AGING

Progressive loss of function
Reduced survival capacity, increased morbidity and death probability

Mean life span:

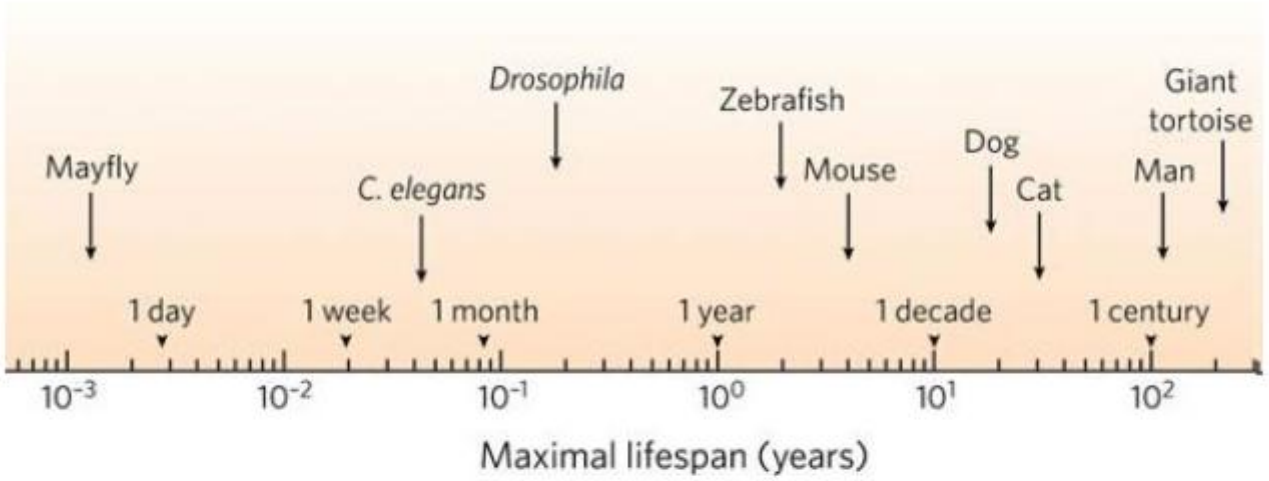
paleolithic	20 yr	
middle age	30 yr	
1880	36 yr	
1900	**46 yr (4% ≥ 65 anni)**	
nowadays	**80 (♂) - 84 (♀)**	
people ≥ 65 yr	4%	1900
	> 12%	1990
	>20% projection to 2020	
people ≥ 85 yr	10%	2000 (age range that is actively increasing)

Max life span estimated 115-120 yr (on a genetic basis)

Late aging: populations characterized by long life span (Caucasus and Andes)

A. genetic program
B. errors and/or toxic metabolite accumulation
(cf. accelerated metabolism and short life span in little animals)

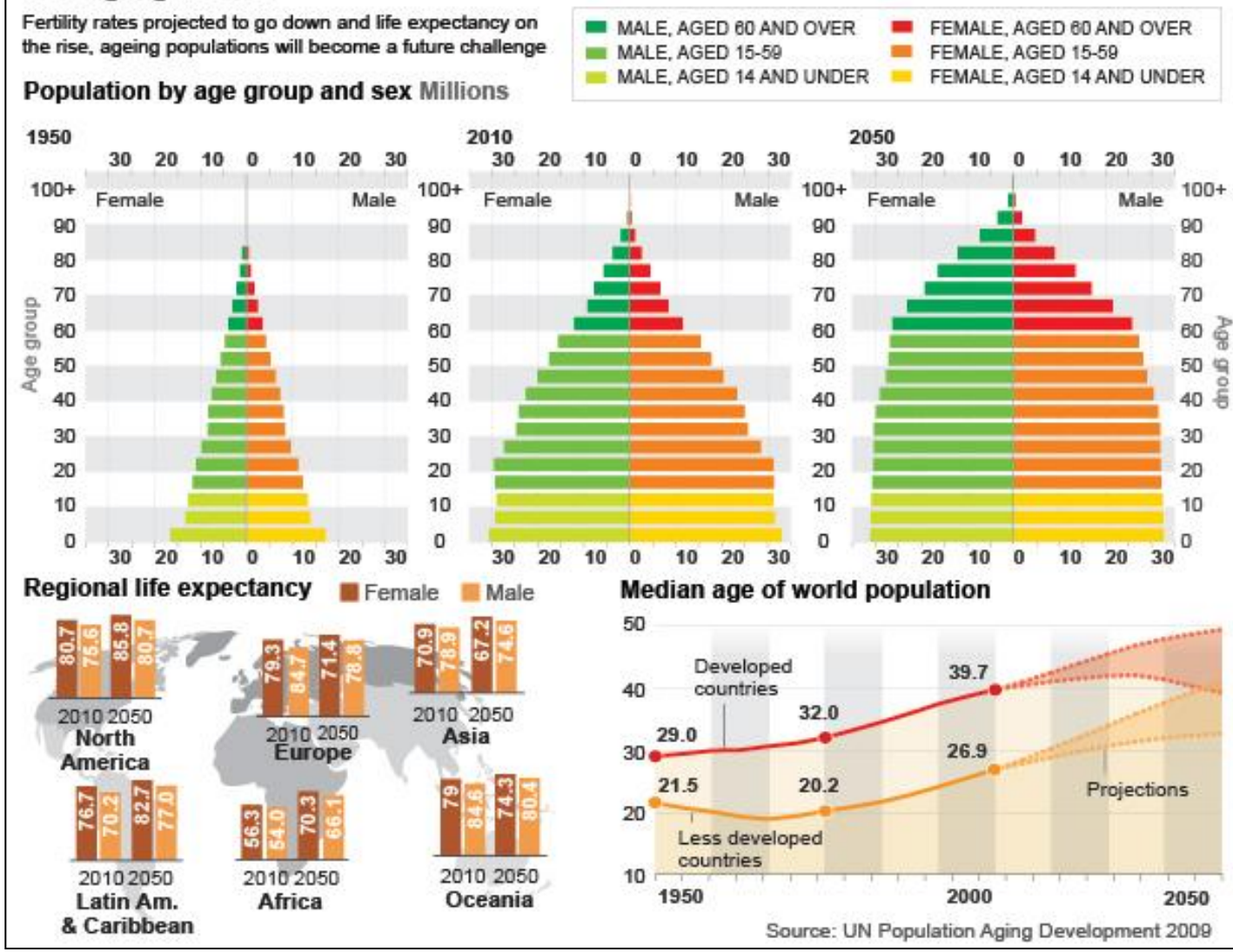
Variation of maximal lifespan across species



Range of maximal lifespans at the extremes (mayfly and giant tortoise), in some of man's favourite pets (dog and cat) and experimental animals (*Caenorhabditis elegans*, *Drosophila*, zebrafish and mouse), and in man himself.

An aging world

Fertility rates projected to go down and life expectancy on the rise, ageing populations will become a future challenge



