Biology of Aging

- **What is aging? – definition of aging**
- **Why do we age? – theories of aging**
- **How do we age? – mechanism of aging**
- **Is aging same across the tree of life?**
- **Can we cure aging?**

What is aging?

Aging: all of the time-dependent changes that occur in the molecules, cells and tissues of an organism.

Aging: the time-sequential deterioration that occurs in most animals including weakness, increased susceptibility to disease and adverse environmental conditions, loss of mobility and agility, and age-related physiological changes. Aging is usually understood to include reductions in reproductive capacity.

Term ***senescence*** is sometimes used to indicate the deteriorating effects of aging as opposed to the simple passage of time.

Life expectancy (longevity) is a statistical measure of how long a person or organism may live.

***Aging*: drop in survival probability and fertility with advancing adult age.**

Mortality in the United States in 1999 as a function of age

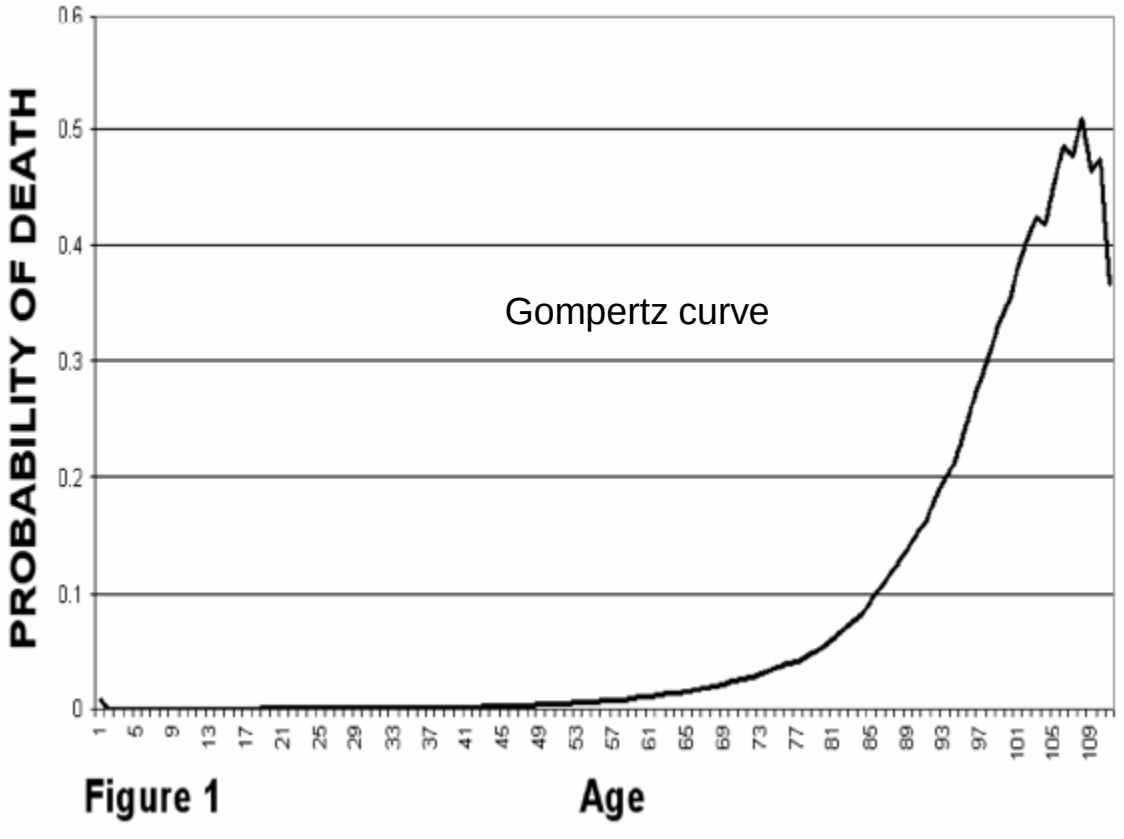


Figure 1

PROBABILIY OF DEATH = The chance of dying any given year.

Aging: the decline of cell/organ/organisms peak function that continues until its failure or death.

Table 4
Peak ages for physiological performance as clinical norms for humans (gender and race averaged, then rounded to nearest whole value)

Peak ages of physiological performance
Hearing peaks at 5 years old
Smell peaks at 10 years old
Taste peaks at 10 years old
Flexibility and balance peaks at 13 years old
Muscle strength peaks at 18 years old
Tissue repair peaks at 13 years old
Short term memory peaks at 20 years old
Creativity peaks at 4–6 years old
Immune response peaks at 13 years old
Lung capacity peaks at 20 years old

Creativity data was highly variable and best expressed in a range. Flexibility, tissue repair capacity and immune response all peaked right before puberty, after which there was a sharp decline due to sex steroids. There was a notable difference between the peak lung capacity of female (17 years) and males (21 years) because of the 3.5-year extension of bone growth in males. Peak height for females is 17 years and males is 21 years of age (Kaga and Tanaka, 1980; Schulz and Curnow, 1988; Schulz et al., 1994; Nakamura et al., 1998; Baker et al., 2003; Anton et al., 2004).

