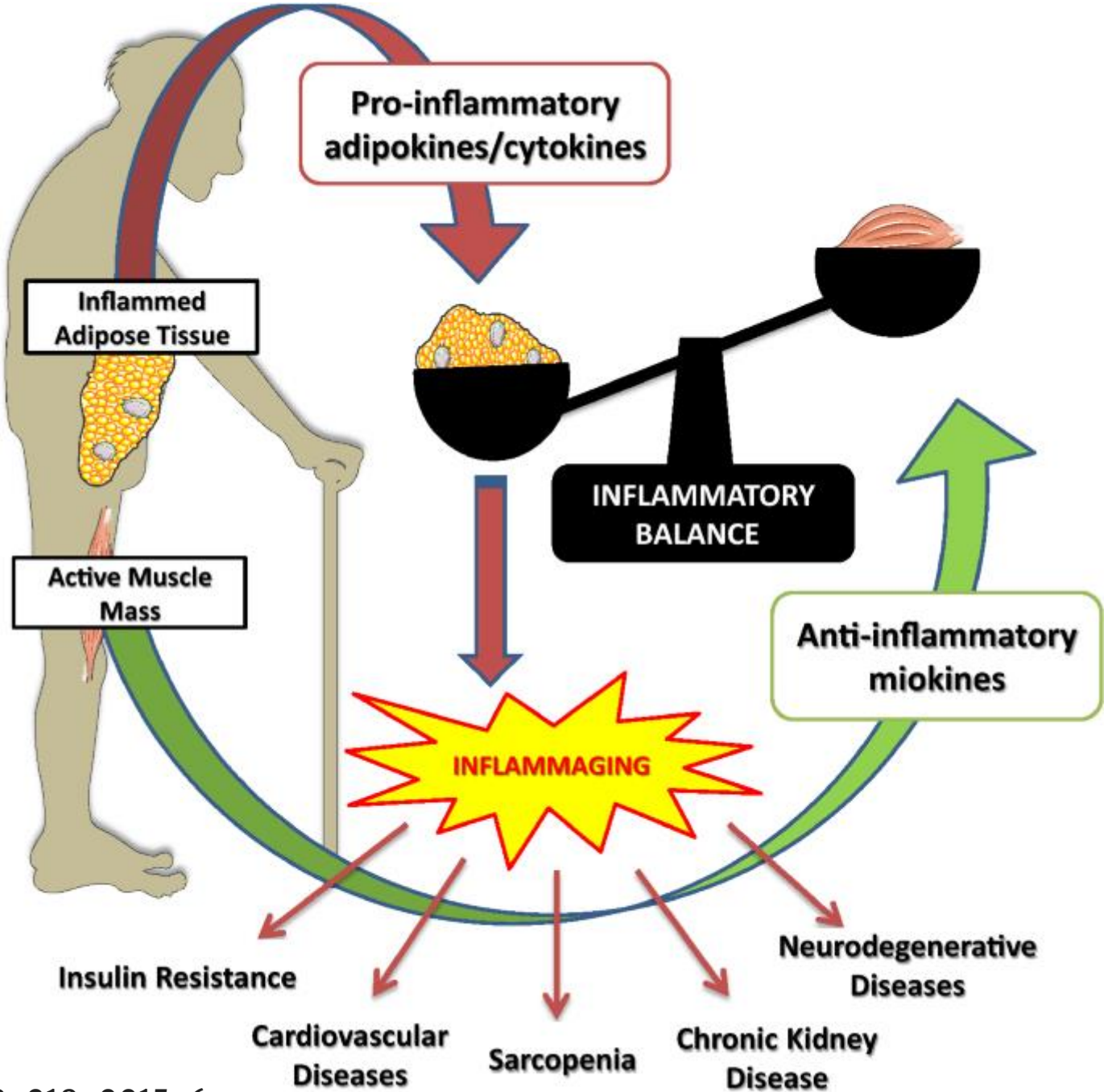
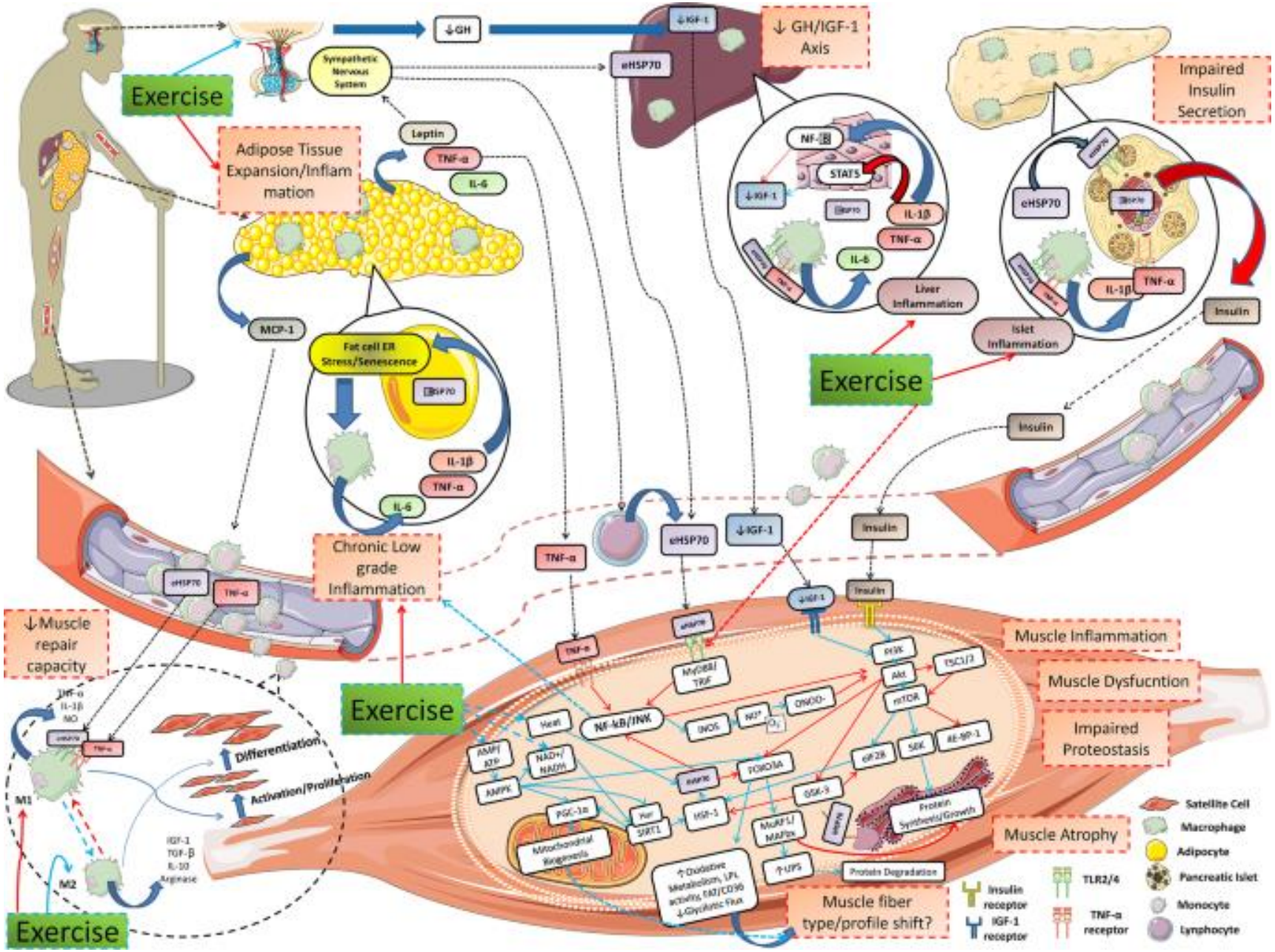
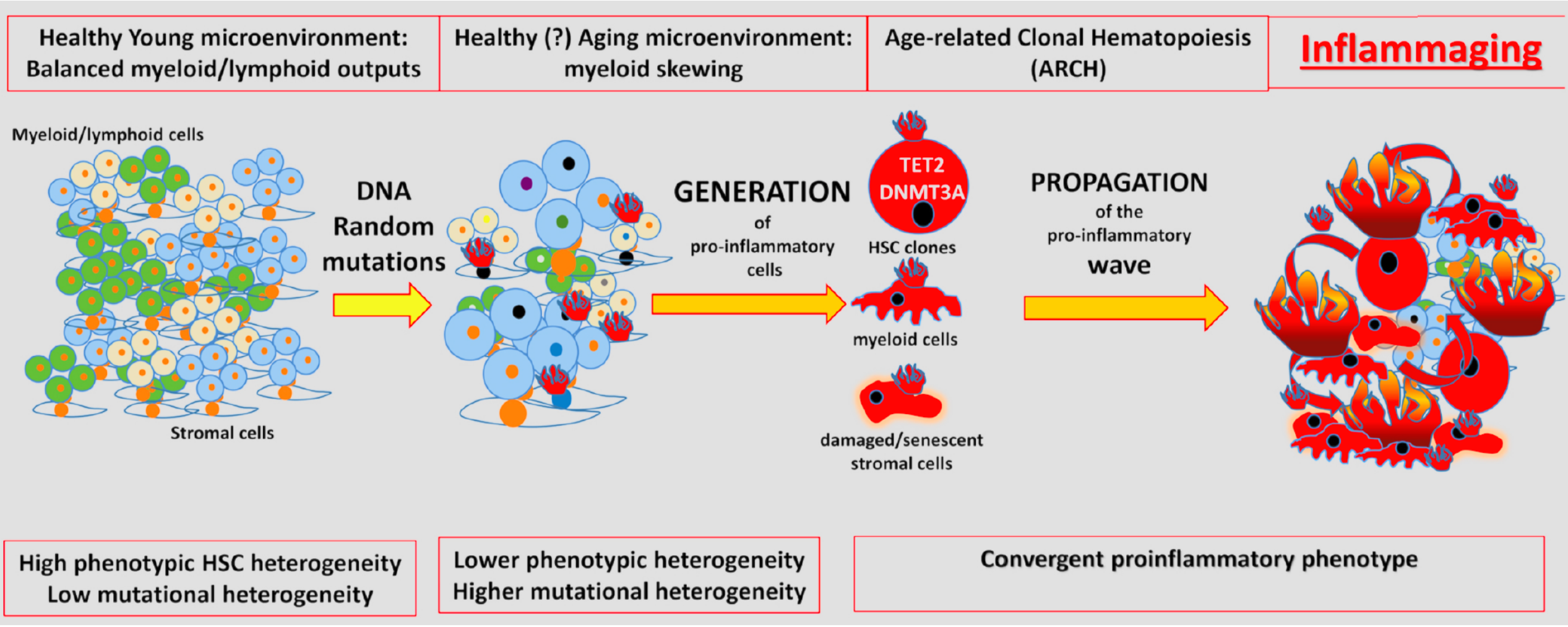