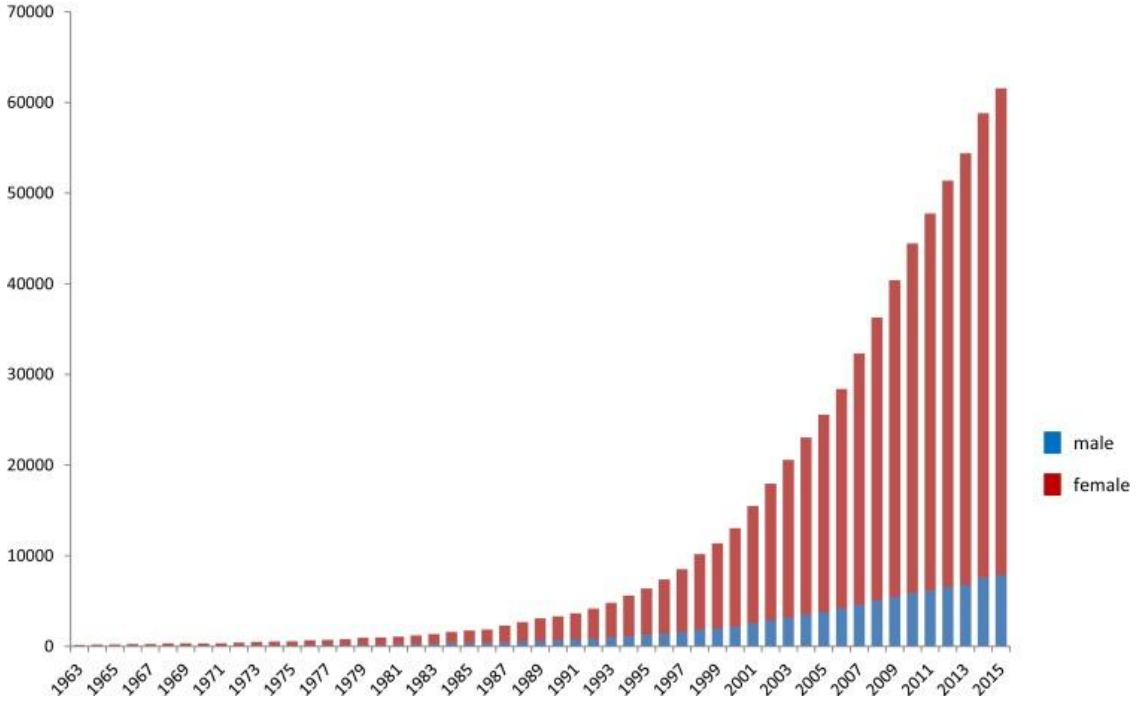


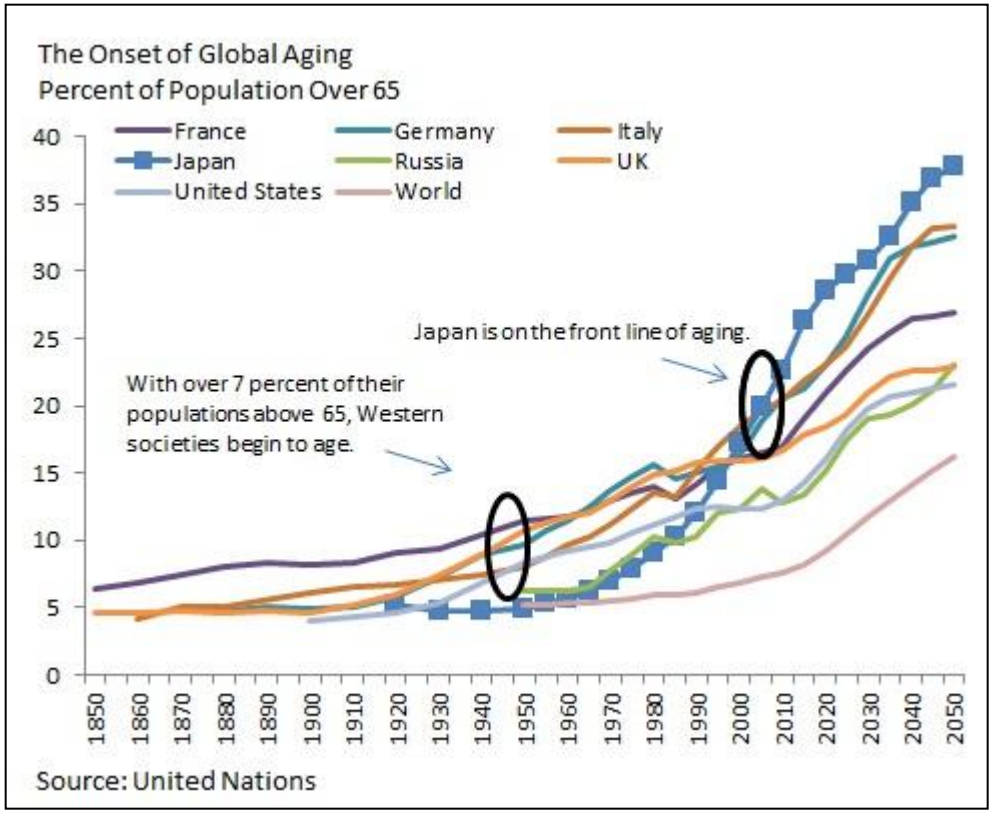
Fig. 1. The figure is constructed according to data published by the Ministry of health, Labor, and Welfare (http://www.mhlw.go.jp/stf/houdou/0000097089.html).

Yasumichi Arai, Takashi Sasaki, Nobuyoshi Hirose

Demographic, phenotypic, and genetic characteristics of centenarians in Okinawa and Honshu, Japan: Part 2 Honshu, Japan

Mechanisms of Ageing and Development, 2017, Available online 16 February 2017

http://dx.doi.org/10.1016/j.mad.2017.02.005


The Onset of Global Aging
Percent of Population Over 65
France
Germany
Italy
Japan
Russia
UK
United States
World
Japan is on the front line of aging.
With over 7 percent of their populations above 65, Western societies begin to age.
40
35
30
25
20
15
10
5
0
1850
1860
1870
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
2030
2040
2050
Source: United Nations

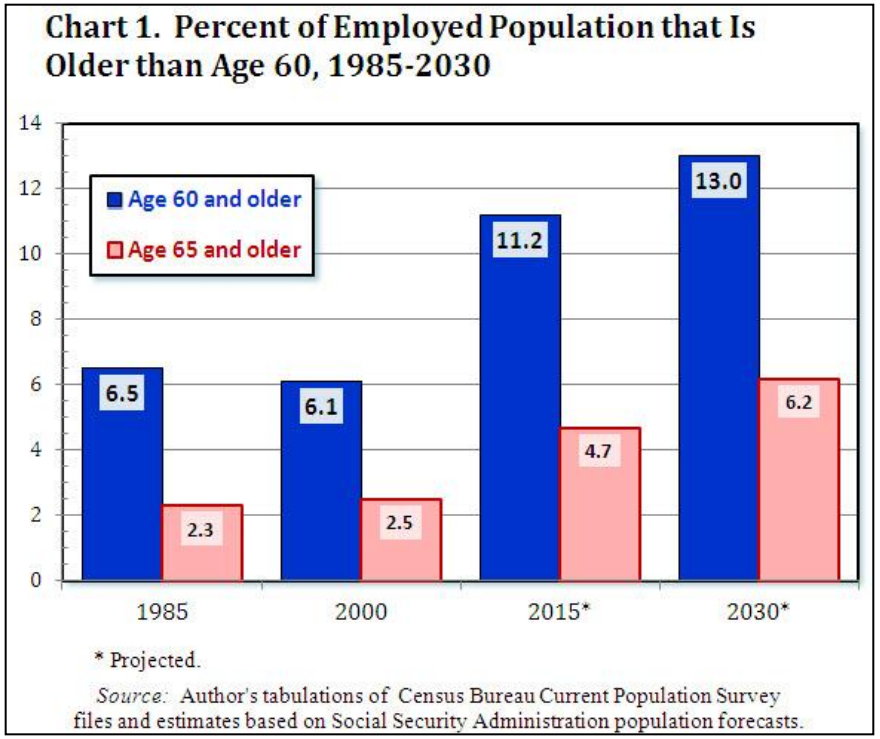
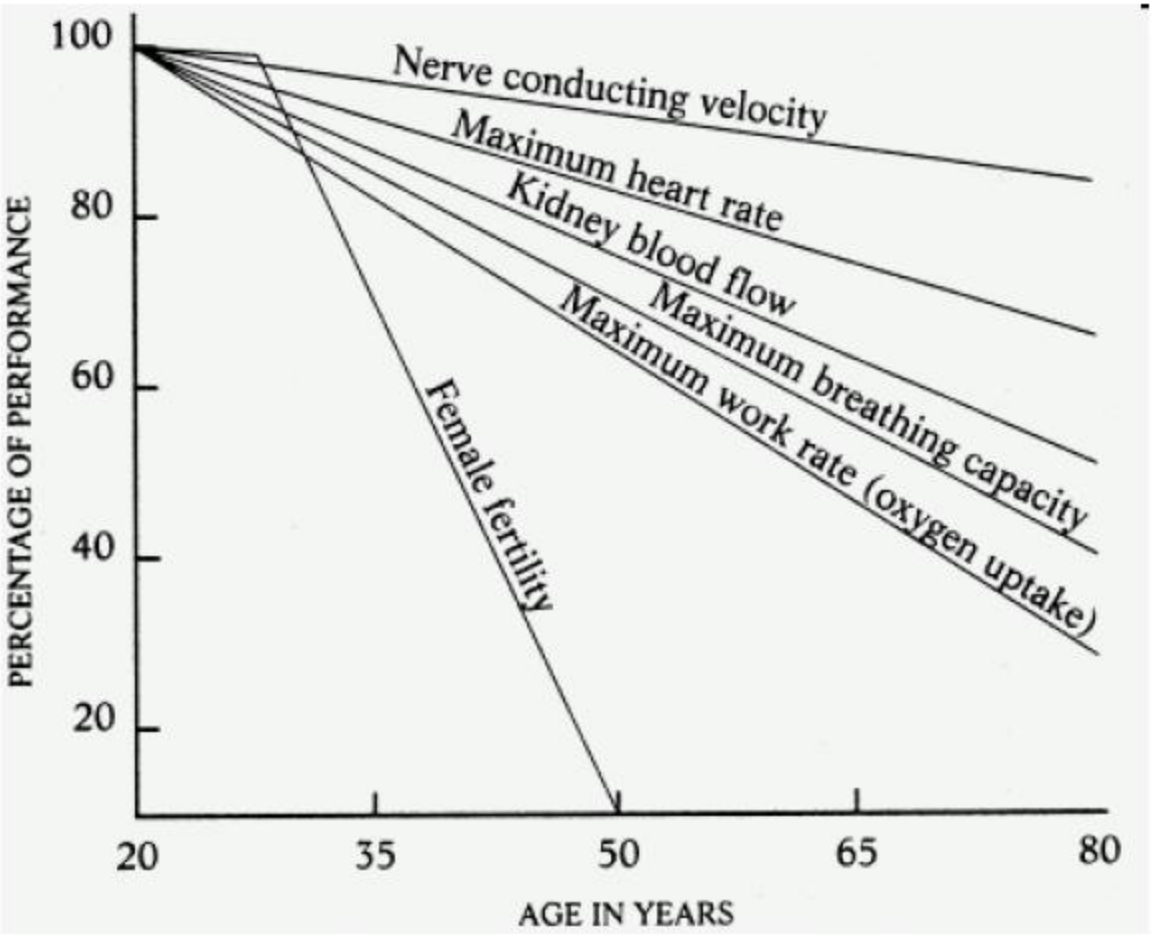