Cutler & Mattson, Ag. Res. Rev. (2006)

Why do we age?

Features of life

- life is cellular
- reproduction/replication
- homeostasis
- metabolism
- selfassembly
- ability to harvest energy
- life has history: ability to evolve

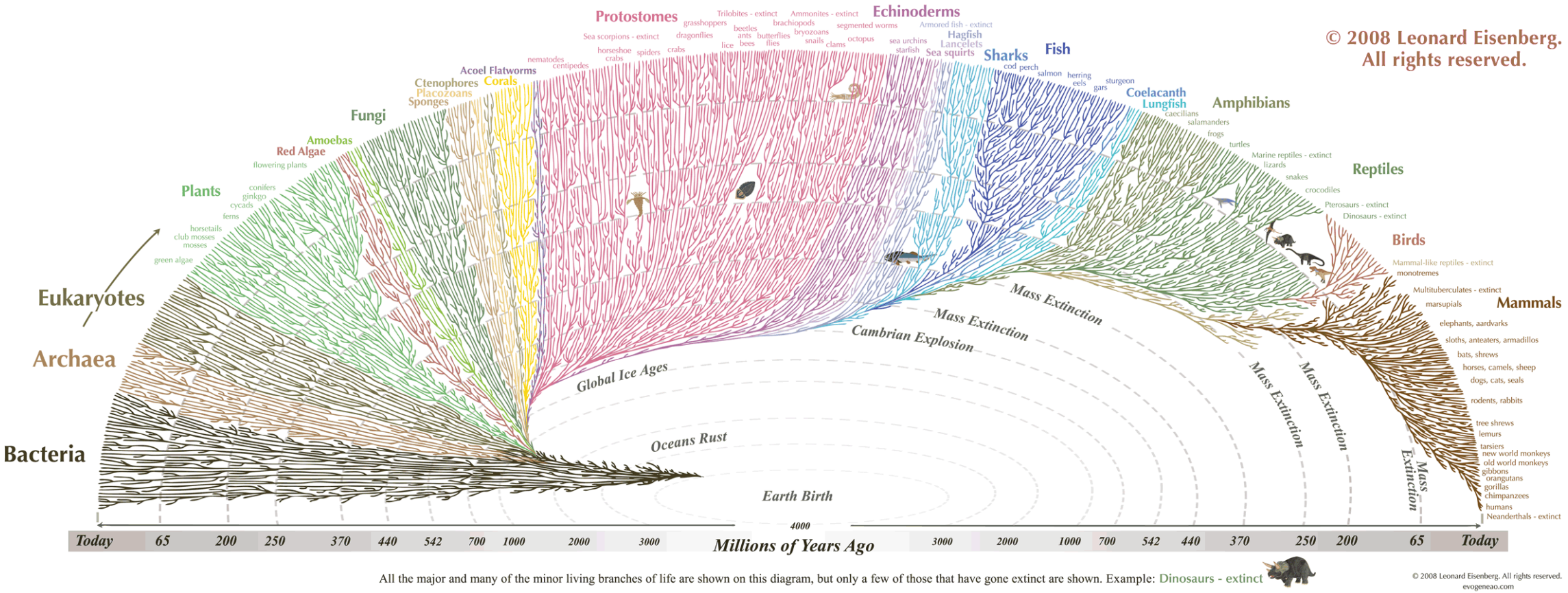
Life is very good at harvesting energy from its surroundings

In the long run, **nothing escapes the Second Law of Thermodynamics**. The pull of entropy is relentless. Everything decays. Disorder always increases.

How life defies entropy?

"The ultimate purpose of life, mind, and human striving: **to deploy energy** and information to fight back the tide of entropy and carve out refuges of beneficial order." —Steven Pinker