https://doi.org/10.1007/s42978-019-0015-6

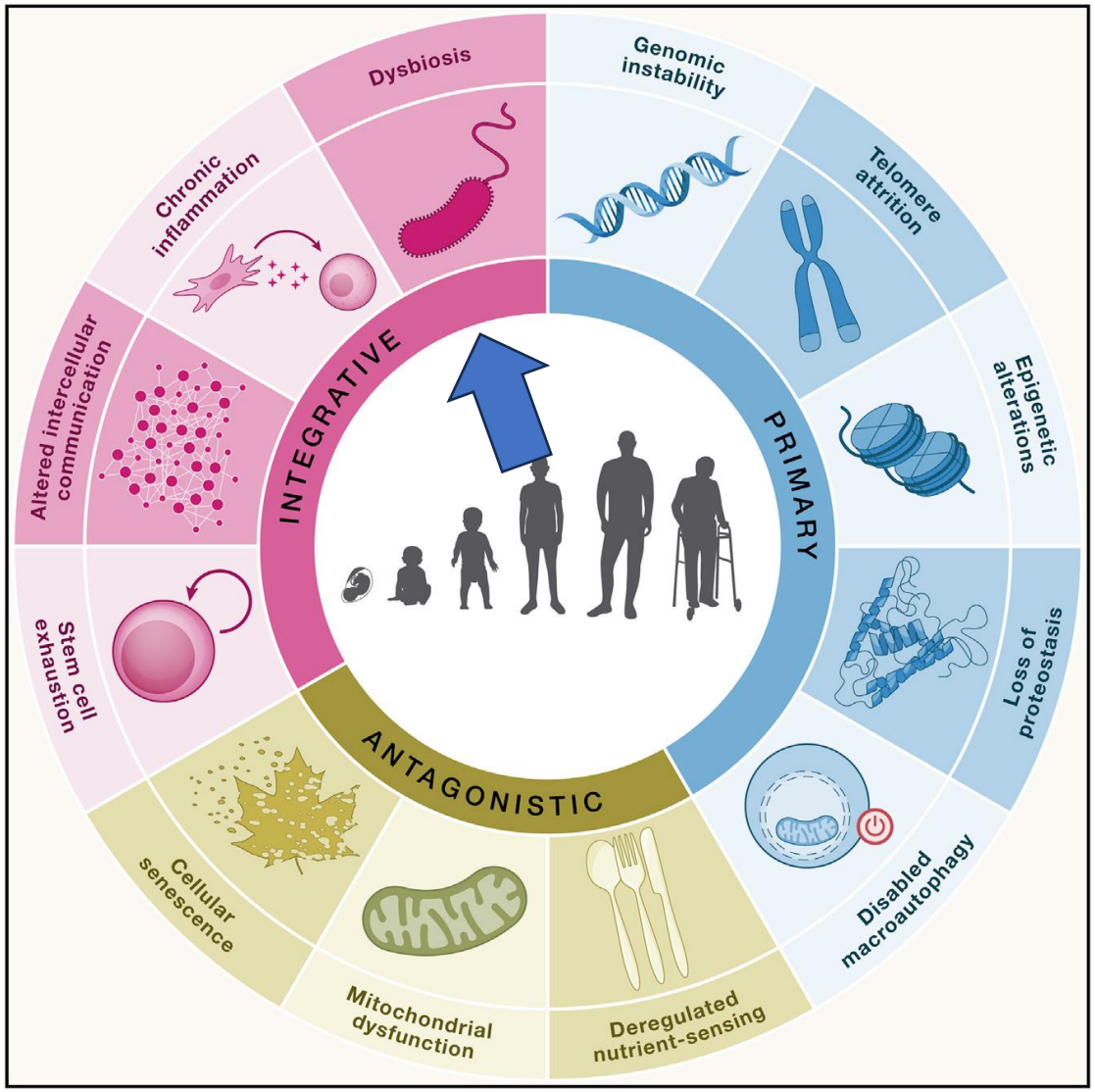


Proposed integrative tissue crosstalk in inflammaging and the role of HSR and HSP70. This model suggests the crosstalk between main organs/tissues affected by the chronic low-grade inflammation (please consult the text for full detailed explanation). Exercise can change the inflammatory balance by its anti-inflammatory effects, improving insulin sensitivity (key for HSR maintenance), reducing adipose tissue (lipolysis) and the inflammatory profile of infiltrated macrophages, improving muscle metabolism (by increasing heat production and energy challenge), activating important molecular pathways that leads to protein synthesis, mitochondrial biogenesis and maintenance of proteostasis. Red arrows: inhibition; Blue arrows: activation

https://doi.org/10.1007/s42978-019-0015-6



Inflamm-aging of the bone marrow. Aging is characterized by the accumulation of random mutations in the DNA (increased mutation heterogeneity). Parallel to this phenomenon, the phenotypic diversity of HSC decreases owing to the progressive skewing towards the myeloid lineage (predominance of HSC myeloid skewed clones) and by the emergence of oligoclones that carry definite mutations (e.g. DNMT3A, TET2). As aging increases, expanded HSC clones promote the onset of a pro-inflammatory environment.
At the same time, stromal cells activate the pro-inflammatory DNA damage response and ultimately undergo senescence. By interacting with myeloid cells, they propagate the pro-inflammatory signal along the tissue. In the final picture, the bone-marrow homeostatic regulation is taken over by pro-inflammatory HSC clones, stromal and myeloid cells.



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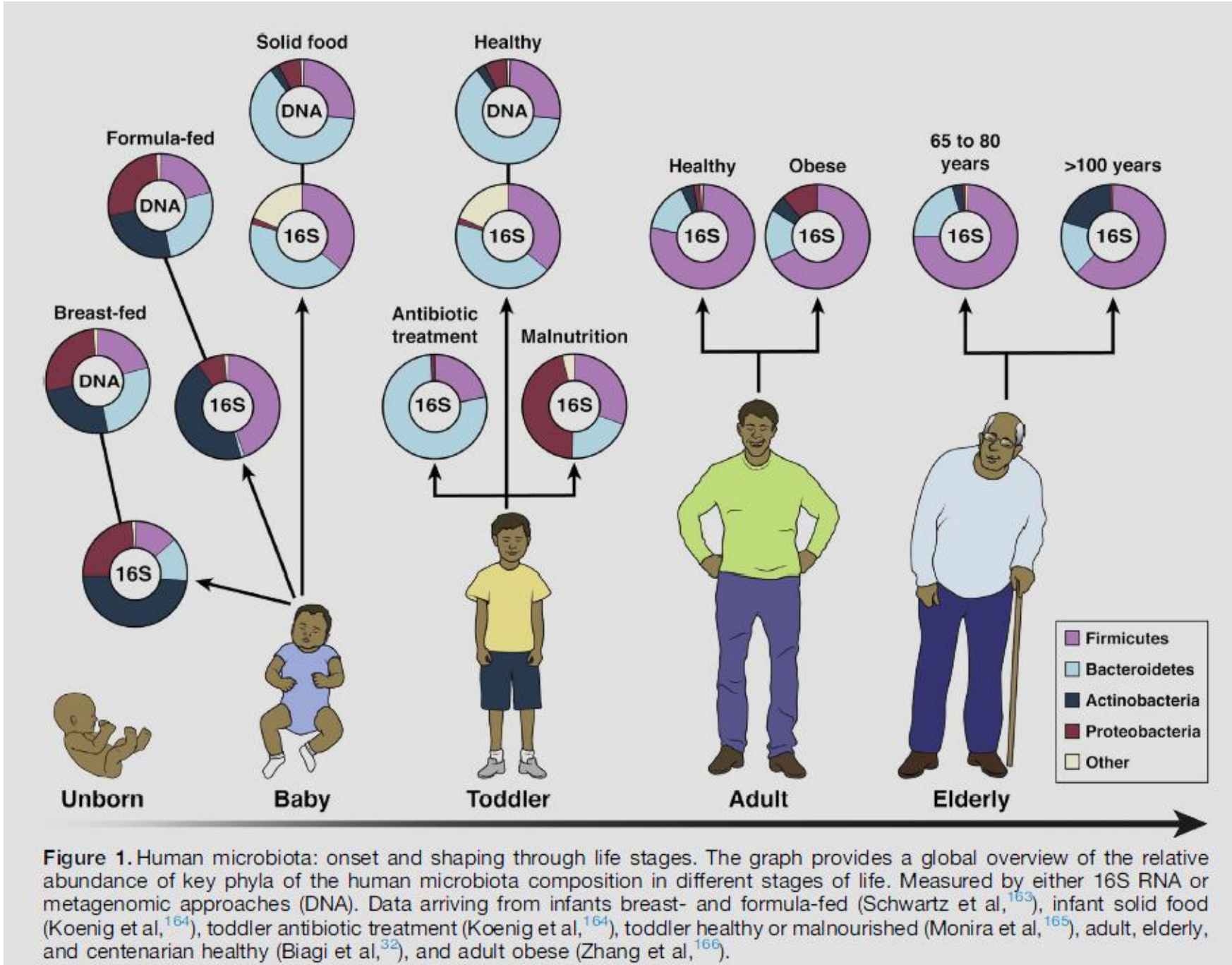


Figure 1. Human microbiota: onset and shaping through life stages. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving from infants breast- and formula-fed (Schwartz et al,[163]), infant solid food (Koenig et al,[164]), toddler antibiotic treatment (Koenig et al,[164]), toddler healthy or malnourished (Monira et al,[165]), adult, elderly, and centenarian healthy (Biagi et al,[32]), and adult obese (Zhang et al,[166]).

https://doi.org/10.1053/j.gastro.2020.09.060

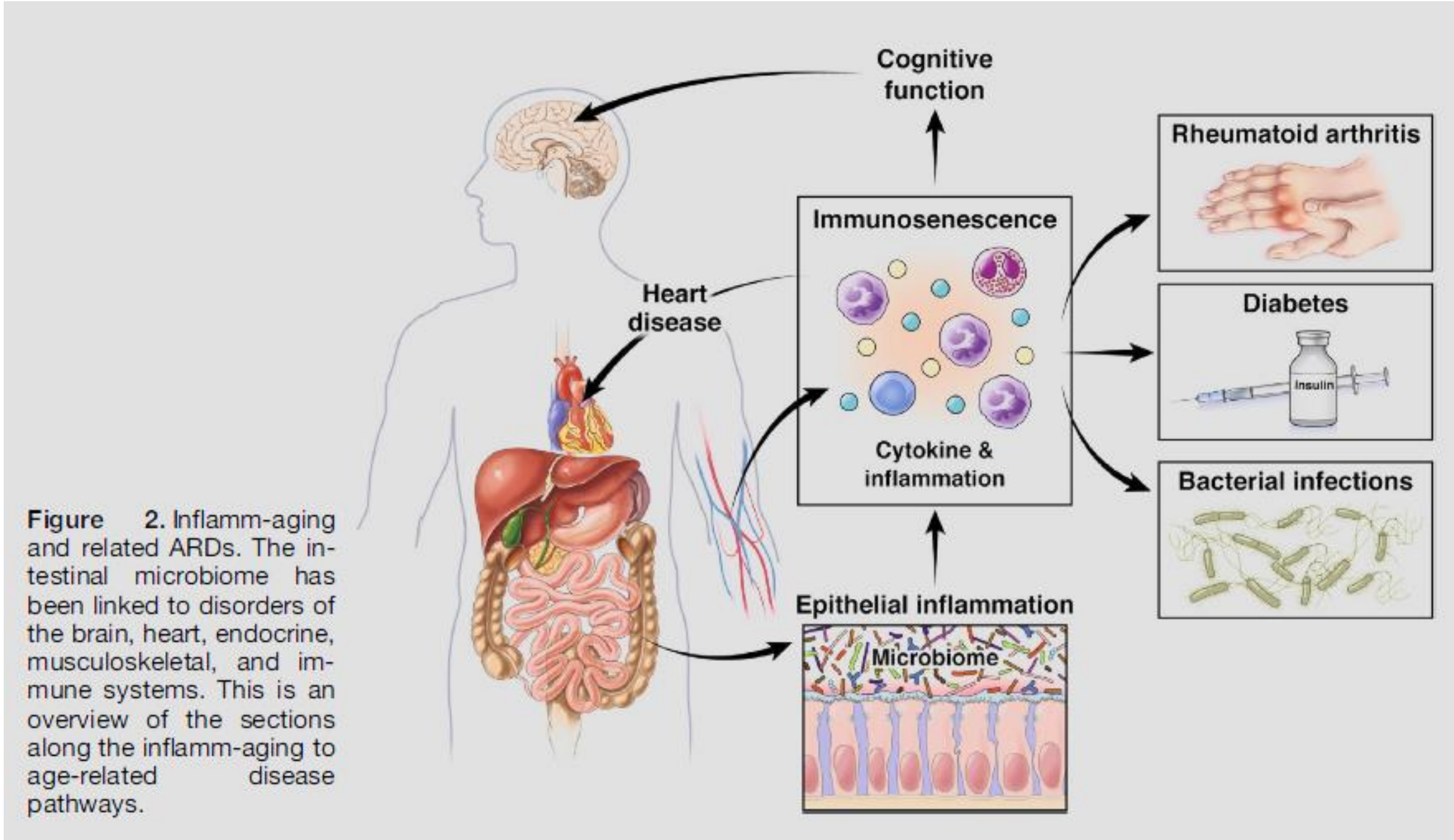


Figure 2. Inflamm-aging and related ARDs. The intestinal microbiome has been linked to disorders of the brain, heart, endocrine, musculoskeletal, and immune systems. This is an overview of the sections along the inflamm-aging to age-related disease pathways.