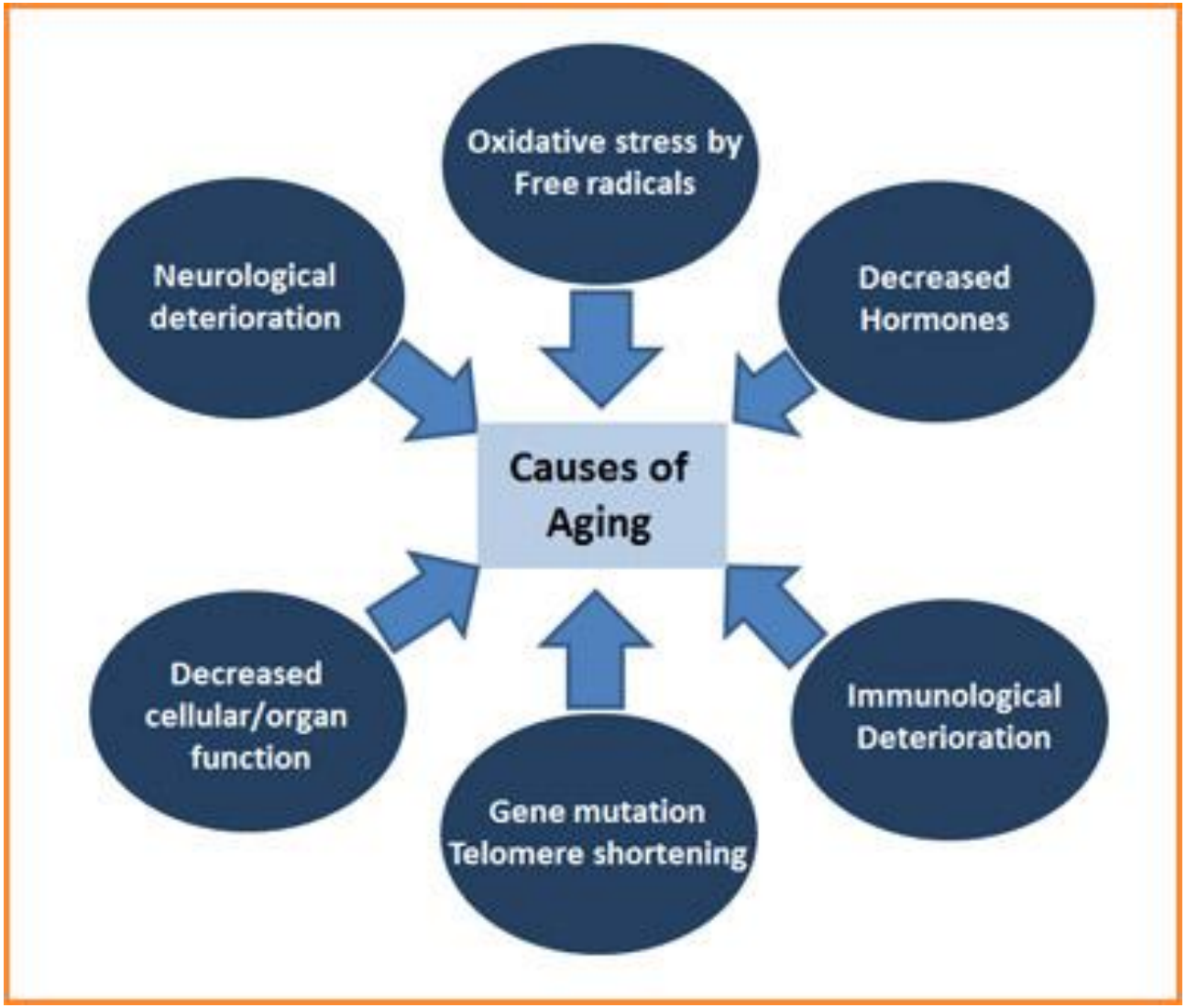
Chart 1. Percent of Employed Population that Is Older than Age 60, 1985-2030
Age 60 and older
Age 65 and older
14
12
10
8
6
4
2
0
6.5
2.3
6.1
2.5
11.2
4.7
13.0
6.2
1985
2000
2015*
2030*
* Projected.
Source: Author's tabulations of Census Bureau Current Population Survey files and estimates based on Social Security Administration population forecasts.

The hallmarks of aging

Cell, 2013

Vital function




Oxidative stress by Free radicals
Neurological deterioration
Decreased Hormones
Causes of Aging
Decreased cellular/organ function
Immunological Deterioration
Gene mutation Telomere shortening

Aging and senescence (not synonyms)