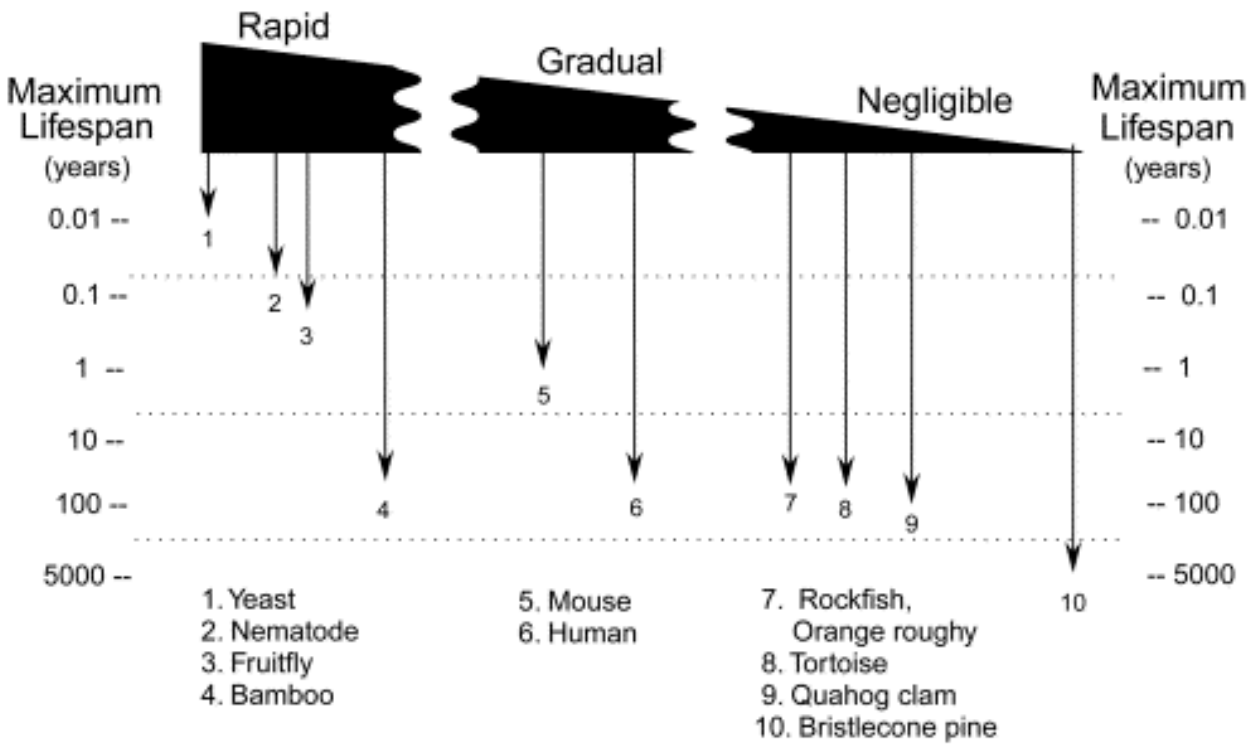
Life has history: Back to One



All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct

LUCA: last universal common ancestor

Ageing is determined genetically



Finch & Austad, Exp. Gerant. (2001)

Theories of aging

Accumulation damage theories:

The laws of entropy say that everything goes from an ordered to a less ordered state as time passes. Wouldn't aging be an example of entropy?

Weismann's theory of programmed death:

"Programmed death" was a genetically programmed, evolved characteristic, (an adaptation), and that this characteristic had evolved through natural selection because it conveyed a benefit to the species even though it had a negative effect on individual fitness.

Is aging adaptive characteristic evolved by natural selection or is it instead some fundamental property of life or some fundamental physical limitation?

- *Aging is not a defect;* it is a feature that has a purpose.
- *Aging is a defect;* it is a fundamental property of life or unavoidable side effect of necessary process.

"Unorthodox" theories of aging

advocate the hypothesis that aging is a evolved adaptation that has its purpose.

Darwin's dilemma: Since longevity was of value increasing the survival time and breeding opportunity of any organism, wouldn't natural selection (if true) result in ever-increasing longevity? Wouldn't aging, since it was obviously adverse to fitness be "selected out" by the process of natural selection? In other words, Darwin's theory predicts that animals and humans should not age (if it is indeed "genetically programmed mechanism").

These "adaptive" theories are all based on the idea that the theory of natural selection, although correct, is not complete and that therefore exceptions, additions, or expansions are possible.

Evolvability: capacity for evolution. According to Darwin, organisms evolve incrementally in tiny steps. Each generation of an evolving species is only minutely more adapted than the previous generation. A species with a shorter life span would accumulate such incremental improvements in adaptation more rapidly and therefore would have an advantage over a species with a longer life span. A species needs a life span sufficient to fully develop, breed at least once, and nurture and protect progeny (if applicable). A longer life span would have a progressively smaller survival and reproduction advantage and a progressively larger evolvability disadvantage.

Group (kin) selection: characteristics beneficial to a *group* could be selected (parallel with altruism).

The challenge effect: Animals have to pass a test in order to breed. As animals become older and weaker, they are less able to pass the challenge. However, and exceptional animal possessing a beneficial trait pass the ritual despite of aging.

Problem: how genes for aging can be selected for?

- Aging genes should be ignored by selection as their effect is manifested mostly post-reproductively
- Aging rarely occurs in nature

Goldsmith, Evolution of aging (2004)

Evolutionary theories of aging

combine natural selection with “accumulation of damage”.

The factors that cause aging are genetically transmitted but not “genetically programmed”.