https://doi.org/10.1053/j.gastro.2020.09.060

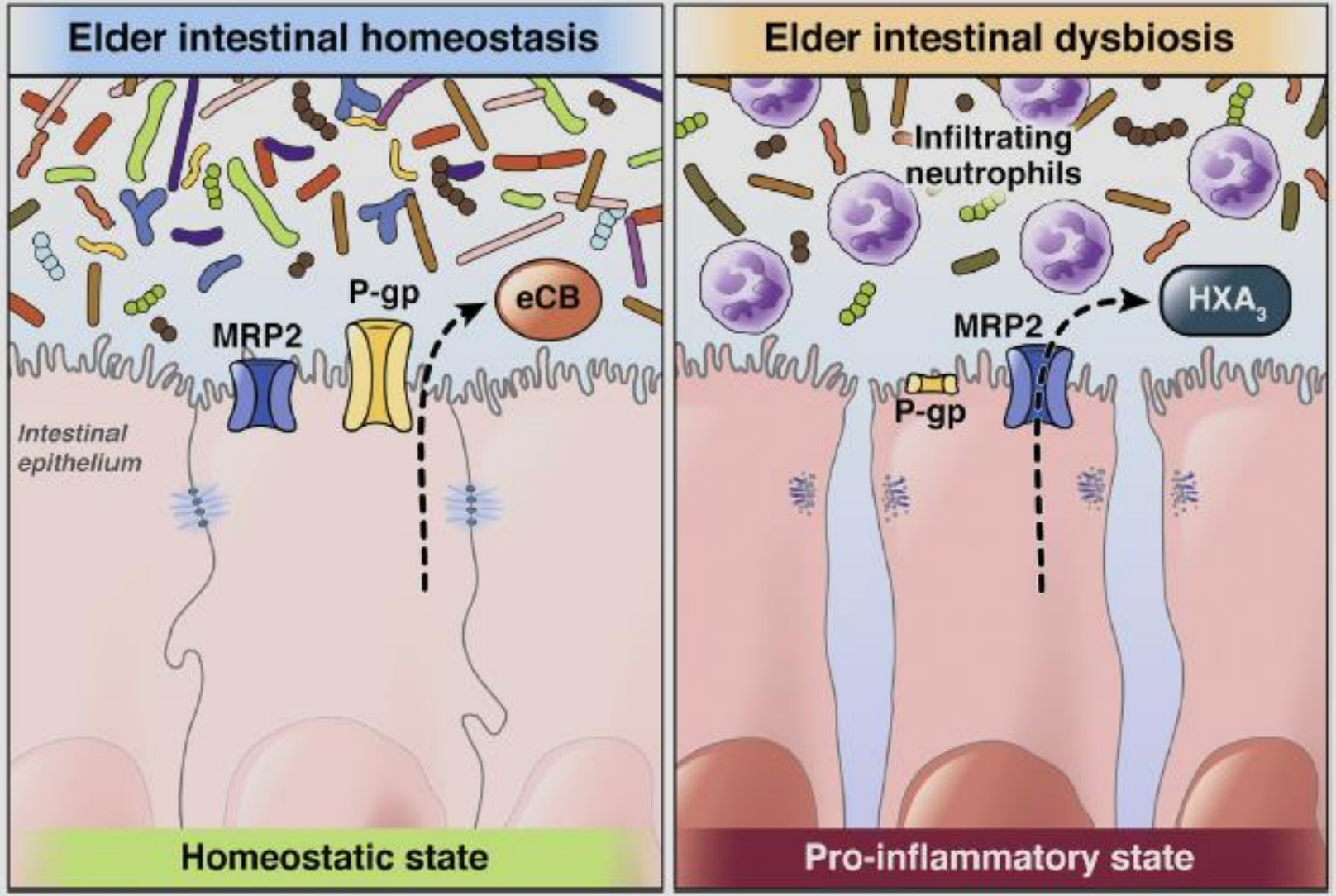
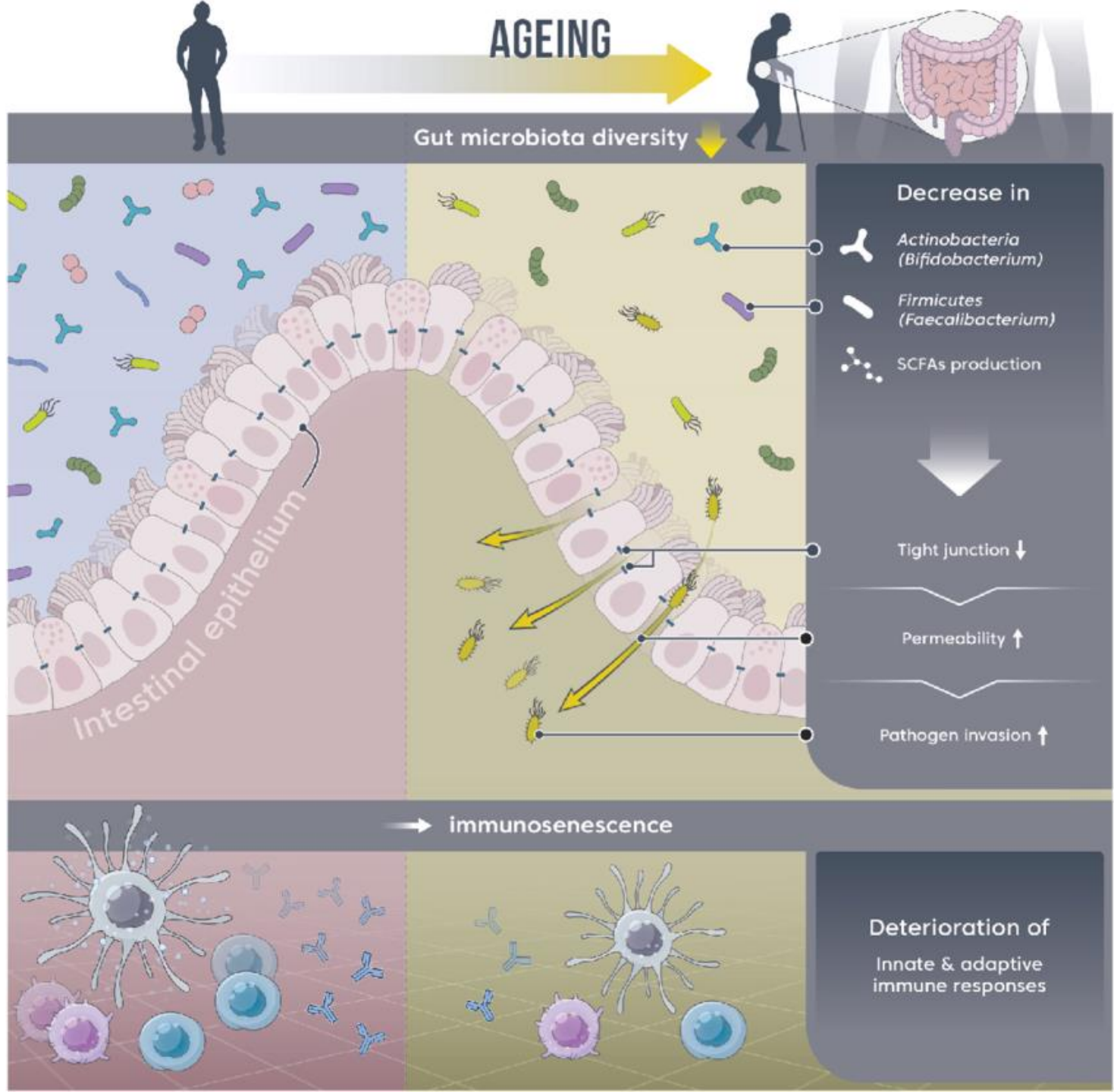
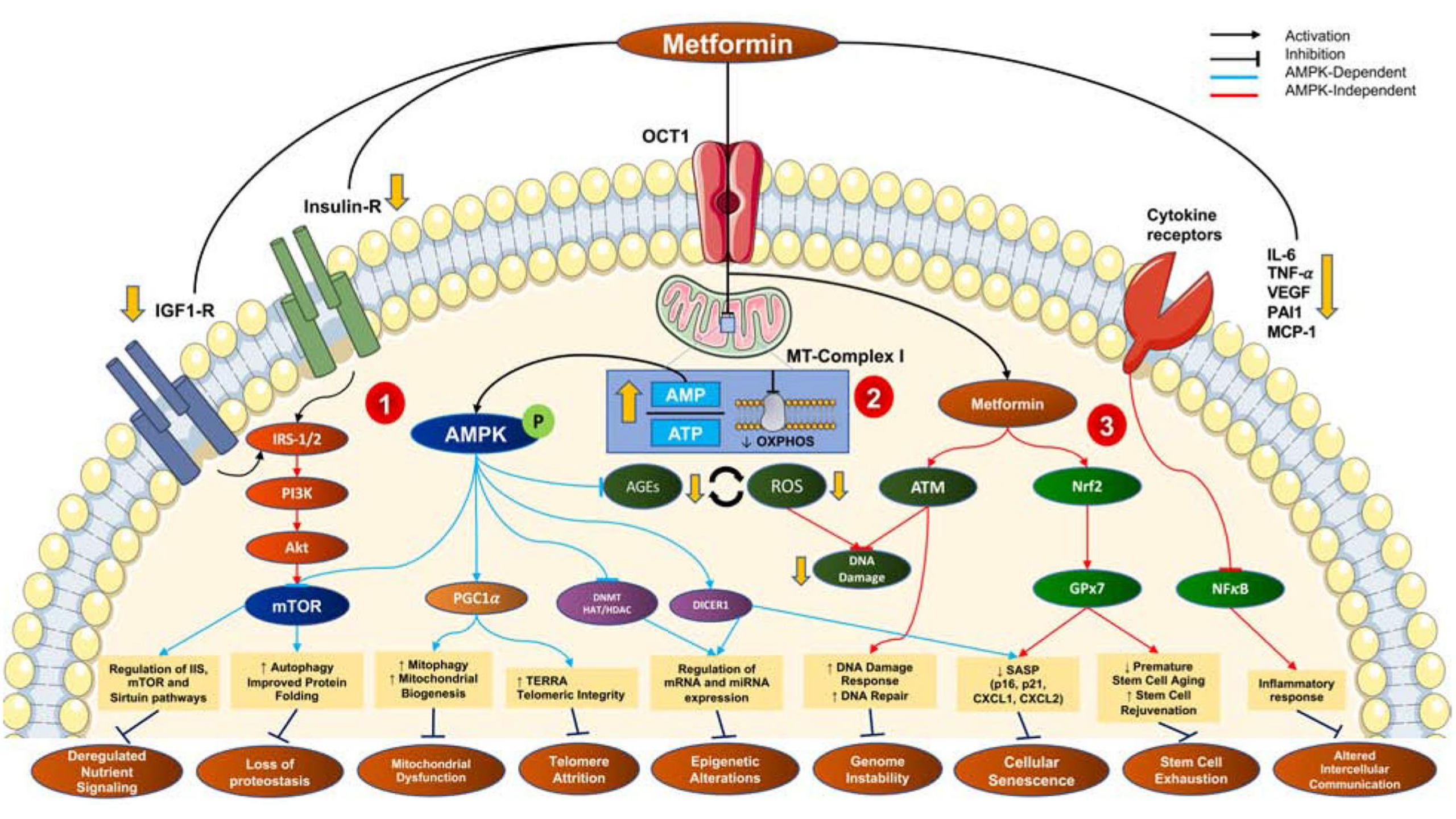


Figure 3. The MRP2/HXA_3 (hepoxilin A3) axis forms the proinflammatory arm of a dynamically regulated system in which inflammatory pathways that activate responses to pathogens or aberrant signals are balanced against the anti-inflammatory P-glycoprotein (P-gp)/endocannabinoid (eCB) pathway that suppresses neutrophil responses in the context of normal commensal colonization. The 2 sets of lipid-based signaling molecules (eCB and HXA_3) are released from the apical surface during periods of either tolerance or inflammation, which control the recruitment of neutrophils to the intestinal lumen. Dysregulation of this critical balance may contribute directly to inflammatory disorders of the intestine.

https://doi.org/10.1053/j.gastro.2020.09.060


AGEING
Gut microbiota diversity
Intestinal epithelium
Decrease in
Actinobacteria (Bifidobacterium)
Firmicutes (Faecalibacterium)
SCFAs production
Tight junction
Permeability
Pathogen invasion
immunosenescence
Deterioration of
Innate & adaptive immune responses


Metformin
Activation
Inhibition
AMPK-Dependent
AMPK-Independent
OCT1
Insulin-R
IGF1-R
Cytokine receptors
IL-6
TNF-α
VEGF
PAI1
MCP-1
MT-Complex I
AMP
ATP
↓ OXPHOS
1
2
3
IRS-1/2
PI3K
Akt
mTOR
AMPK
P
AGEs
ROS
Metformin
ATM
Nrf2
DNA Damage
GPx7
NFκB
PGC1α
DNMT
HAT/HDAC
DICER1
Regulation of IIS, mTOR and Sirtuin pathways
↑ Autophagy Improved Protein Folding
↑ Mitophagy ↑ Mitochondrial Biogenesis
↑ TERRA Telomeric Integrity
Regulation of mRNA and miRNA expression
↑ DNA Damage Response ↑ DNA Repair
↓ SASP (p16, p21, CXCL1, CXCL2)
↓ Premature Stem Cell Aging ↑ Stem Cell Rejuvenation
Inflammatory response
Deregulated Nutrient Signaling
Loss of proteostasis
Mitochondrial Dysfunction
Telomere Attrition
Epigenetic Alterations
Genome Instability
Cellular Senescence
Stem Cell Exhaustion
Altered Intercellular Communication

Aging Research Landscape

Epigenetic Alteration

turn.bio

iduna THERAPEUTICS

salk Where cures begin.