Age

chronologic

biologic

Senescence

result of functional deficit

Cell types

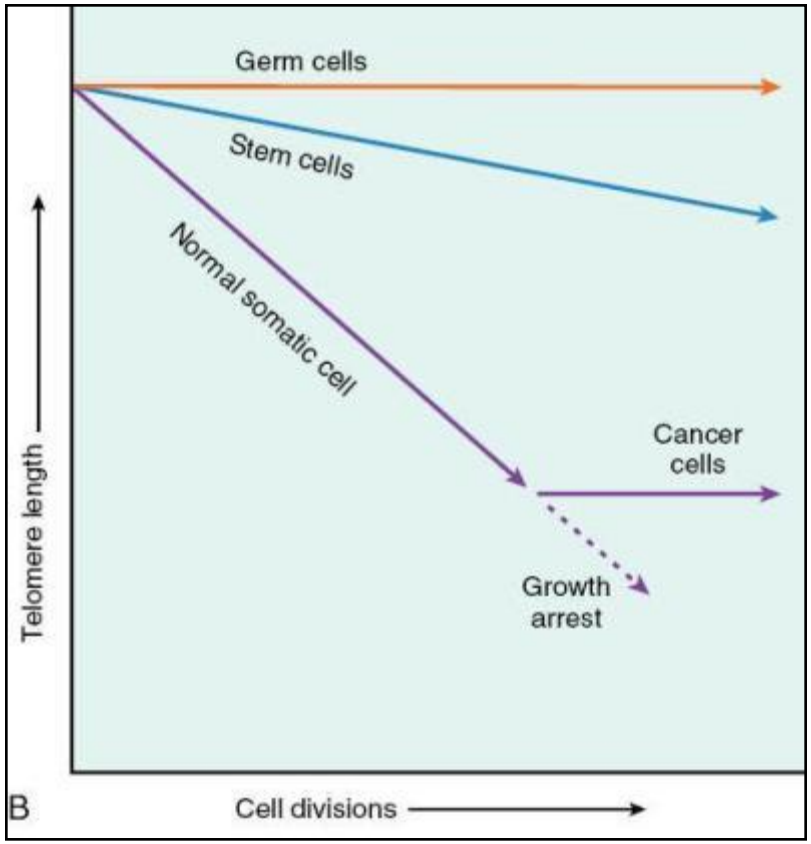
germ

somatic

stem

No aging in cancer cells

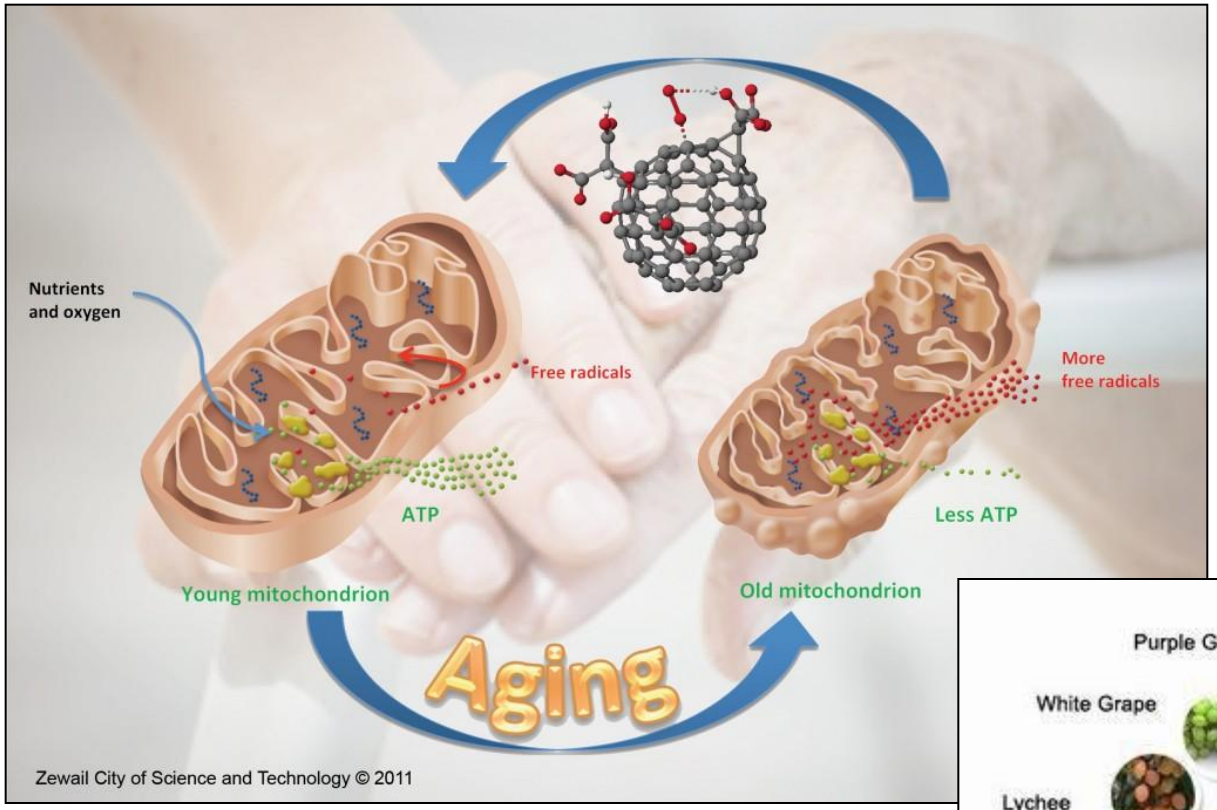
Aging of extracellular components

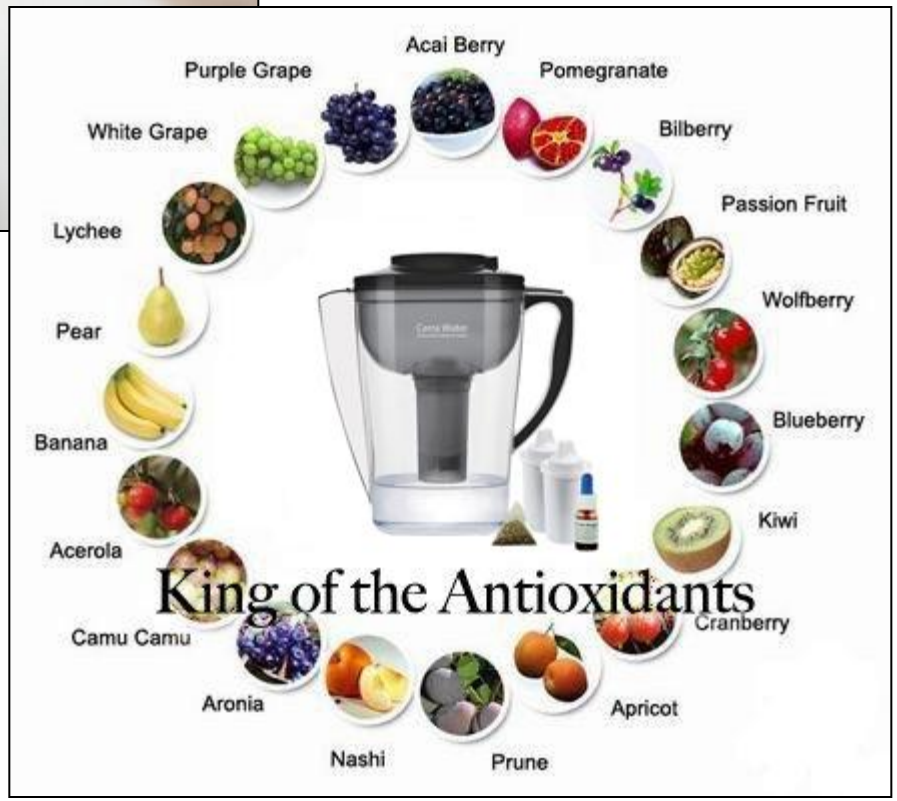


Robbins and Cotran, VIII ed.

FIGURE 1–38B The role of telomeres and telomerase in replicative senescence of cells. **A,** Telomerase directs RNA template-dependent DNA synthesis, in which nucleotides are added to one strand at the end of a chromosome. The lagging strand is filled in by DNA polymerase. **B,** Telomere-telomerase hypothesis and proliferative capacity of cells. Telomere length is plotted against the number of cell divisions. Germ cells and stem cells both contain active telomerase, but only the germ cells have sufficient levels of the enzyme to stabilize telomere length completely. In normal somatic cells there is no telomerase activity, and telomeres progressively shorten with successive cell divisions until growth arrest, or senescence, occurs. Telomerase activation in cancer cells counteracts the telomere shortening that limits the proliferative capacity of normal somatic cells.

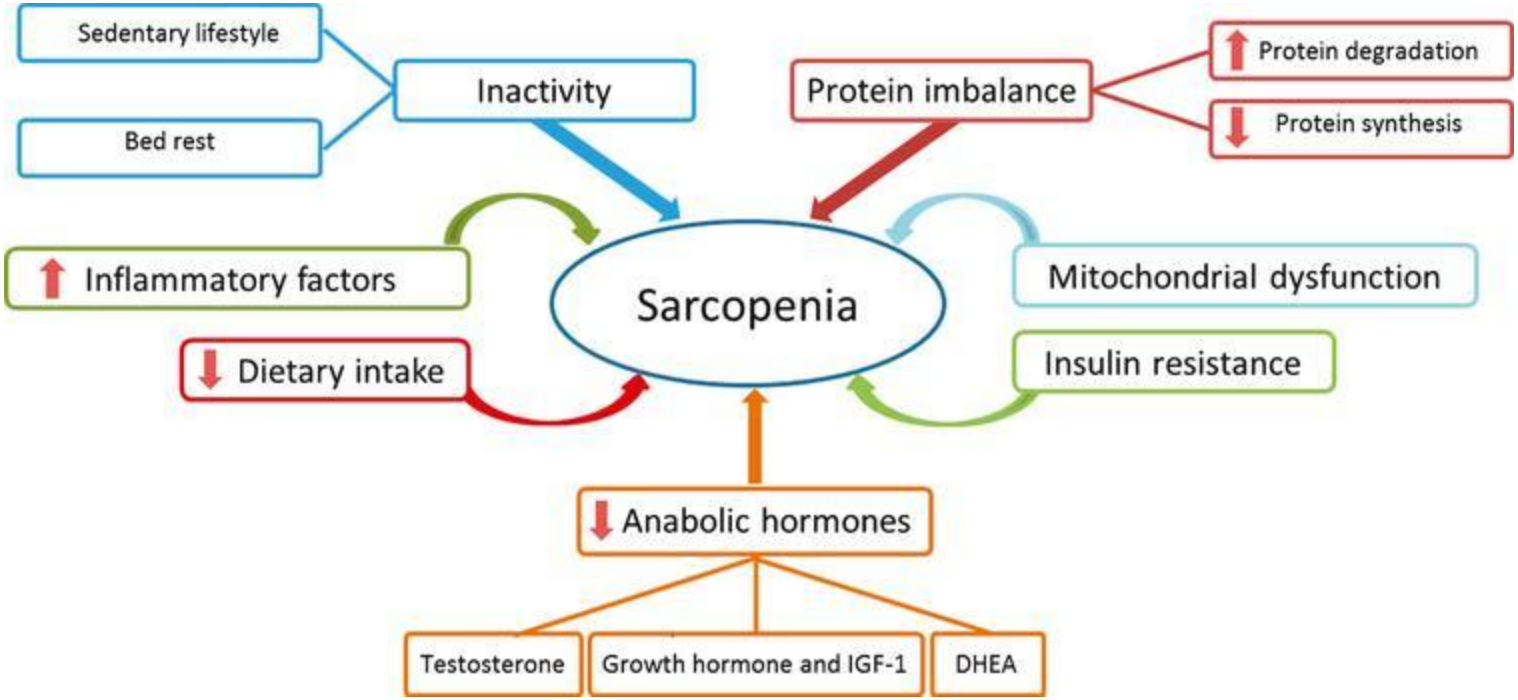
(Modified and redrawn with permission from Holt SE, et al: Refining the telomere-telomerase hypothesis of aging and cancer. Nat Biotechnol 14:836, 1996. Copyright 1996, Macmillan Magazines Limited.)


Nutrients
and oxygen
Free radicals
ATP
Young mitochondrion
More
free radicals
Less ATP
Old mitochondrion
Aging
Zewail City of Science and Technology © 2011


Acai Berry
Purple Grape
Pomegranate
White Grape
Bilberry
Passion Fruit
Lychee
Wolfberry
Pear
Blueberry
Banana
Kiwi
Acerola
King of the Antioxidants
Cranberry
Camu Camu
Aronia
Apricot
Nashi
Prune

CHARACTERISTICS

non fatal processes	↓ sex hormone production
	↓ efficiency of cell-mediated immunity
	arthritis/osis
	ostheoporosis
	asthenia
	presbyopia (↑ crystalline rigidity)
	cataract (crystalline opacity)
	hearing impairment
	systemic senile amyloidosis
	fibrosis
	cerebral amyloidosis
diseases	neoplasia
	late onset diabetes (type II)
	autoimmune phenomena
	liver cirrhosis
	Parkinson
other	incidents
	atherosclerosis
	hypertension
	CNS vaculopathies
	vascular nephropathies
	respiratory infections



Farnaz et al., 2016

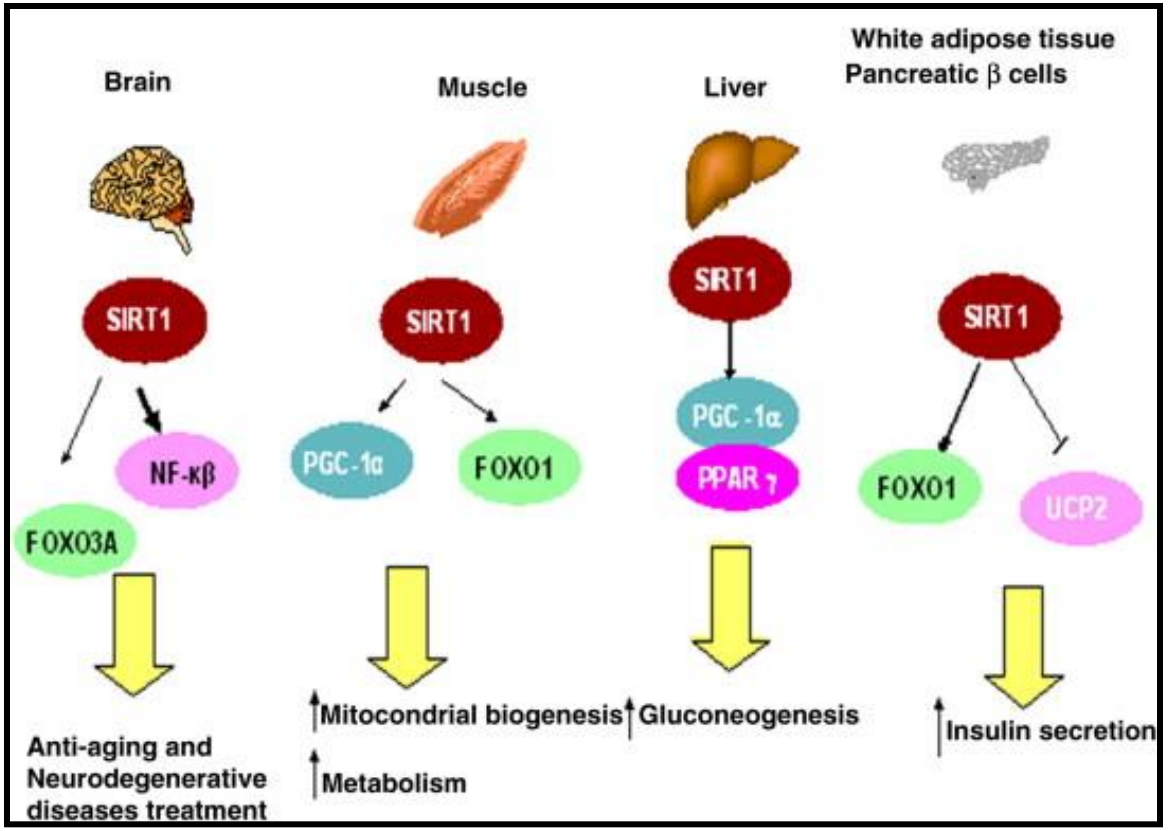


Fig. 1. SIRT1 produces different outputs as a result of different stimuli. Activation of SIRT 1 to the brain causes an increase in the expression of the transcription factor FOXO 3A with antiaging properties. Besides an increase in NF transcription factor may explain, among others, the neuroprotective properties of SIRT1. SIRT1 protects pancreatic cells and muscle cells against stress-induced apoptosis by increasing activity of the forkhead protein FOXO1. In the liver, SIRT1 deacetylases the coactivator PGC-1α, thereby increasing the expression of genes for gluconeogenesis. In the muscles, the effect of SIRT1 on FOXO1 increases mitochondrial biogenesis and insulin secretion (Camins et al., 2010).