Medawar’s mutation accumulation theory:

Medawar proposed that aging was caused by random mutations causing adverse aging characteristics. In effect, aging is caused by an assortment of genetic diseases, each of which has adverse symptoms only at advanced ages. The adverse mutations are only gradually selected out because of their minor negative effect on individual fitness but are replaced by new, random mutation, aging characteristics at a rate that is in equilibrium with the rate at which old adverse characteristics are selected out.

Williams’ antagonistic pleiotropy theory:

proposed that aging was caused by the combined effect of many pleiotropic genes that each had a beneficial effect in an animal’s youth but had an adverse side effect in older age. Williams predicted that species with younger age of sexual maturity and more vigorous reproduction traits would tend to have shorter life spans.

Disposable soma theory:

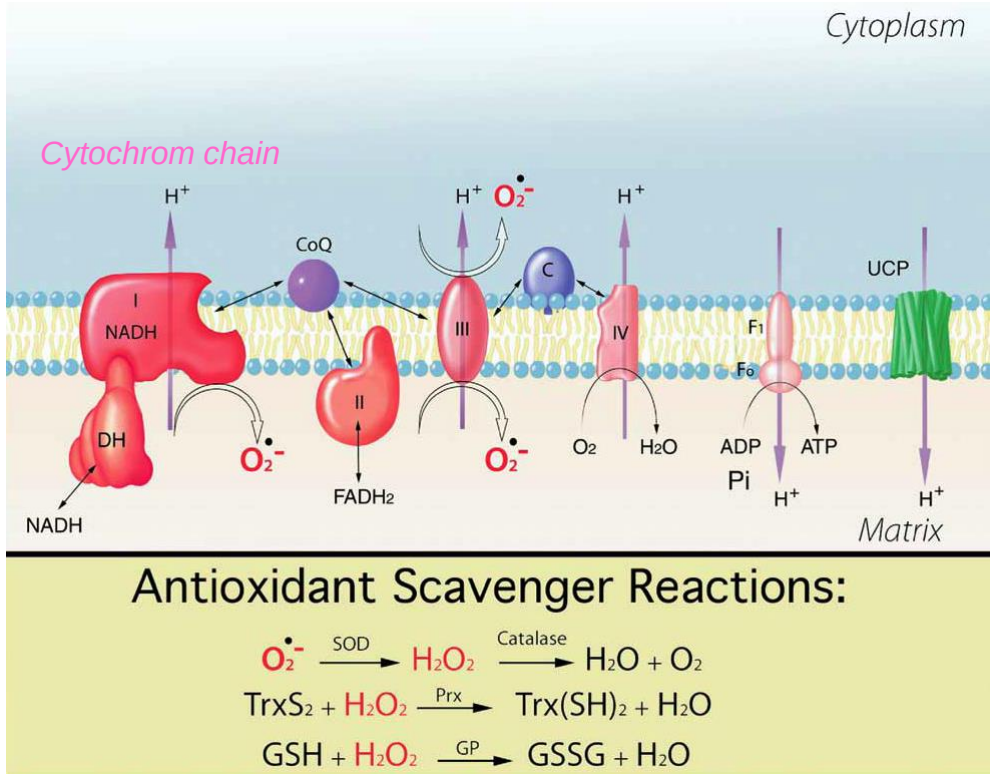
Organisms only have a limited amount of energy that has to be divided between reproductive activities and the maintenance of the non-reproductive aspects of the organism (soma). Aging is the result of natural degrading processes that result in accumulation of damage but the damage can be repaired by the organism at the expense of reproductive effort.

Aging is trade off

How do we age?

(Mechanisms of aging)

Reactive Oxygen Species
(Oxydative damage theory of aging)



Balaban et al., Cell 2005

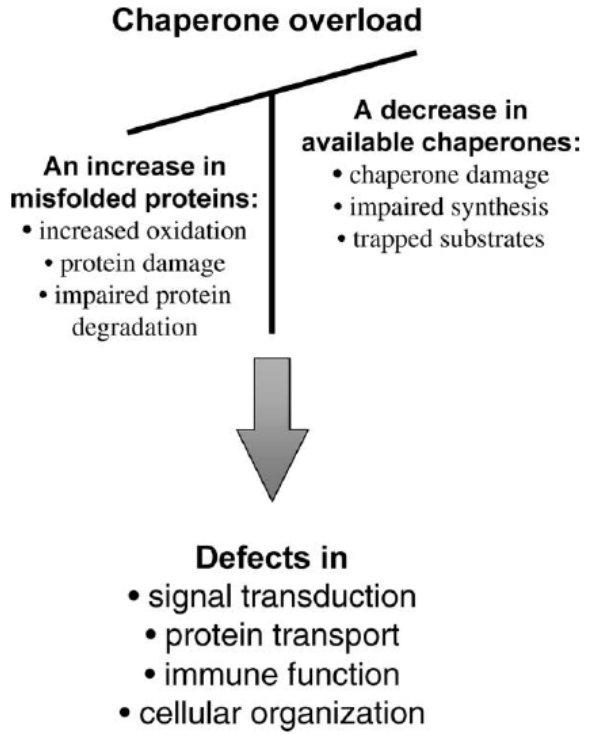
Superoxide is also produced in phagocytes by the NADPH oxydase and used to kill invading pathogenes.