Deregulated Nutrient Sensing

UCSF University of California San Francisco

Biophytis LIVE HEALTHIER LONGER

NUS National University of Singapore

Genomic Instability

The Sinclair Lab

jumpstart

ChromaDex

Loss of Proteostasis

LYSOCLEAR

pti PROTEOSTASIS THERAPEUTICS, INC.

LEUCADIA Therapeutics

sens research foundation reimagine aging

Proclara BIOSCIENCES

COVALENT BIOSCIENCE, Inc

Nature-Made Catalytic Antibodies for Health

UNDERDOG PHARMACEUTICALS

Revel

Alterity THERAPEUTICS

AURORA BIO

selphagy

DENALI

GRIFOLS

Cellular Senescence

Insilico Medicine

MAYO CLINIC

UNITY BIOTECHNOLOGY

ANTOXERENE

CLEARA

ATROPOS THERAPEUTICS

senolytx

SIWA THERAPEUTICS

OISÍN BIOTECHNOLOGIES

Scripps Research

SENISCA

Aging Clocks

DEEP LONGEVITY

ZYMO RESEARCH

CHRONOMICS

Telomere Attrition

TELOCYTE A FUTURE BEYOND ALZHEIMER'S

AGEX THERAPEUTICS

cnio

Mitochondrial Dysfunction

salk Where cures begin.

CONTINUUM BIOSCIENCES

sens research foundation

animal BIOSCIENCES

Amazentis

Stem Cell Exhaustion

Intervene Immune

LONGEVERON

LYGENESIS

BlueRock Therapeutics

CRATUS MEDICAL VITALITY INSTITUTE

Altered Intercellular Communication

Berkeley UNIVERSITY OF CALIFORNIA

SCHOLAR ROCK

resTORbio

Spotlight Biosciences

biosplice

rejenevie THERAPEUTICS

Elevian

ALKAHEST

Definizioni

- INVECCHIAMENTO: Secondo gli antichi, è una perdita **progressiva**, **continua** e **irreversibile** della “forza vitale” che determina la perdita delle capacità di **adattamento** all'ambiente e a una diminuita **sopravvivenza** o, inversamente, un progressivo aumento del rischio di **mortalità**.

- INVECCHIAMENTO e SENESCENZA sono sinonimi;

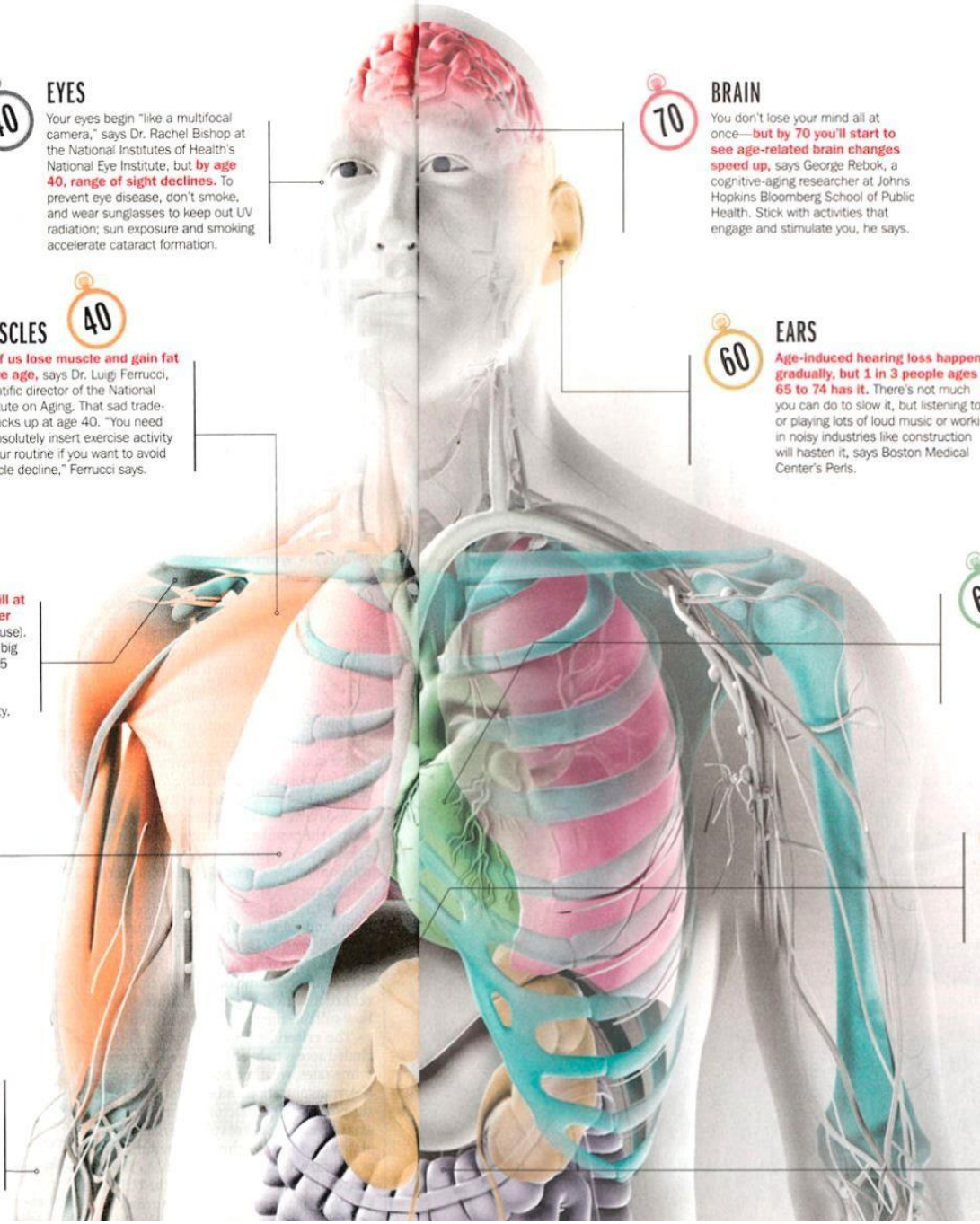
- SENILITÀ: *aspetto **patologico** della vecchiaia.*

- … solo le forme più complesse di organizzazione biologica mostrano un invecchiamento fisiologico con l'aumento dell'età. Forse esiste un **motivo finalistico** che impedisce la riproduzione di individui già danneggiati nel loro patrimonio genetico; che porterebbe alla rapida estinzione della specie…

STRETCH YOUR TIMELINE

BY MANDY OAKLANDER

AS SUDDEN AS AGING CAN feel, no one wakes up in a 90-year-old body without getting some warning signs first. But if you know what's coming, you can plan to give certain parts some extra care early on. Already in the throes of aging? (Trick question. We all are.) "You're never too old to do anything to help to maintain wellness of your body," says Dr. Ronan Factora, geriatric-medicine expert at Cleveland Clinic.



40 EYES

Your eyes begin "like a multifocal camera," says Dr. Rachel Bishop at the National Institutes of Health's National Eye Institute, but **by age 40, range of sight declines.** To prevent eye disease, don't smoke, and wear sunglasses to keep out UV radiation; sun exposure and smoking accelerate cataract formation.

40 MUSCLES

All of us lose muscle and gain fat as we age, says Dr. Luigi Ferrucci, scientific director of the National Institute on Aging. That sad trade-off picks up at age 40. "You need to absolutely insert exercise activity in your routine if you want to avoid muscle decline," Ferrucci says.

35 BONES

Bone mass tends to go downhill at a rate of up to 1% per year after age 35 (and faster after menopause). Weight-bearing exercise makes a big difference in bone density. A 2015 study found that simply jumping 20 times twice a day significantly improved hip-bone mineral density.

30 LUNGS

Lung function begins dropping 1% a year at 30 and declines more in people who are sedentary than in those who are active, says Dr. Thomas Perls, geriatrician and principal investigator of the New England Centenarian Study at Boston Medical Center. The antidote: exercise.

18 SKIN

From around 18, resilient collagen and stretchy elastin decline at about 1% per year. You can slow the process by not smoking, eating well and wearing titanium or zinc sunscreen every day—even if you're indoors. A 2012 study found that some compact fluorescent bulbs emit skin-damaging UV light.

70 BRAIN

You don't lose your mind all at once—**but by 70 you'll start to see age-related brain changes speed up,** says George Rebok, a cognitive-aging researcher at Johns Hopkins Bloomberg School of Public Health. Stick with activities that engage and stimulate you, he says.

60 EARS

Age-induced hearing loss happens gradually, but 1 in 3 people ages 65 to 74 has it. There's not much you can do to slow it, but listening to or playing lots of loud music or working in noisy industries like construction will hasten it, says Boston Medical Center's Perls.

65 HEART

As you age, your heart-muscle cells shrink in number but expand in size, which makes your heart wall thicker. Your arteries tend to get stiffer too. Starting at age 20 to 30, peak aerobic capacity drops by about 10% per decade, and **heart disease typically kicks in around age 65.**

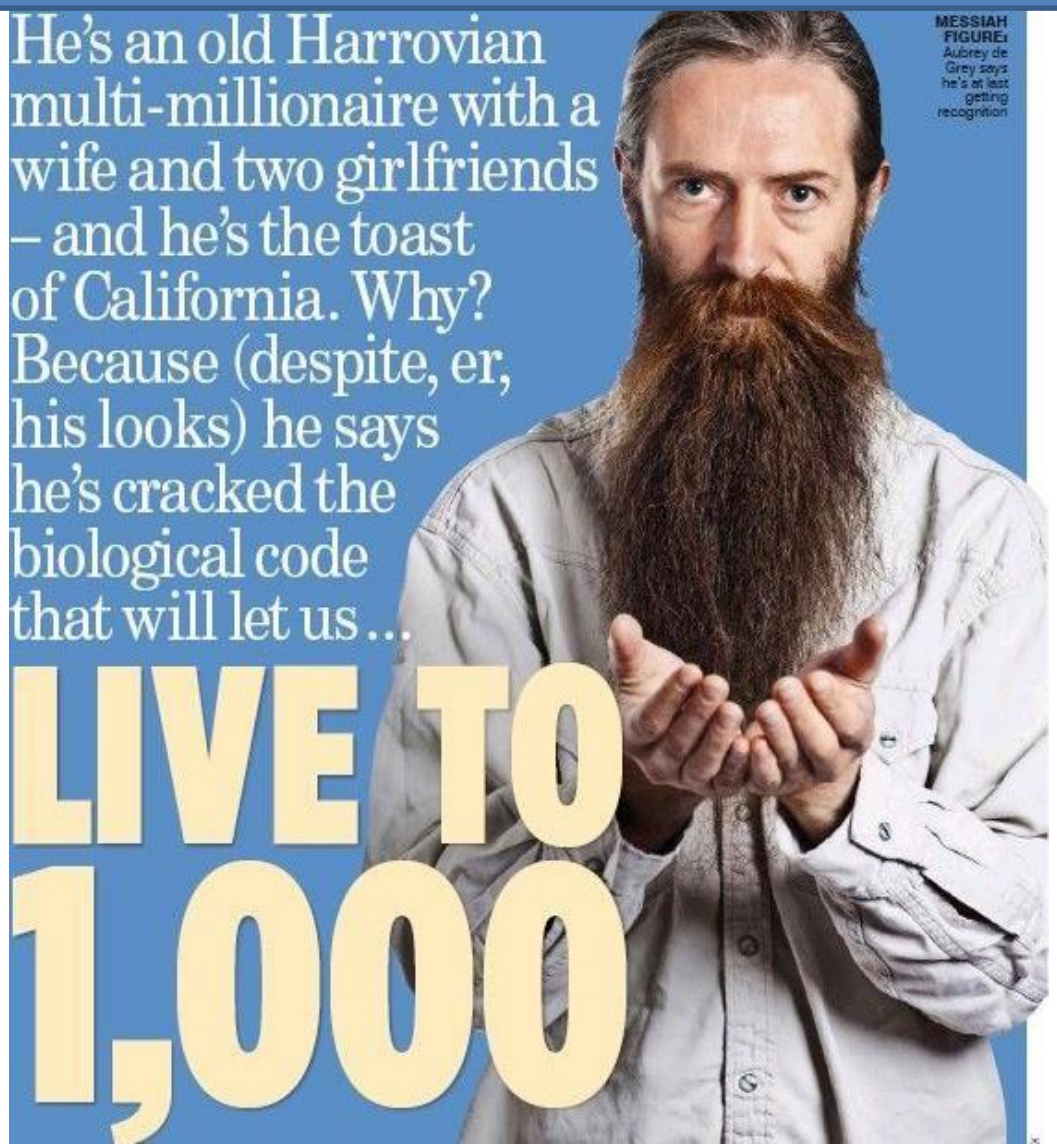
50 KIDNEYS

You won't necessarily feel it, but decline in kidney function starts around 50. The best thing to do is drink plenty of water. Since thirst decreases with age, you may have to remind yourself. One study found people who drank the most fluids were less inclined to kidney decline.