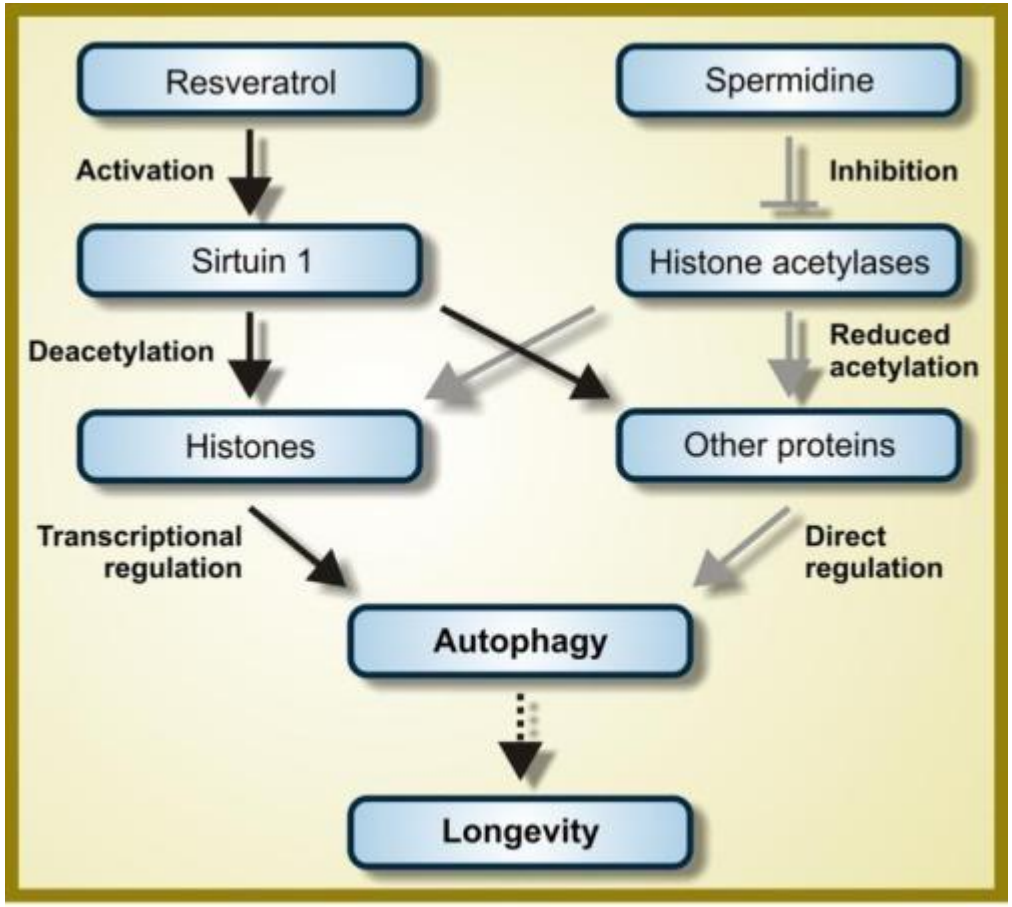
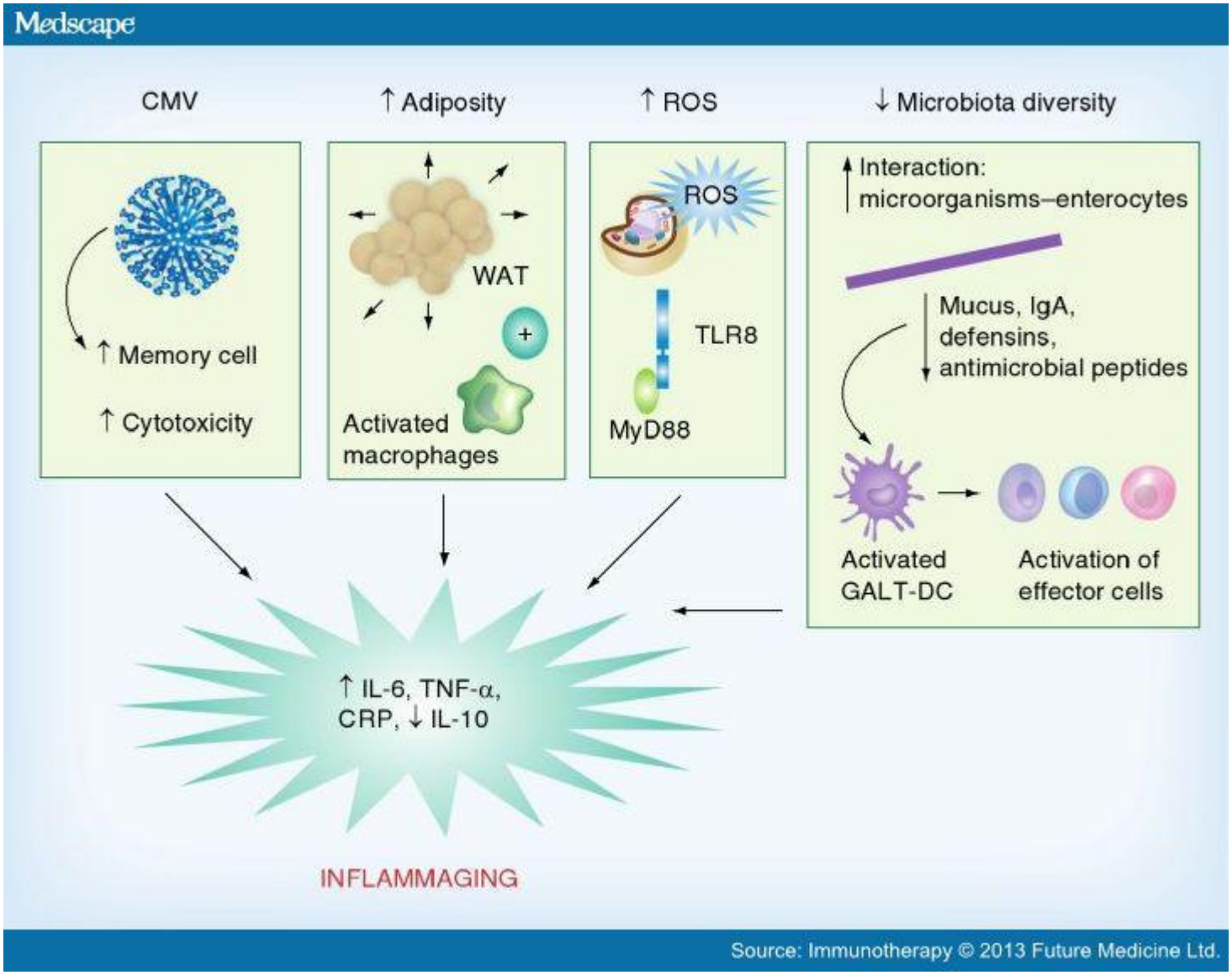
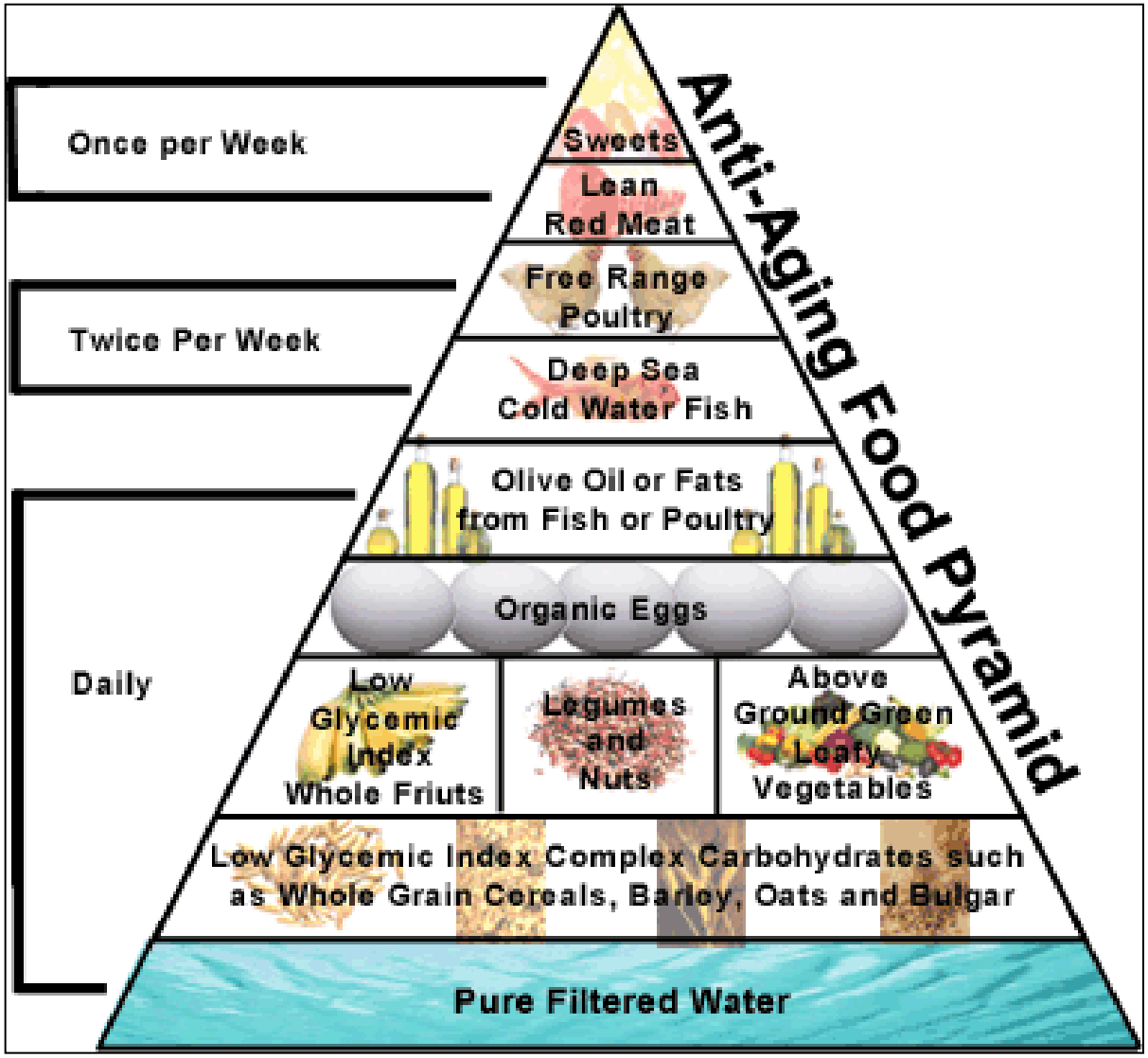
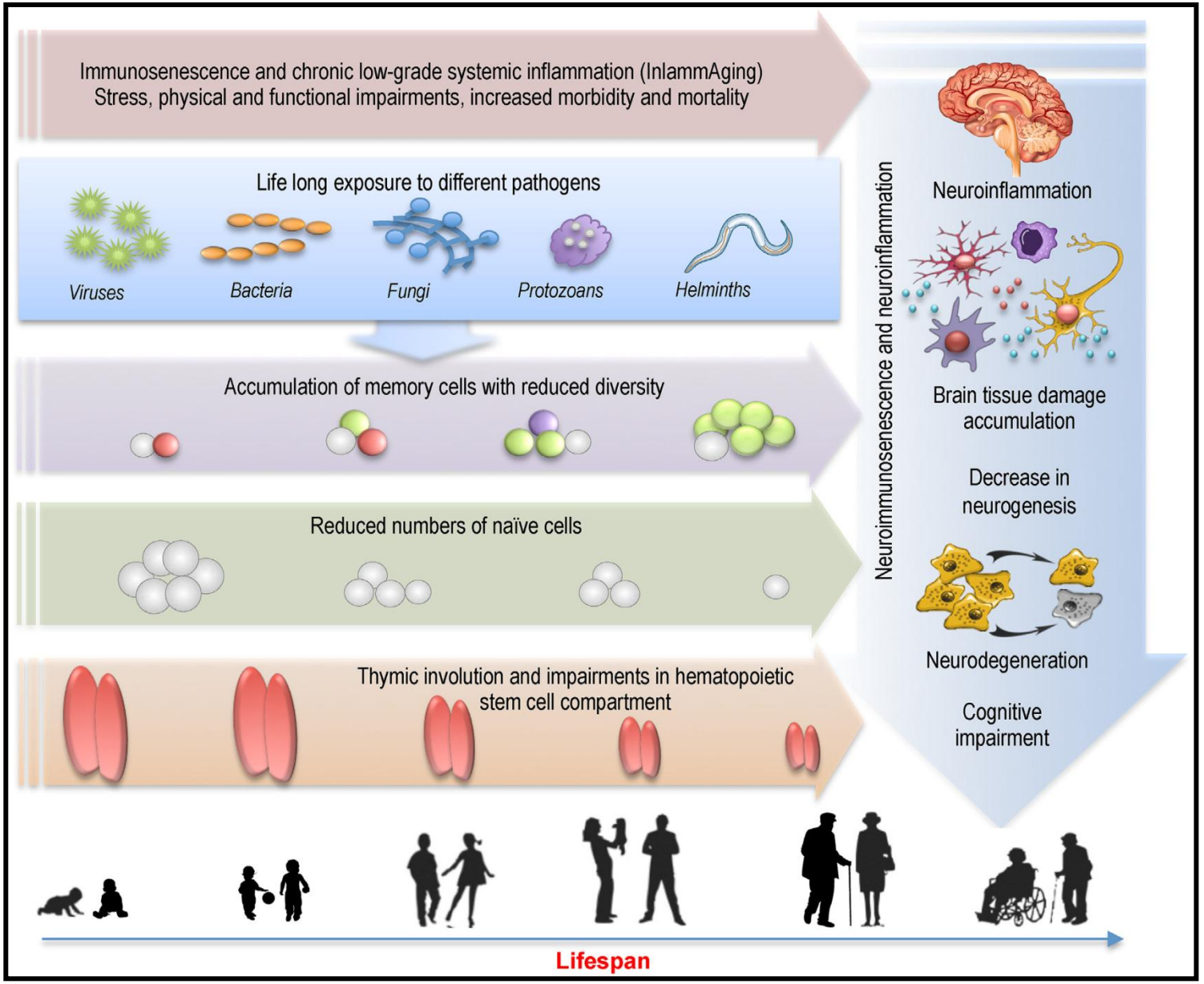