Aging and molecular chaperones

In an 80-year old human, half of all proteins may become oxidized.

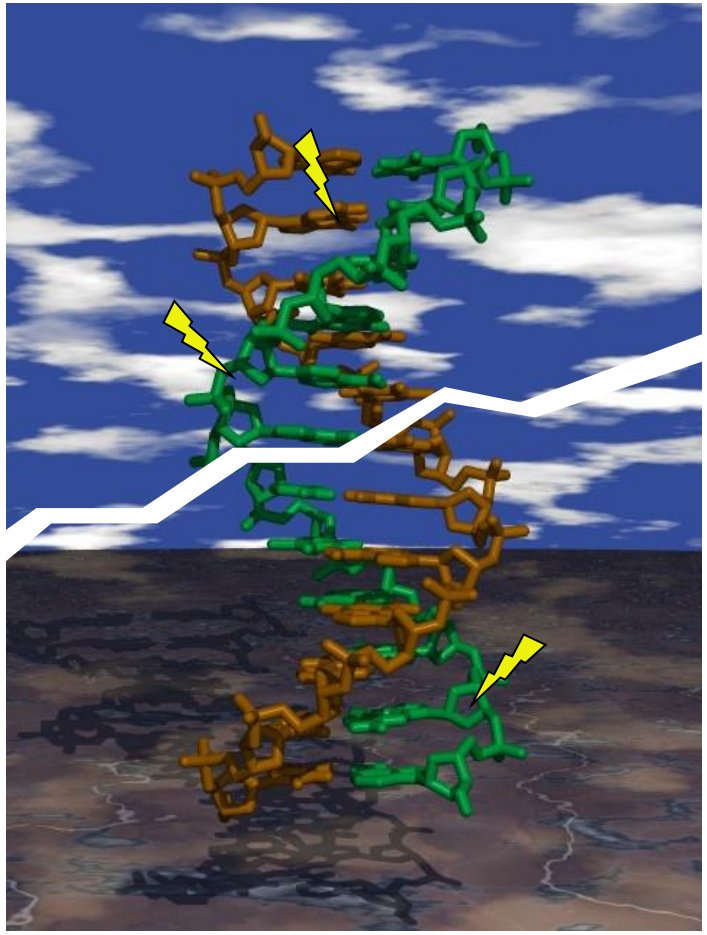
Chaperones are ubiquitous, highly conserved proteins, either assisting in the folding of newly synthesized or damaged proteins in an ATP-dependent active process or working in an ATP-independent passive mode sequestering damaged proteins for future refolding or digestion.

Performance of chaperones may decrease with aging.



Soti & Csermely, Exp. Geront. (2003)

Damage to DNA



Crude estimates of the number of DNA-damage events in single human cell range from 10^4 - 10^6 per day, which thus requires 10^{16} - 10^{18} repair events in adult human (10^{12} cells) per day.