60 GUT

The hairs on your head aren't the only strands to go. **Villi in your intestine—tiny hairlike projections that absorb the nutrients in food—tend to flatten out around age 60,** says Cleveland Clinic's Factora, and the loss means you'll absorb fewer nutrients.

Ageing Process



EXPO MEETING

innov-aging

21 - 23 JUNE 2018 - Ancona, Italy

FONDAZIONE MARCHE

Ageing Process

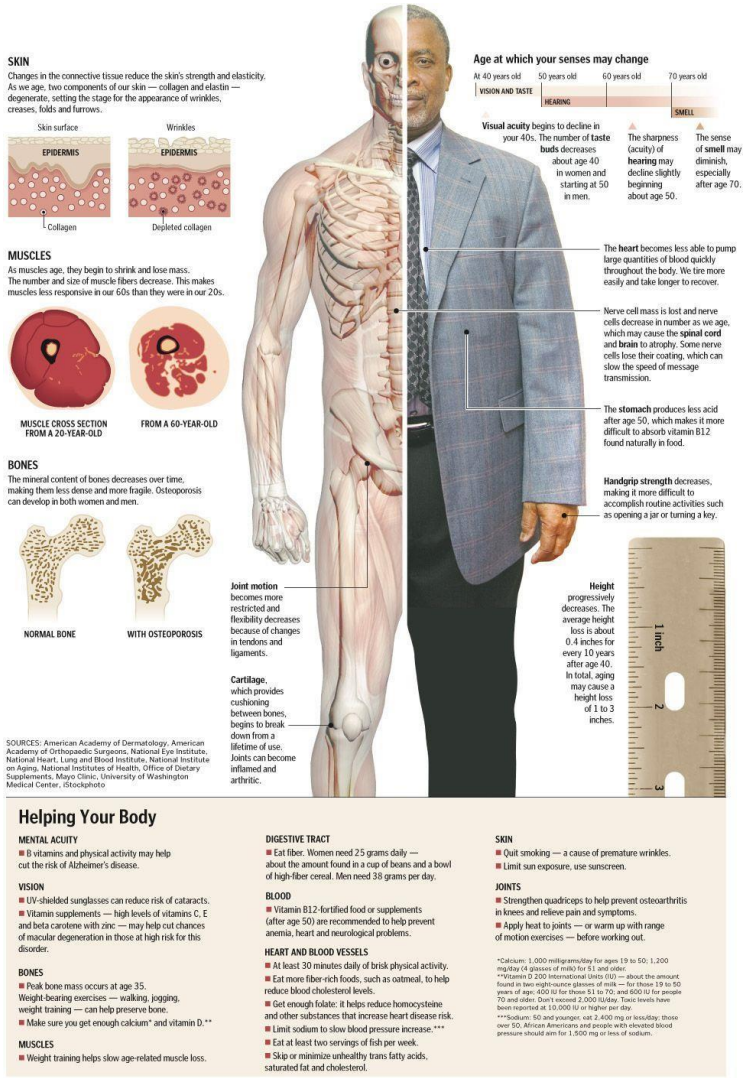
Inizio del PROCESSO d'invecchiamento intorno ai 65 anni di età.

Esistono 3 aspetti eterogenei, contemporanei e non coincidenti:

1. ***biologico*** (il mutare e il decadere del corpo, avviene **su TUTTO** il corpo e per **TUTTI**, ma il **ritmo** può essere diverso),

2. ***psicologico*** (il modificarsi dell'adattamento alla vita quotidiana),

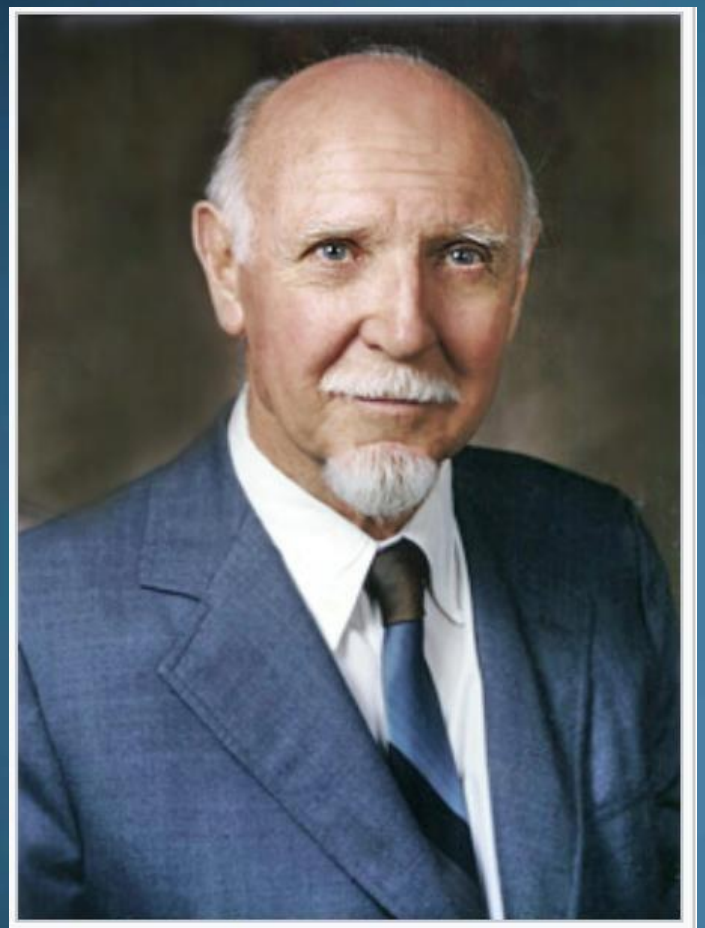
3. ***sociale*** (il cambiamento del ruolo dell'anziano nella società).



Il «puzzle» della longevità

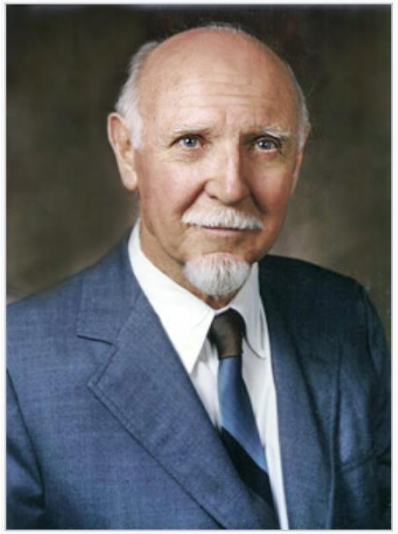
- ✓ La longevità umana non ha senso per l'ipotesi darwiniana di sopravvivenza del più adatto.
- ✓ In natura, la maggior parte dei grandi animali non vive molto tempo dopo aver perso la fertilità ed essere diventato fiisicamente debole.
- ✓ La durata della vita umana continua ad aumentare, ma la durata della fertilità non è aumentata.
- ✓ Le persone che vivono fino a 90 anni trascorrono metà della loro vita senza fertilità (e aumentano fisicamente la disabilità, senza benefici per la salute della specie o per se stessi).

… Qualcosa dovrà migliorare con la età…!



Raymond Bernard Cattell (1905-1998)

Modello di intelligenza di Cattell: intelligenza fluida e cristallizzata



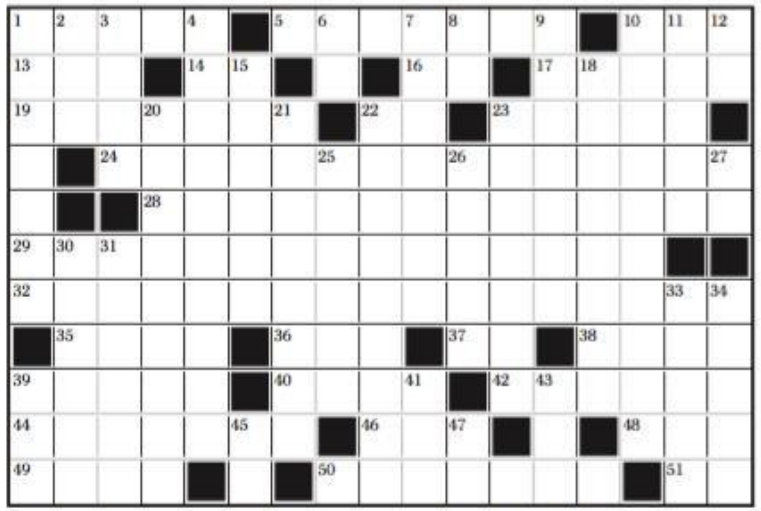
Raymond Bernard Cattell (1905-1998)

1- L'intelligenza fluida è la capacità di pensare logicamente e **risolvere** i problemi in situazioni **nuove**, indipendentemente dalle conoscenze acquisite. È la capacità di **analizzare** problemi nuovi, **identificare** gli schemi e le relazioni sottostanti per **estrapolare** una soluzione usando il ragionamento logico, induttivo e deduttivo.

Questo tipo di intelligenza è **fortemente legato a fattori genetici e allo sviluppo dell'individuo**. Osserviamo che l'intelligenza fluida raggiunge il suo massimo potenziale durante **l'adolescenza.**

Modello di intelligenza di Cattell: intelligenza fluida e cristallizzata

4877. **PAROLE CROCIATE BIFRONTALI** *(Guernica)*

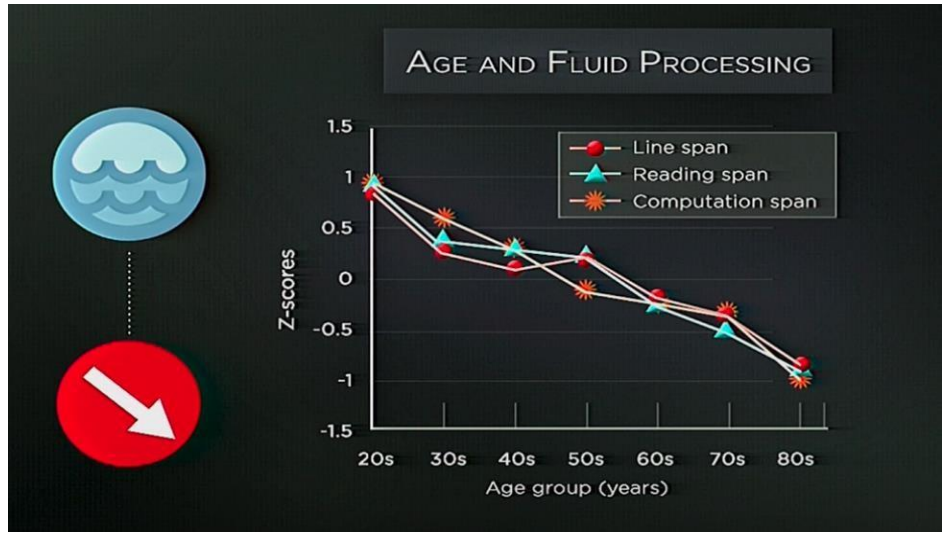


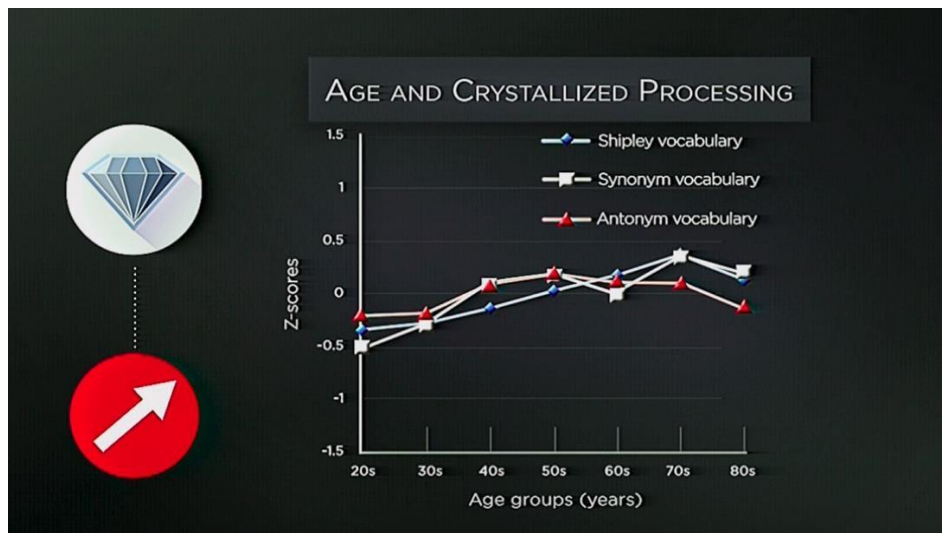
Il solutore tenga presente che molte parole non vanno scritte da sinistra a destra o dall'alto in basso, ossia come in un normale gioco di parole crociate, ma viceversa.