Figure 2. Hypothetical mode of action of resveratrol and spermidine as autophagy inducers. While resveratrol functions as an activator of the deacetylase Sirtuin 1, spermidine inhibits one or several histone acetylases. Therefore, both resveratrol and spermidine are expected to favor protein hypoacetylation. However, the autophagy-relevant substrates whose deacetylation is induced by resveratrol and spermidine are not fully characterized and it is even not known if they are completely distinct, partially overlapping or identical (Morselli et al., 2009).

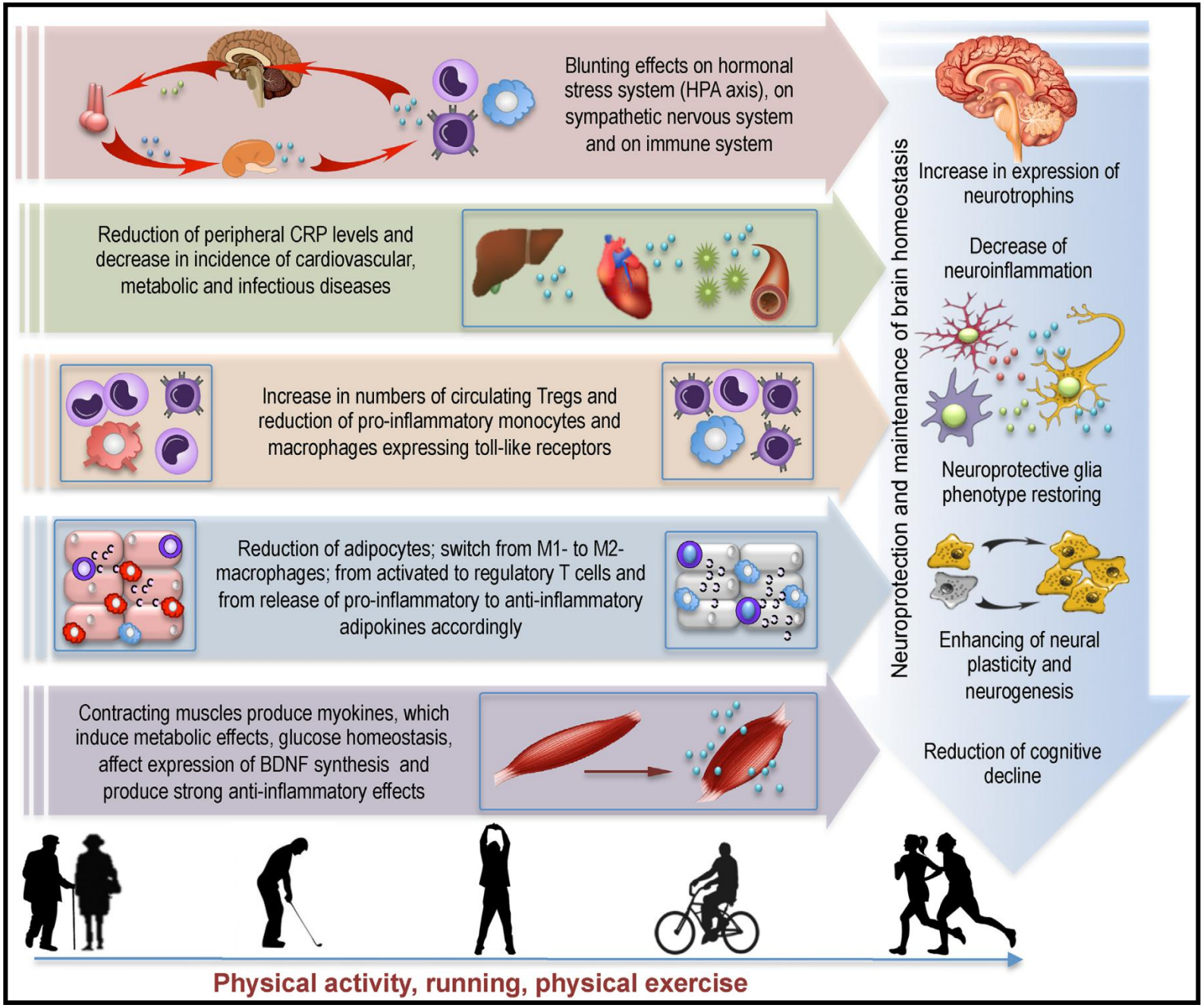
INFLAMMAGING




Anti-Aging Food Pyramid
Once per Week
Twice Per Week
Daily
Sweets
Lean Red Meat
Free Range Poultry
Deep Sea Cold Water Fish
Olive Oil or Fats from Fish or Poultry
Organic Eggs
Low Glycemic Index Whole Friuts
Legumes and Nuts
Above Ground Green Leafy Vegetables
Low Glycemic Index Complex Carbohydrates such as Whole Grain Cereals, Barley, Oats and Bulgar
Pure Filtered Water