⟶ Robust DNA repair

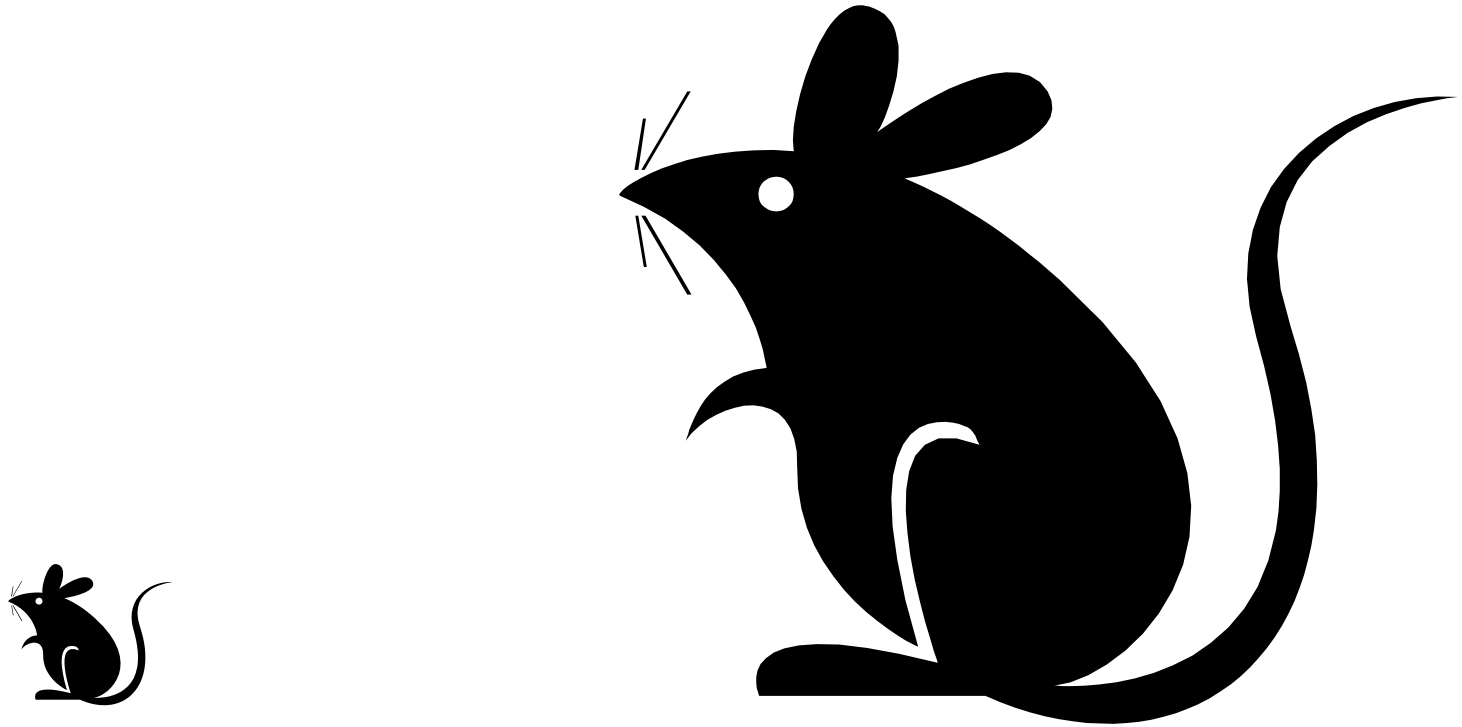
Manifestations of aging

Table 1 | Manifestations of ageing and homeostatic defences

Position in hierarchy	Manifestations of ageing	Homeostatic mechanisms/defence
Molecular changes that lead to cellular dysfunction	Cumulative mutations in nuclear and mitochondrial DNA	DNA repair activities; telomerase activity
	Oxidative damage to cellular constituents	Antioxidant enzymes, cytosolic and membrane free-radical scavengers
	Accumulation and aggregation of abnormal proteins, lipids and other macromolecular constituents	Mechanisms to recognize and degrade abnormal proteins and other macromolecules
Cellular changes that lead to tissue dysfunction	Cell death	Anti-apoptotic pathways
	Oncogenesis	Cell-cycle checkpoints, tumour-suppressor genes, apoptosis pathways
	Senescence	Immune surveillance
Tissue changes that lead to organismal dysfunction	Atrophy from cell loss and diminished regenerative capacity	Stem cells for tissue maintenance and repair
	Extracellular matrix changes	Matrix remodelling activities such as those of metalloproteinases
	Extracellular deposits	Phagocytic activities of resident and circulating cells

Rando, Nature (2006)

Stem cells and cell intrinsic mechanisms of aging

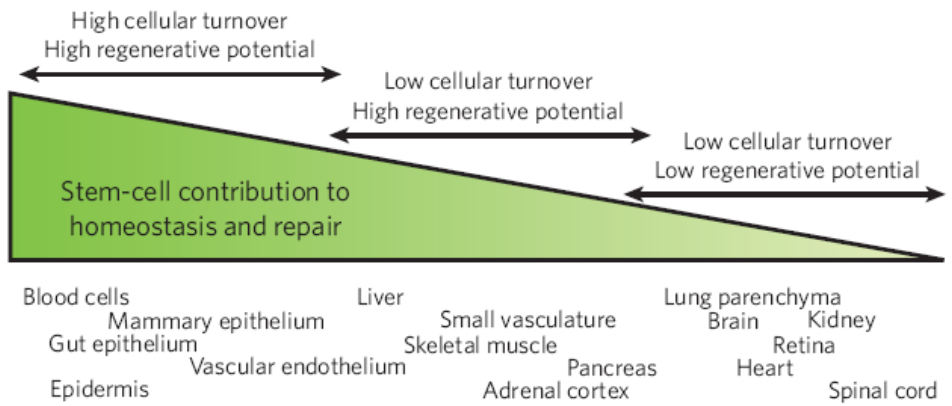


Proliferation of tissue stem cells in adult animals is mainly responsible for the maintenance of diverse tissues.

Cell intrinsic mechanisms of aging: cellular senescence

Stem cells

- Stem cells are self-renewable populations that can differentiate into single or multiple cell types.
- Depending on their origin, stem cells can be divided into two basic types: embryonic and adult.
- Cells that give rise to embryonic stem cells exist for only a short time during development and form all the tissues of the future organism.
- Embryonic stem cells are pluripotent: have a capacity to differentiate into cells from all three germ layers.
- Like cancer cells, embryonic stem cells express telomerase and have an indefinite replicative life span.
- Adult stem cells reside in adult tissues and are multipotent: differentiate into one or more of the cell types within certain tissue.
- Adult stem cells are responsible for the tissue renewal capacity of the organism.