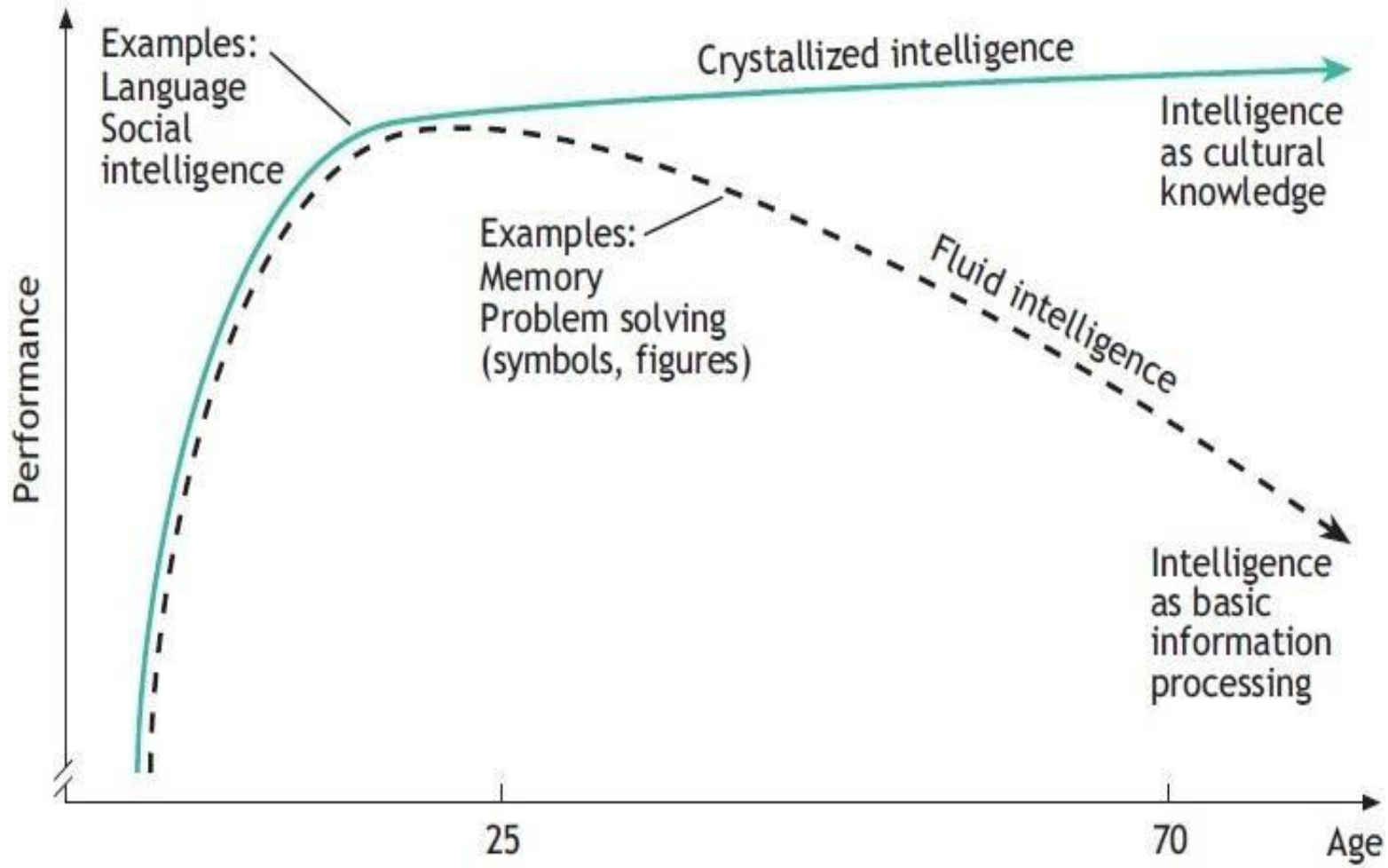
ORIZZONTALI: 1. ... Zola, romanziere - 5. Gli angoli del tavolo - 10. Sono caratteristici di ciascuna regione - 13. Il *carpet* di Hollywood - 14. Le consonanti degli atomi - 16. In fondo al tunnel - 17. La città francese con la famosa *Place Stanislas* - 19. Il Pino che cantava *Je so' pazzo* - 22. Se non è out è ... - 23. Si passa per quello della cuffia - 24. Lo è tanto l'Appia quanto l'Aurelia - 28. Gustoso pesce dalle carni rosate - 29. Allena a seconda delle esigenze individuali - 32. Vi abita il pesciolino Nemo - 35. Particella con una carica - 36. Assieme ai - 37. Il Twist di Dickens (iniz.) - 38. ..., Speranza, Carità - 39. Equivale a *shop* - 40. Il Michael che ha diretto *Heat - La sfida* - 42. Un famoso collie dello schermo - 44. Avere per argomento - 46. Tabella... abbreviata - 48. *Acqua di* ..., profumo di Armani - 49. Gli antichi Vichinghi le usavano come armi - 50. Timbro a fuoco - 51. In Puglia e in Sardegna.

VERTICALI: 1. Soldato con le frecce - 2. Il Brooks de *L'ultima follia* - 3. Le offusca il vino - 4. Estremamente divertente - 6. Quello *di Volano* bagna Ferrara - 7. Tifosa dei rossoblù liguri - 8. Il cuore di... Topolino - 9. Privi di profumo - 10. Iniziato, intavolato - 11. Francis ... Fitzgerald - 12. I confini dell'Uruguay - 15. Completa rovina a cui porta la vita dissoluta - 18. Si dice di una corsa folle - 20. Può contenerne diverse decine la botte - 21. Teorie filosofiche o scientifiche - 22. Quasi tutti vengono preparati con carne di maiale - 23. Fece completare il tempio di Luxor - 25. Insegna da film western - 26. Il disinfettante usato nelle piscine - 27. L'inizio della salita - 30. Lo sono le notti illuminate dalle stelle - 31. Scrisse *E le stelle stanno a guardare* - 33. Pietra verde durissima - 34. Un tipo di insalata - 39. Preghiera a Maria - 41. Esprime incertezza - 43. Può essere *inclusa* nella fattura - 45. Il prefisso iterativo - 47. Iniziali di Cristel, l'attore

2- L'intelligenza **cristallizzata** è la capacità di utilizzare **competenze**, **conoscenze** ed **esperienze**. Non dovrebbe essere equiparata alla memoria o alla conoscenza, anche se il suo operato le permette di accedere alle informazioni dalla memoria a lungo termine.

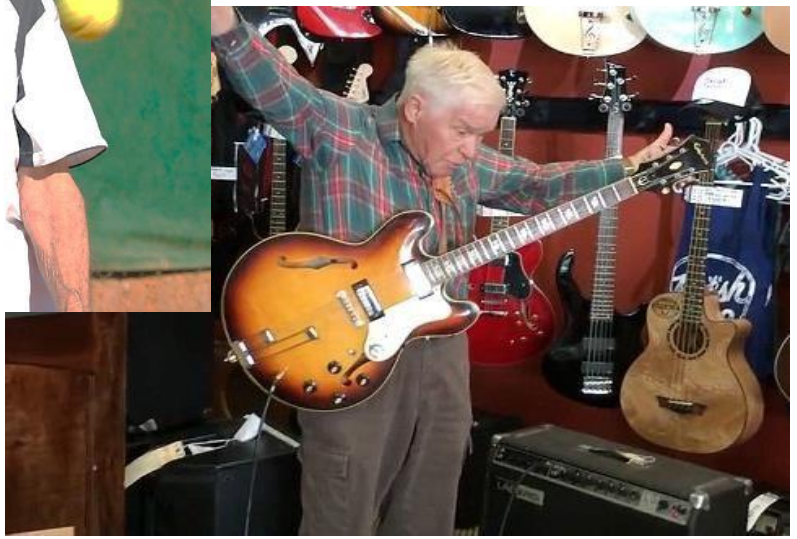

Age and Fluid Processing
Line span
Reading span
Computation span
Z-scores
1.5
1
0.5
0
-0.5
-1
-1.5
20s
30s
40s
50s
60s
70s
80s
Age group (years)

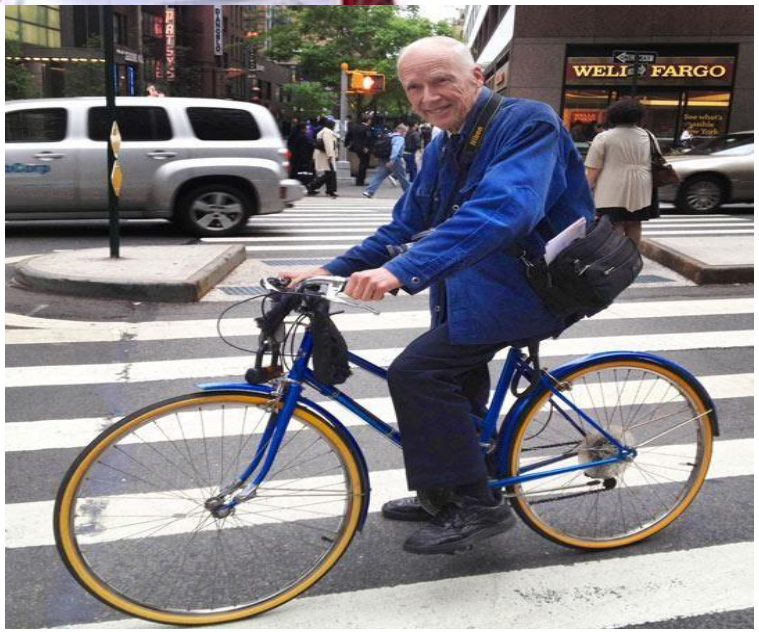

Age and Crystallized Processing
Shipley vocabulary
Synonym vocabulary
Antonym vocabulary
Z-scores
1.5
1
0.5
0
-0.5
-1
-1.5
20s
30s
40s
50s
60s
70s
80s
Age groups (years)


Examples:
Language
Social
intelligence
Crystallized intelligence
Intelligence
as cultural
knowledge
Examples:
Memory
Problem solving
(symbols, figures)
Fluid intelligence
Intelligence
as basic
information
processing
Performance
25
70
Age

Intelligenza procedurale

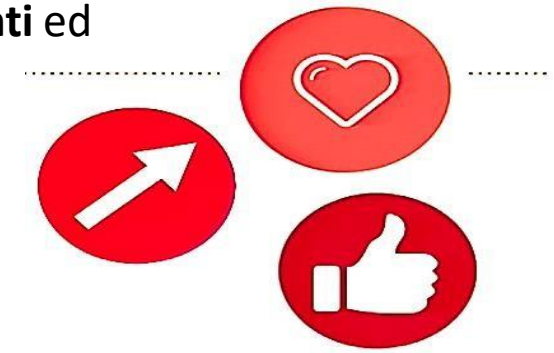
La **memoria procedurale** (o **memoria implicita**), sembra che venga mantenuta più a lungo (**invariata**) della memoria semantica.