Di Benedetto et al., 2017



Di Benedetto et al., 2017

PATHOLOGICAL AGING

Early aging syndromes
- **Progeria (Hutchinson-Guilford)** early death due to cardiac and cerebrovascular diseases
- **Werner syndrome** early telomer shortening, altered Homologous Recombination Repair (HRR)
- **Down syndrome** trisomia cr. 21 (neurodegenerative lesions and other deficits)
- **Alzheimer disease** (neurodegenerative lesions)

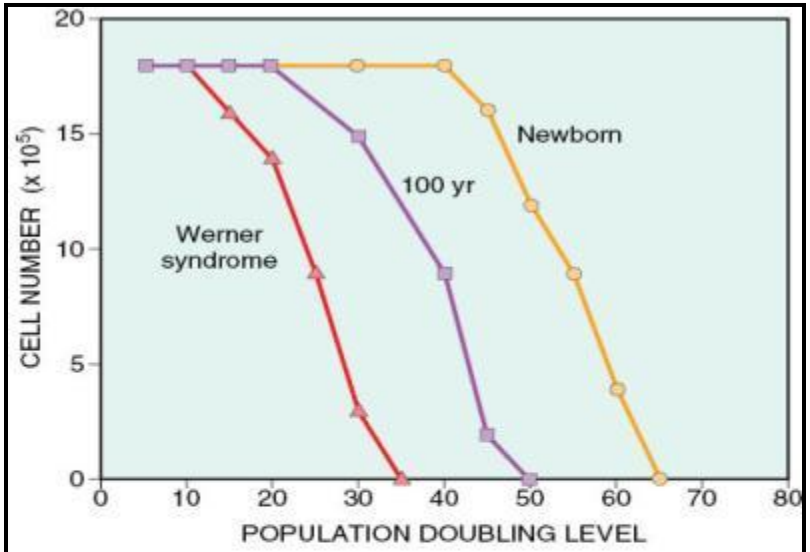


FIGURE 1–37 Finite population doublings of primary human fibroblasts derived from a newborn, a 100-year-old person, and a 20-year-old patient with Werner syndrome. The ability of cells to grow to a confluent monolayer decreases with increasing population-doubling levels.

(From Dice JF: Cellular and molecular mechanisms of aging. Physiol Rev 73:150, 1993.)

Werner syndrome (adult progeria)

Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

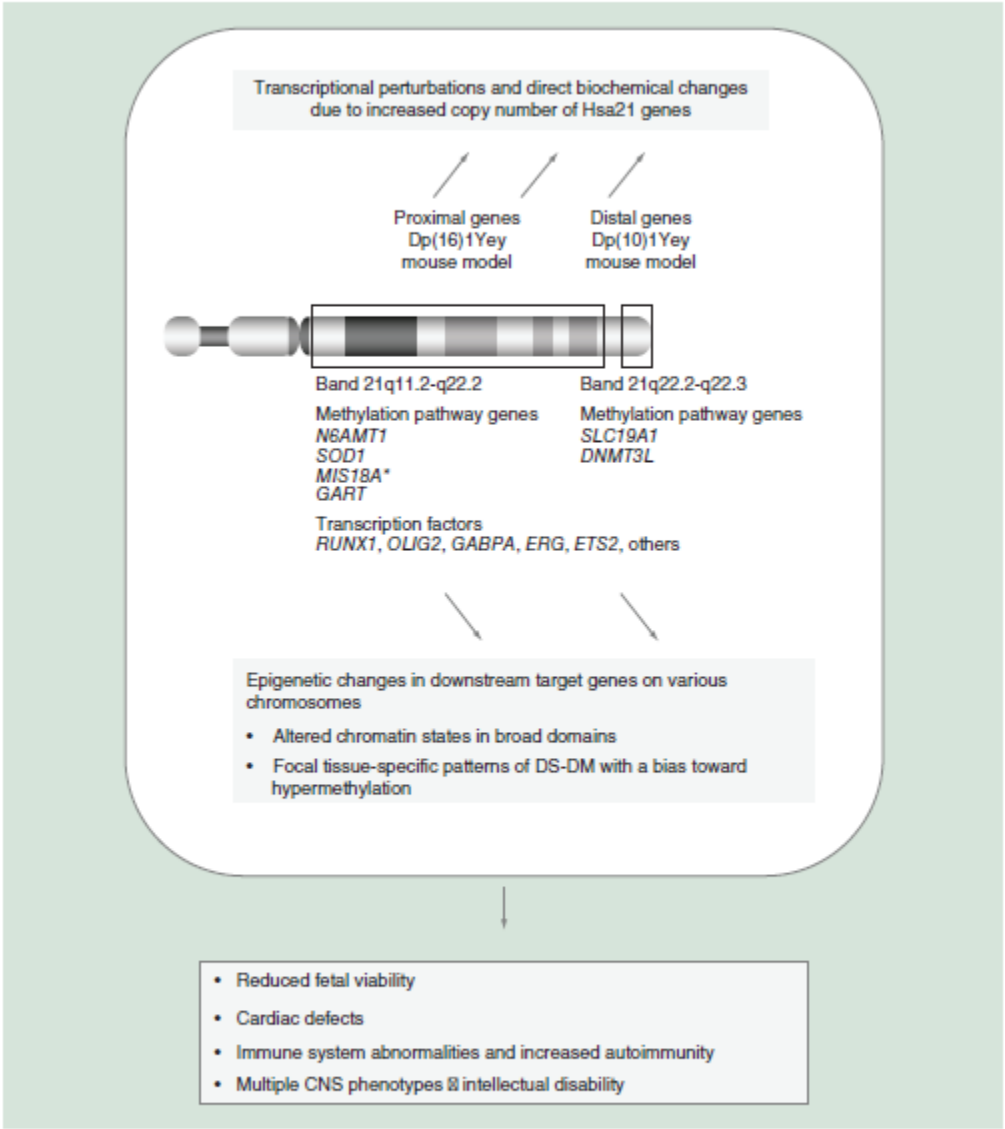


Figure 1. Chromosomal aneuploidies and disease pathogenesis: role of trans-acting epigenetic effects. Diagram of chromosome 21 (Hsa21), which is trisomic in Down syndrome. Effector genes on the triplicated Hsa21 act on downstream target genes, mostly on other chromosomes, both by acute transcriptional effects and via epigenetic effects, including alterations in DNA methylation that can propagate to daughter cells in growing and self-renewing tissues, to produce biological phenotypes.
DS-DM: Differential CpG methylation.