Rando, Nature (2006)

Cell senescence and aging

Hayflick limit: Human fetal fibroblast have only finite replicative capacity *in vitro* – evidance for cellular aging *in vitro* (Hayflick, Exp. Cell Res. 1965).

The major features of the cells undergoing senescence:

- Irreversible arrest of cell division
- Resistance to apoptosis
- Secretion of variety of molecules that can drastically alter tissue environment

Animals must continuously substitute for the loss of cells, such as granulocytes, keratinocytes, hepatocytes and erytrocytes to maintain organismal homeostasis.

Increased cell senescence in populations of adult stem cells can impair tissue regeneration and contribute to organismal aging.

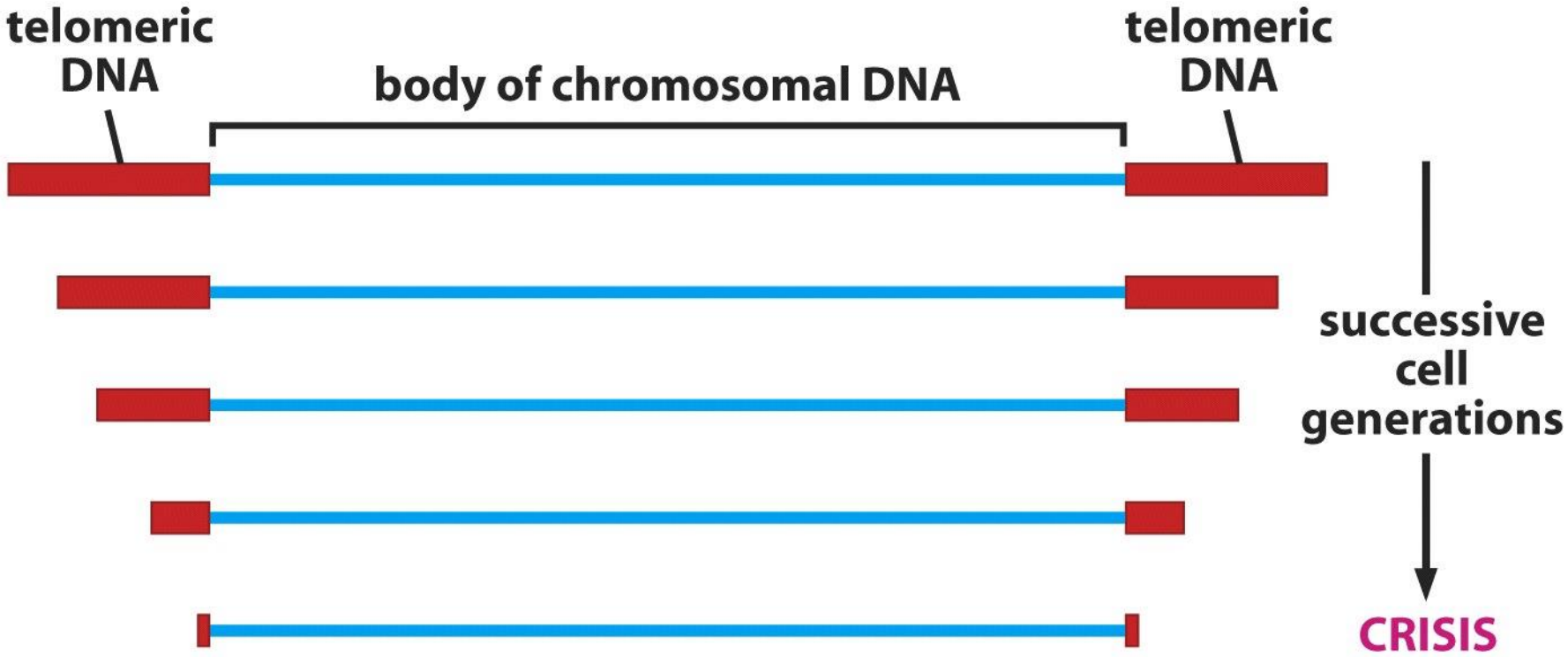


Figure 10.13b *The Biology of Cancer* (© Garland Science 2007)