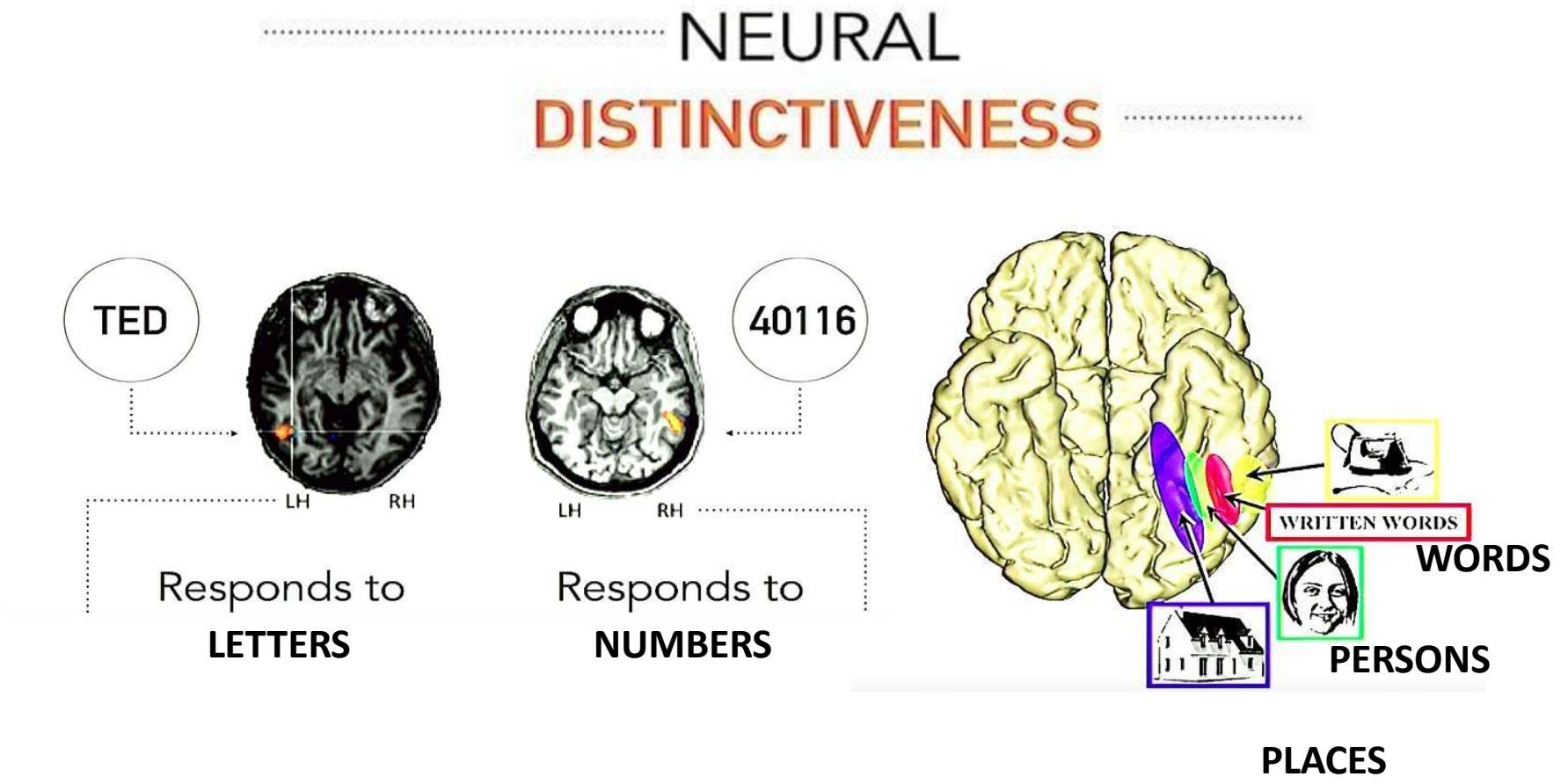
Intelligenza emotiva

Trattata la prima volta nel 1990 dai prof. Peter Salovey e John D. Mayer nel loro articolo “Emotional Intelligence”.
Intelligenza emotiva: “La capacità di **controllare** i **sentimenti** ed **emozioni**, **distinguere** tra di esse e di **utilizzare** queste informazioni per guidare i propri **pensieri** e **azioni**”.

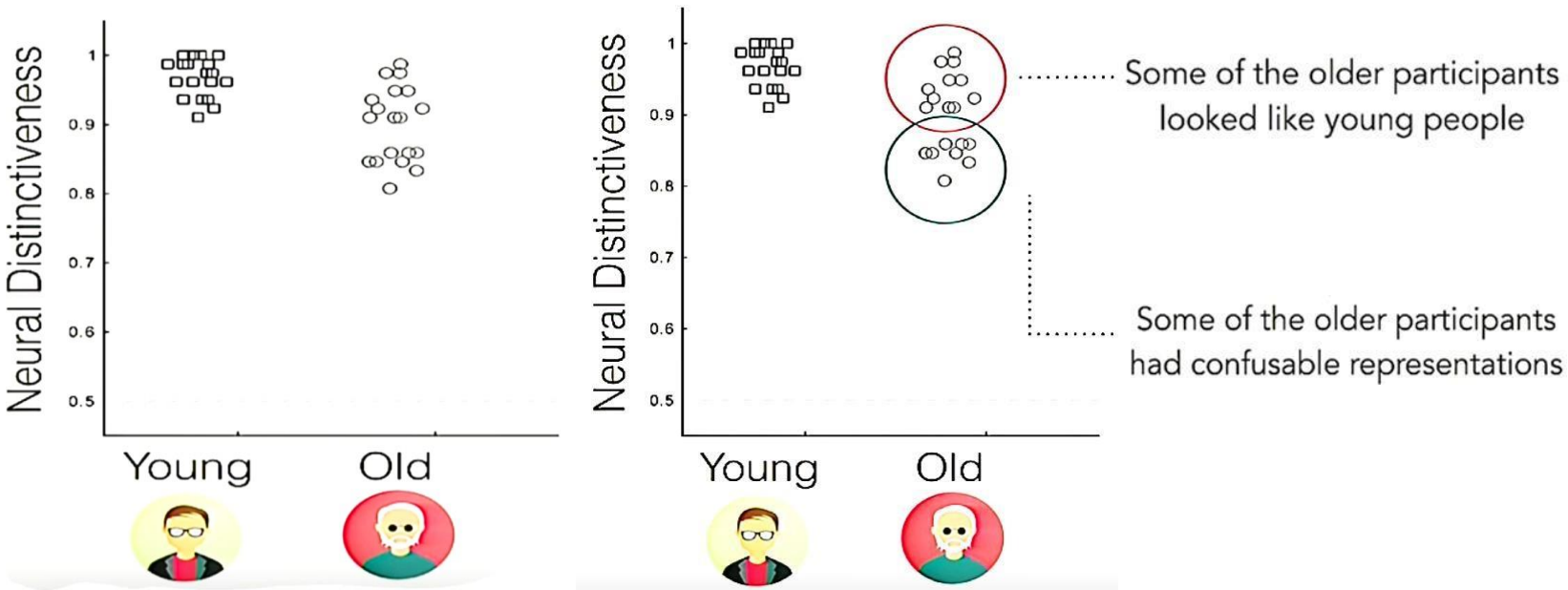


Mentre la personalità del giovane è di tipo centrifugo, proiettata verso l'esterno e verso il futuro, la personalità dell'anziano è centripeta, ossia rivolta al proprio Io, con tutto il carico di ricordi, esperienze e sentimenti che lo caratterizza.

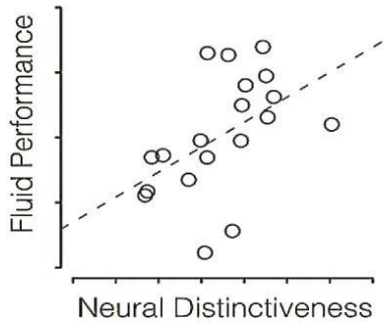
Differenziamento Neuronale



NEURAL DISTINCTIVENESS AND AGING

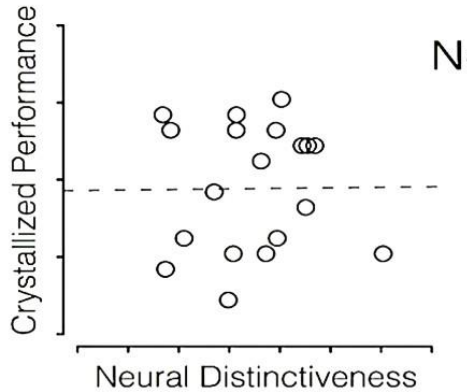


FLUID PROCESSING



Participants with the
MOST DISTINCTIVE
brain representations perform best.

CRYSTALLIZED PROCESSING



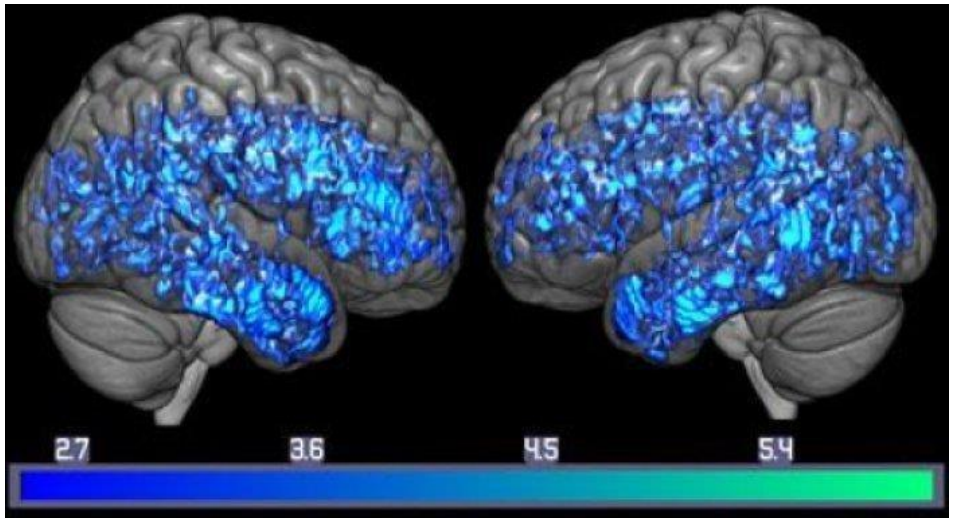
Neural distinctiveness has
NO EFFECT
on performance.

Riorganizzazione neuronale (plasticità)

Esistono prove certe della stretta dipendenza tra alterazioni strutturali e alterazioni funzionali del cervello. La **minore interconnessione** nel cervello degli anziani viene evidenziata dalla **riduzione della ramificazione dendritica** e dal **declino di neurotrasmettitori** quali acetilcolina, dopamina e noradrenalina.

Più che lo **spopolamento**, c'è **depauperamento** dei **neurotrasmettitori**.

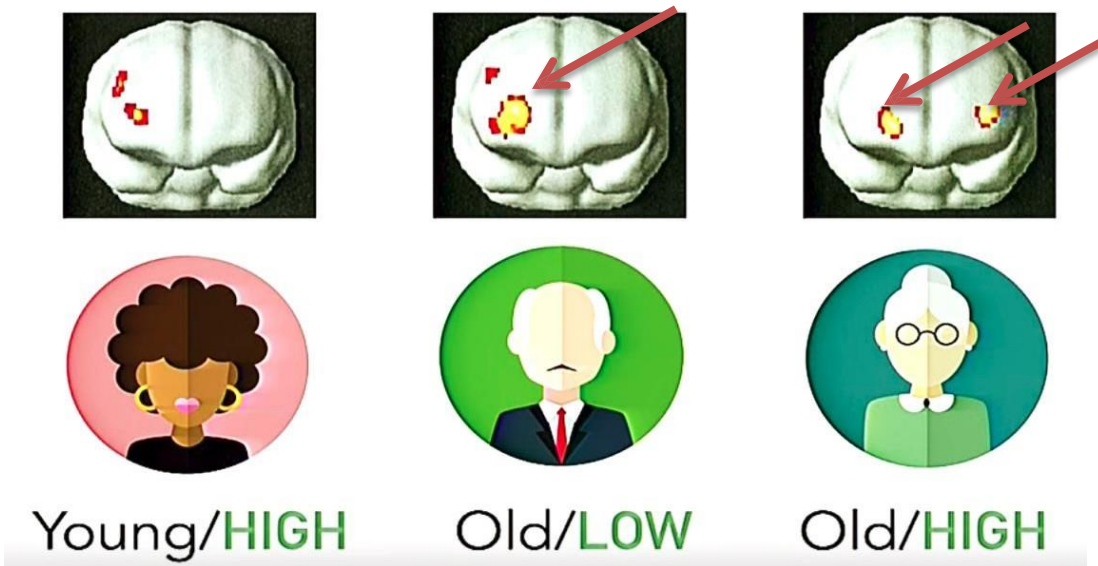
Le "perdite" possono essere in parte contrastate e compensate dal fenomeno della **plasticità neuronale***.*



Cervello che mostra diminuzioni dei trasportatori di serotonina (blu) nell'intero gruppo di danno cognitivo lieve rispetto all'intero gruppo di controllo sano.