Do et al., 2017

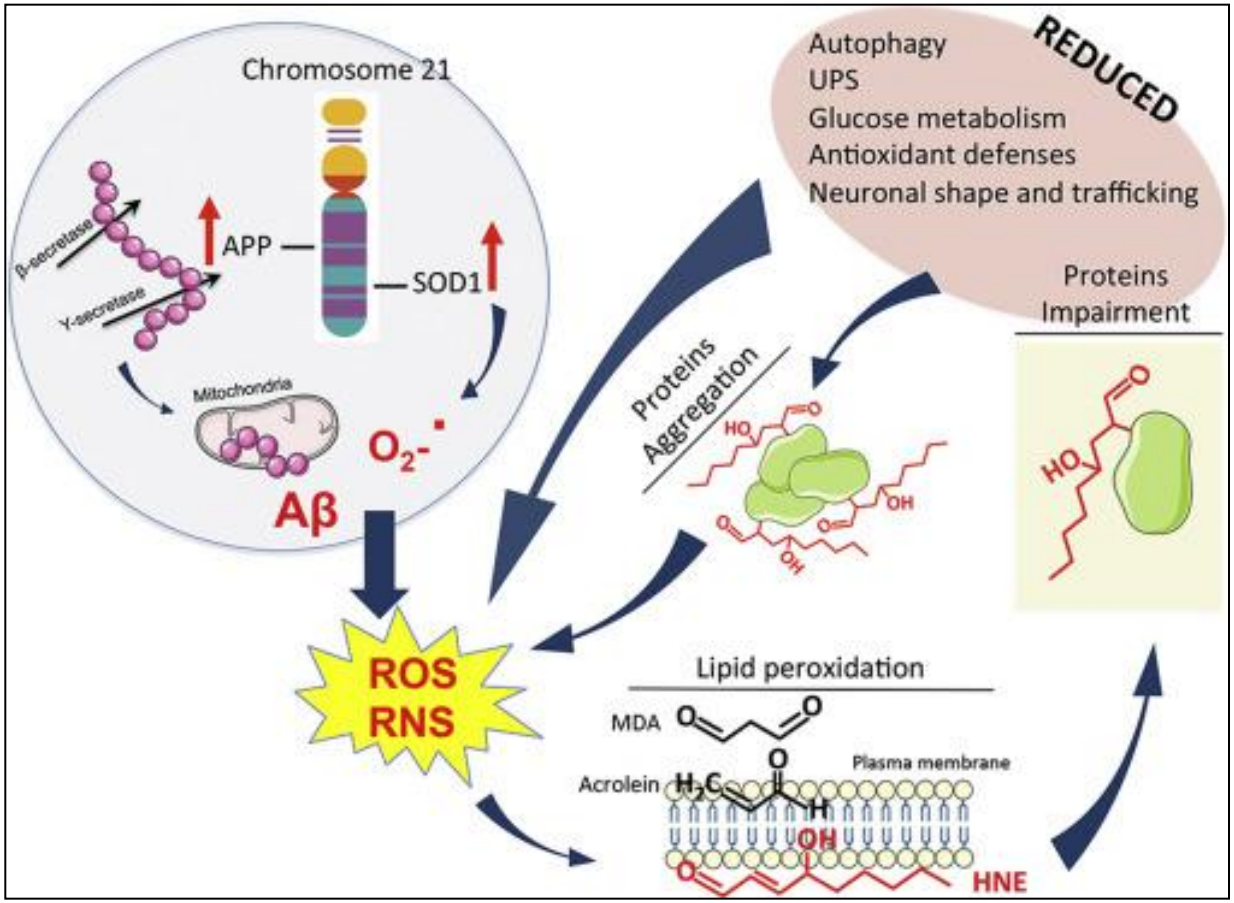


Fig. 1. Increased lipid peroxidation product HNE leads to neurotoxic effects in Down syndrome brain. Trisomy of chromosome 21 in Down syndrome (DS) brain is associated with the overexpression of a number of proteins among which are amyloid precursor protein (APP) and superoxide dismutase 1 (SOD1). Overexpression of APP and SOD1 is considered to be associated with an increased production of amyloid beta-peptide (Aβ) and superoxide anion ($O_2^{-\cdot}$), respectively. Furthermore, increased Aβ levels are able to promote mitochondrial damage and thus to sustain a further elevation of $O_2^{-\cdot}$ levels. These events are associated with an increase of both reactive oxygen species (ROS) and reactive nitrogen species (RNS), known to promote proteins and lipids peroxidation. Among the LPO products, 4-hydroxy-2-nonenal (HNE) is known to bind proteins, thus modifying protein structure and promoting proteins impairment. Proteins found to be HNE-modified in DS brain are associated with reduced: (I) autophagy; (II) unfolded protein response (UPS); (III) glucose metabolism; (IV) antioxidant defense and (V) neuronal trafficking. All these events contribute to sustain a further increase of ROS/RNS, thus amplifying a vicious cycle. In addition, HNE modifications would promote proteins aggregation, which, because the observed defects in autophagy and UPS, are less cleared from neurons. Increased protein aggregation like in the case of Aβ and SOD1, also represent an additional stimulus sustaining ROS/RNS production.

Barone et al, 2016

Fig. 1. Multifunctional role of DYRK1A. The central role of DYRK1A in controlling various physiological processes is outlined using the cartoon above.

L.J. Kay, T.K. Smulders-Srinivasan, M. Soundararajan

Chapter Six – Understanding the Multifaceted Role of Human Down Syndrome Kinase DYRK1A

Advances in Protein Chemistry and Structural Biology, Volume 105, 2016, 127–171

http://dx.doi.org/10.1016/bs.apcsb.2016.07.001

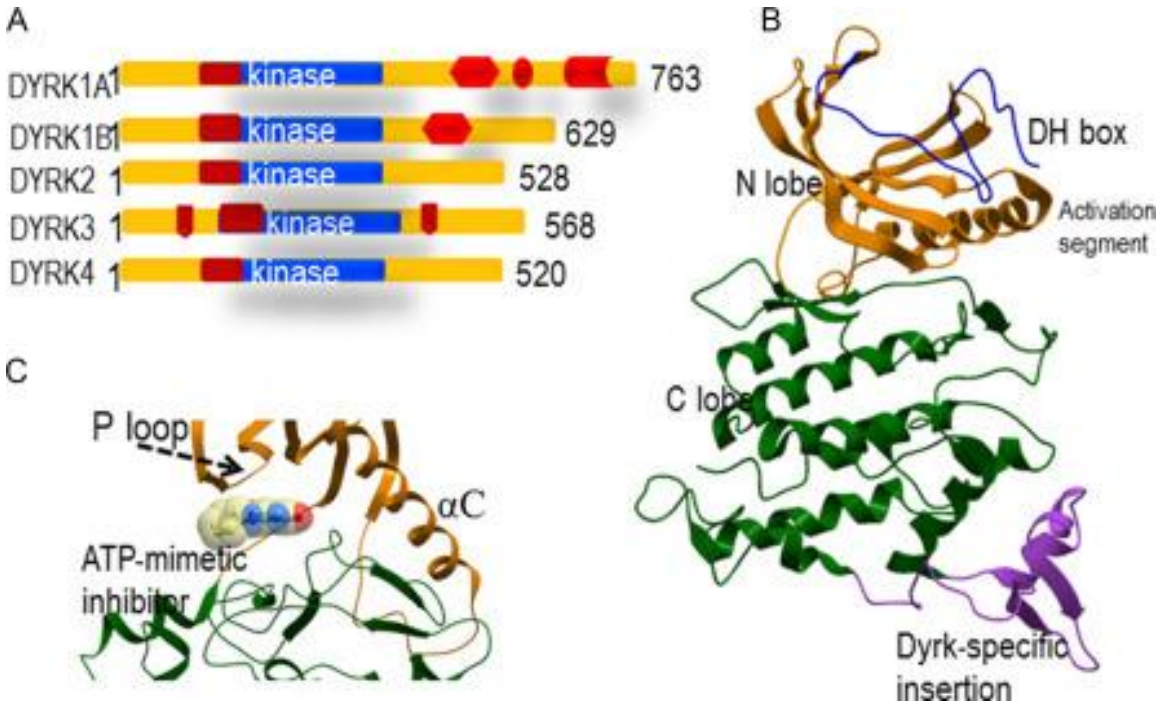


Fig. 2. The DYRK family and DYRK1A structure. (A) Domain architecture of DYRK kinases. DH domain characteristic to DYRK family is given using *red* (*gray* in the print version) *rectangles*. The PEST region is shown using *red* (*gray* in the print version) *hexagons*. *Red* (*gray* in the print version) *oval*, *cylinder*, and *pentagons* show histidine-rich region, serine/threonine-rich region, and nuclear localization sequences, respectively. (B) Overall structure of DYRK1A catalytic domain with N-terminal lobe shown in *orange* (*gray* in the print version). The C-terminal lobe is given in *green* (*dark gray* in the print version) while the DYRK-specific insert region is given in *purple* (*gray* in the print version). (C) A representative figure showing DYRK1A bound to ATP-mimetic small molecule inhibitor in the ATP-binding site in the hinge region of DYRK1A between N and C lobes. The P loop closing over the inhibitor is also shown in the figure along with activation segment αC helix.

L.J. Kay, T.K. Smulders-Srinivasan, M. Soundararajan

Advances in Protein Chemistry and Structural Biology, Volume 105, 2016, 127–171

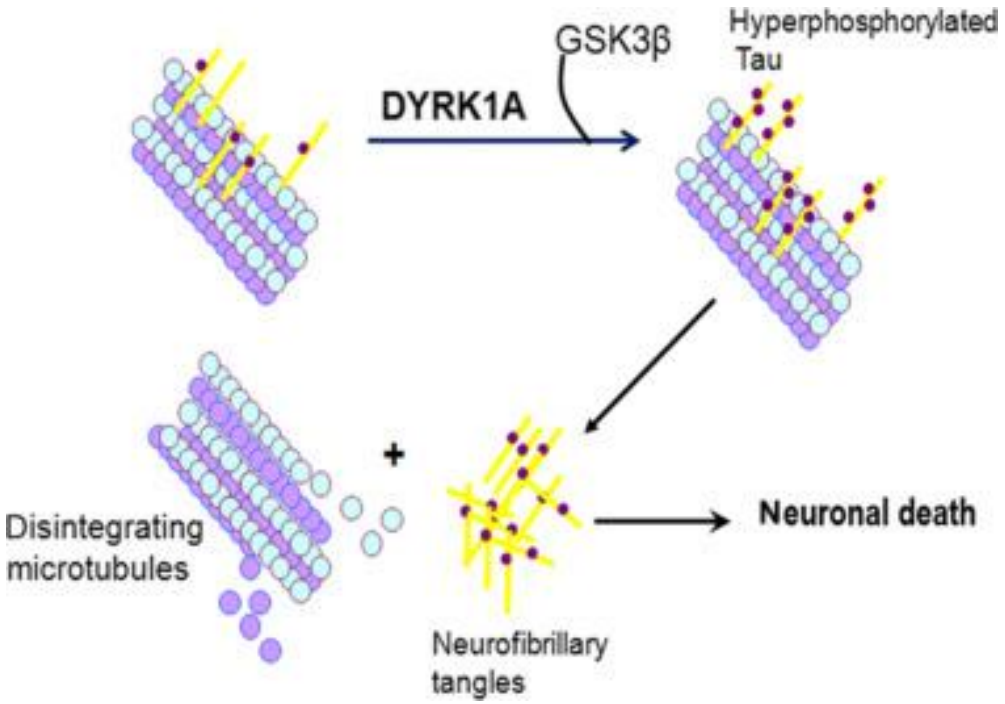


Fig. 4. Role of DYRK1A in tau hyperphosphorylation and neuronal diseases. In tauopathies, there is a reduction in the ability to bind microtubules and promote microtubule assembly. Hyperphosphorylated Tau by DYRK1A and DYRK1A-primed GSKβ contribute toward destabilized microtubule network, impaired axonal transport, results in neurofibrillary tangle (NFT) formation and eventually neuronal death. *Tau spheres* are given as *yellow* (*white* in the print version) *sticks* and the phosphorylation is shown using *small purple* (*dark gray* in the print version). Microtubule is shown using *cyan* (*white* in the print version) and *blue* (*dark gray* in the print version) *spheres*.

L.J. Kay, T.K. Smulders-Srinivasan, M. Soundararajan

Advances in Protein Chemistry and Structural Biology, Volume 105, 2016, 127–171