Fonte: Gwenn Smith Lab

NEURAL REORGANIZATION



Ageing Process

- Crescente e tendenzialmente globale **rallentamento psicosensoriale** e motorio, il quale si traduce in un rallentamento nella elaborazione cognitiva e nella produzione di risposte.
- **Aumento** della **componente cristallizzata** (utilizzo del **patrimonio** di esperienze e di conoscenze) dell'intelligenza rispetto alla componente fluida
- Graduale **compromissione delle capacità fluida**; è opportuno differenziare se il fenomeno fa parte di un'involuzione fisiologica o è il primo sintomo di una situazione patologica di tipo demenziale (alla cui base ci sarebbe un abbassamento dell'acetilcolina).
- Graduale **compromissione delle capacità di apprendimento**, soprattutto in funzione della sua rapidità. Un fattore fondamentale per contrastare in parte il deterioramento mentale resta quello della **stimolazione e dell'esercizio.**

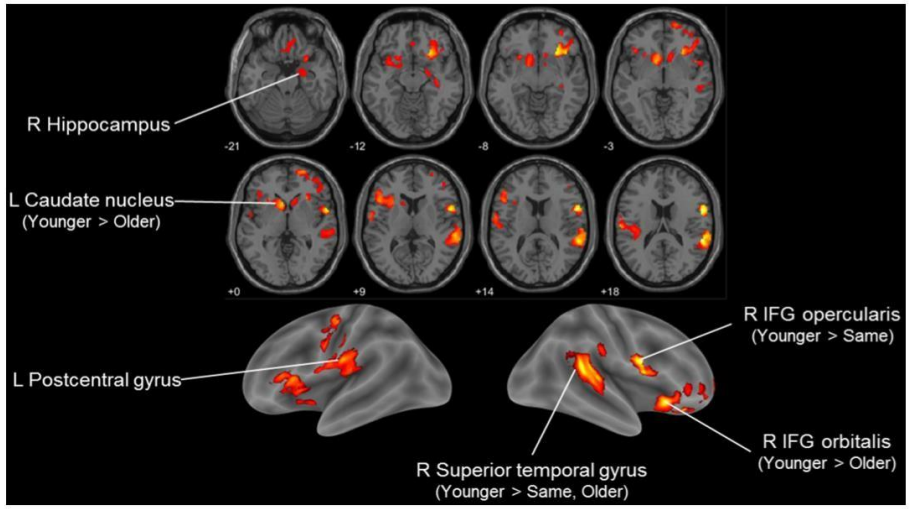
Longevità: età soggettiva

Feeling How Old I Am: Subjective Age Is Associated With Estimated Brain Age

Seyul Kwak[1], Hairin Kim[1], Jeanyung Chey[1] and Yoosik Youm[2]*

frontiers in Aging Neuroscience

GINAL RESEARCH
published: 07 June 2018
doi: 10.3389/fnagi.2018.00168



La età soggettiva è un importante *marker* della **salute neurocognitiva tardiva**.

I risultati suggeriscono che sentirsi soggettivamente più giovani potrebbe corrispondere a strutture più sane e conservate .

Principio dell'eterocronia dell'invecchiamento

Artificiosità di definizione della vecchiaia basata *solo* su il solo criterio cronologico

L'accrescimento nelle organizzazioni strutturali e funzionali negli individui "normali" avviene in modo **sequenziale-stadiale**.

L'invecchiamento è ***eterocronico***, cioè modalità e tempi differenti.

La età soggettiva è associata a:

- Salute fisica
- Depressione
- Fragilità
- Declino cognitivo
- Demenza
- Ospedalizzazione

Concettualizzazione della Saggezza

La **saggezza** è un tratto multi-componente complesso, che implica **l'integrazione equilibrata** di varie componenti, con l'intero risultato superiore alla somma delle sue parti.

La saggezza ha come scopo:

- ✓ **valorizzare la persona**
- ✓ **potenziare il proprio benessere**
- ✓ **migliorare il benessere della società.**

Piacenza, l'asilo dai 3 ai 90 anni dove anziani e bimbi si prendono per mano

Aspetti socio-culturali dell'invecchiamento

- La **produttività** e **l'attività lavorativa** sono elementi fondamentali definizione **dell'identità e del ruolo sociale**. L'inizio della vecchiaia v spesso sanzionato, in modo brusco e repentino, dal **pensionamen** dalla perdita dello status sociale connesso al ruolo di lavoratore.

- Diminuiscono le possibilità di contatto **umano** e di relazione, la necessità di occuparsi degli avvenimenti **futuri**, degli aspetti organizzativi del lavoro, in altri termini, l'atteggiamento **aggressivo** verso il presente e **costruttivo** verso il futuro.

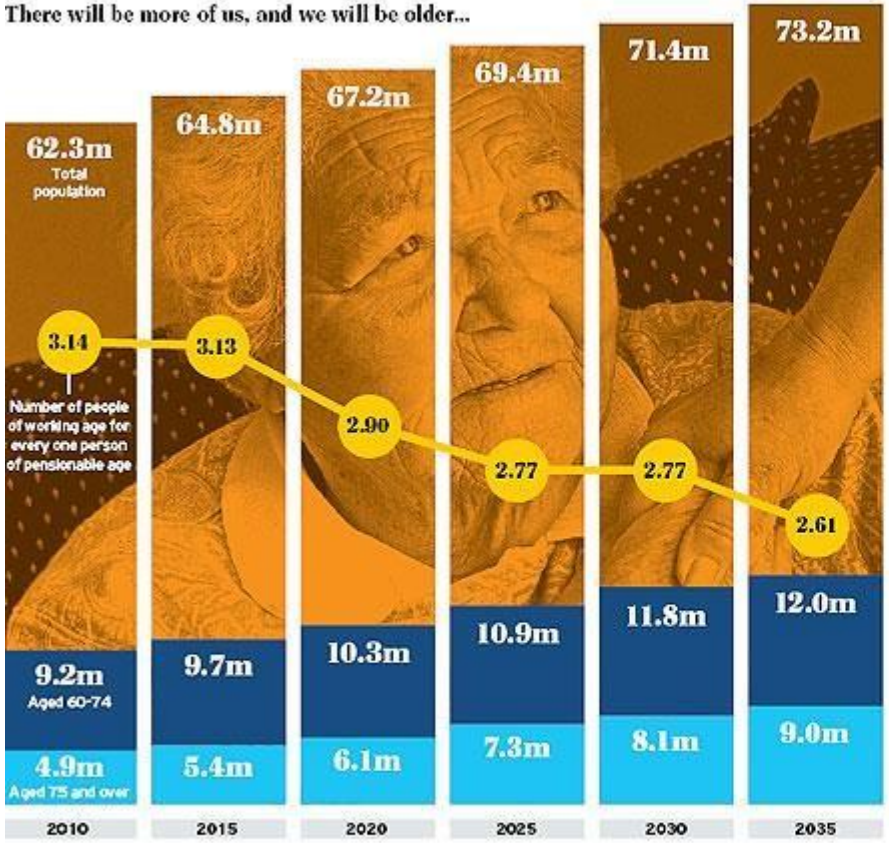
Longevità: fisiologia dell'invecchiamento e nuove attitudini in una visione medica

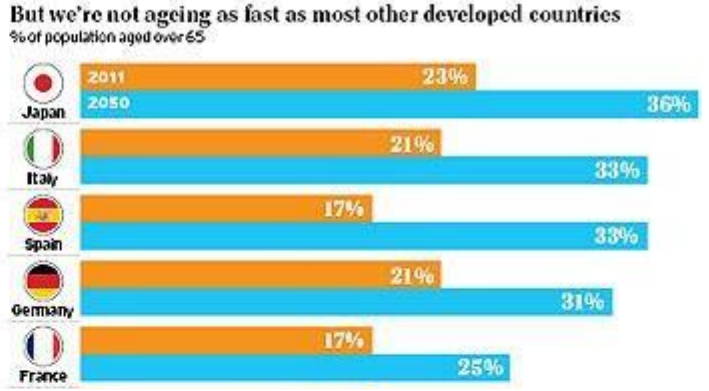
Alcuni fattori risultano influire in modo significativo sul vissuto soggettivo:

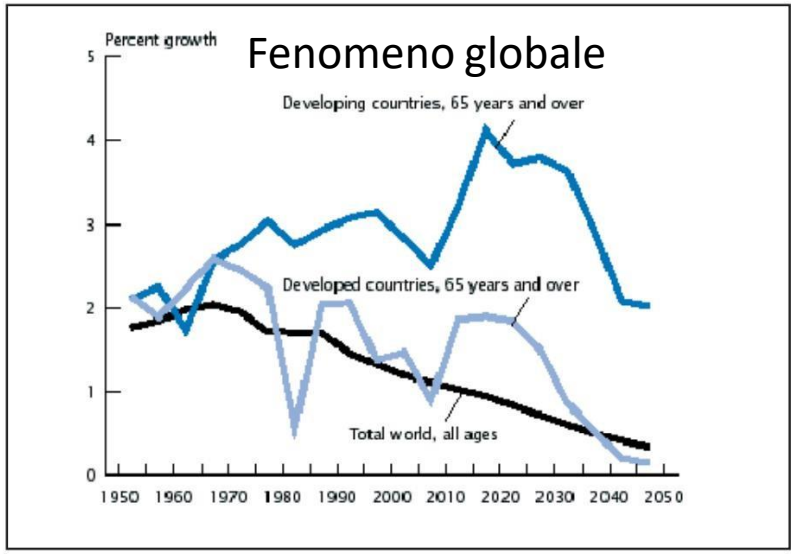
- La percezione che il soggetto aveva del proprio lavoro e dell'ambiente lavorativo;
- Il tempo intercorso dal pensionamento, in quanto è necessario un **periodo di adattamento**;
- La **possibilità di scelta al momento del pensionamento**. Il pensionamento forzato e anticipato sembra avere peggiori conseguenze sulla salute e sull'equilibrio psicologico.

Journal of Psychopathology
Organo Ufficiale della Società Italiana di Psicopatologia

Numero di persone in età lavorativa per ogni persona in età pensionabile







Longevità: fisiologia dell’invecchiamento e nuove attitudini in una visione medica

Le politiche che attuano l'età pensionabile obbligatoria non aiutano a creare posti di lavoro per i giovani, ma **riducono la capacità di contribuire dei lavoratori più anziani.**

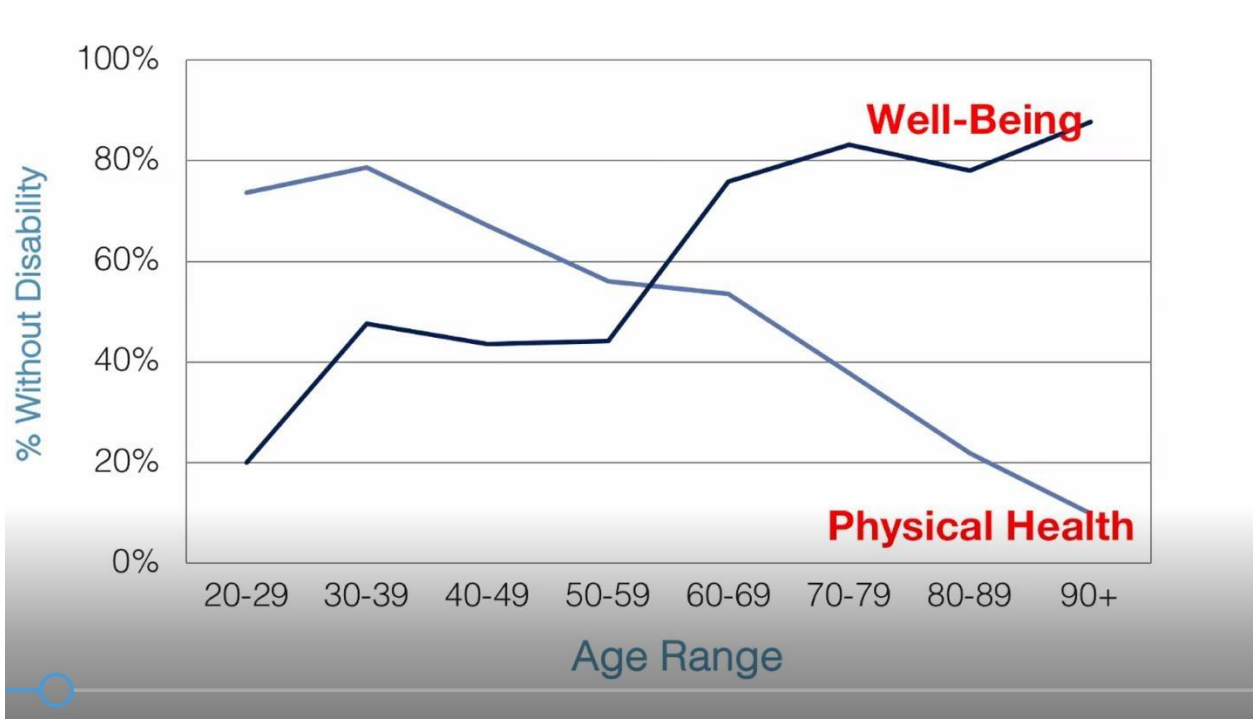
Riducono inoltre le opportunità delle organizzazioni di beneficiarsi delle **capacità** dei lavoratori più anziani.

L'età non ha dimostrato essere un indicatore affidabile per giudicare la potenziale produttività dei lavoratori.

<<Non occorre alcuna abilità per invecchiare, ma occorre abilità per saperlo sopportare>>.

Johann Wolfgang Gothe

Physical Health vs. Mental Well-Being From Age 21 to 100 Years (N=1,547)



(Jeste DV, et al., Am J Psychiatry, 2013;
Thomas M, et al., J. Clin. Psychiatry, 2016)

Rome – Dr. Rita Montalcini, a Nobel Laureate, on her 100th birthday: “My mind is sharper today than when I was 20.”