Telomerase deficient mouse exhibits symptoms of premature aging

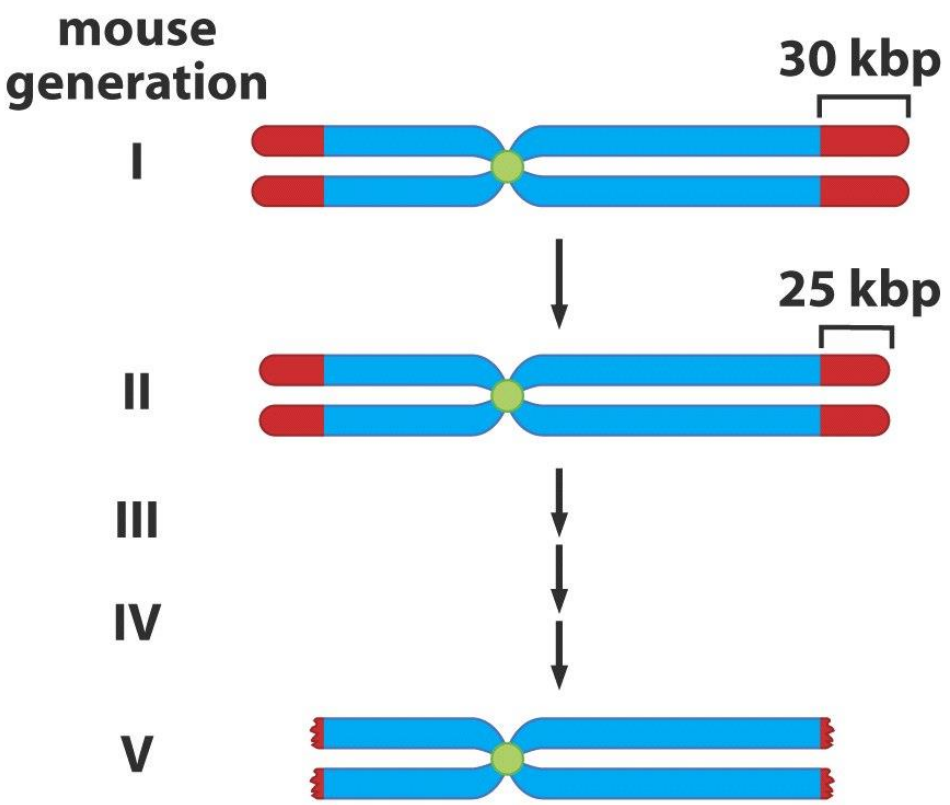
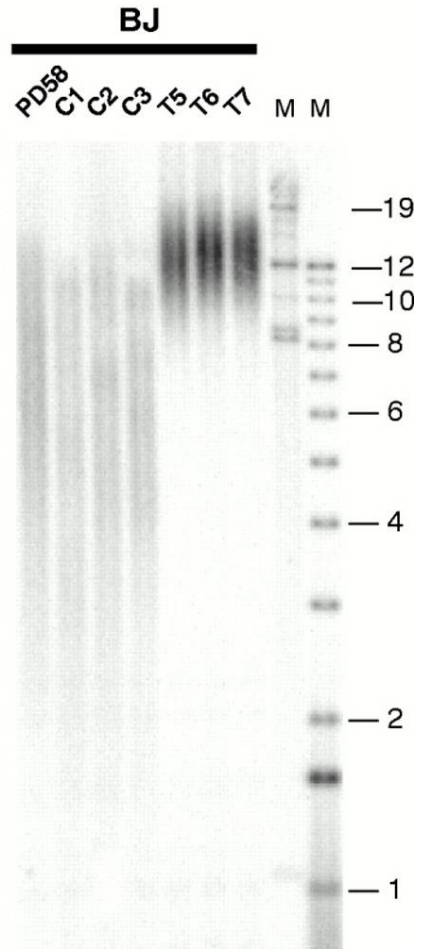
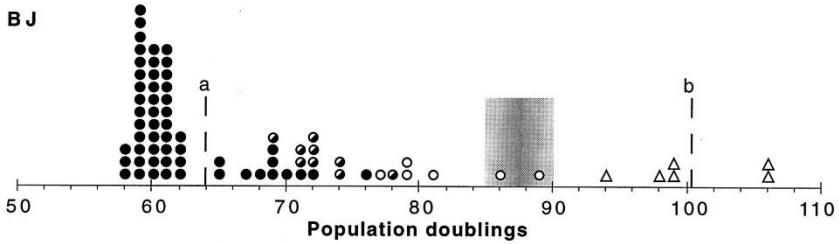
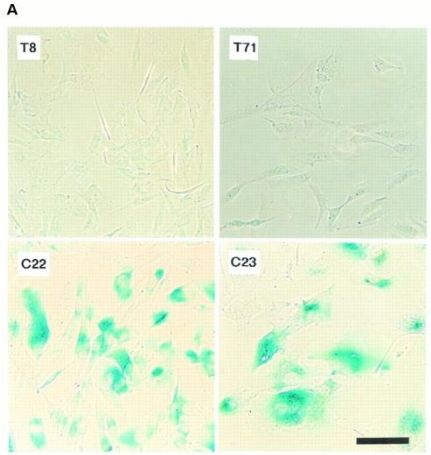


Figure 10.31 *The Biology of Cancer* (© Garland Science 2007)

Telomerase extends replicative lifespan of human cells



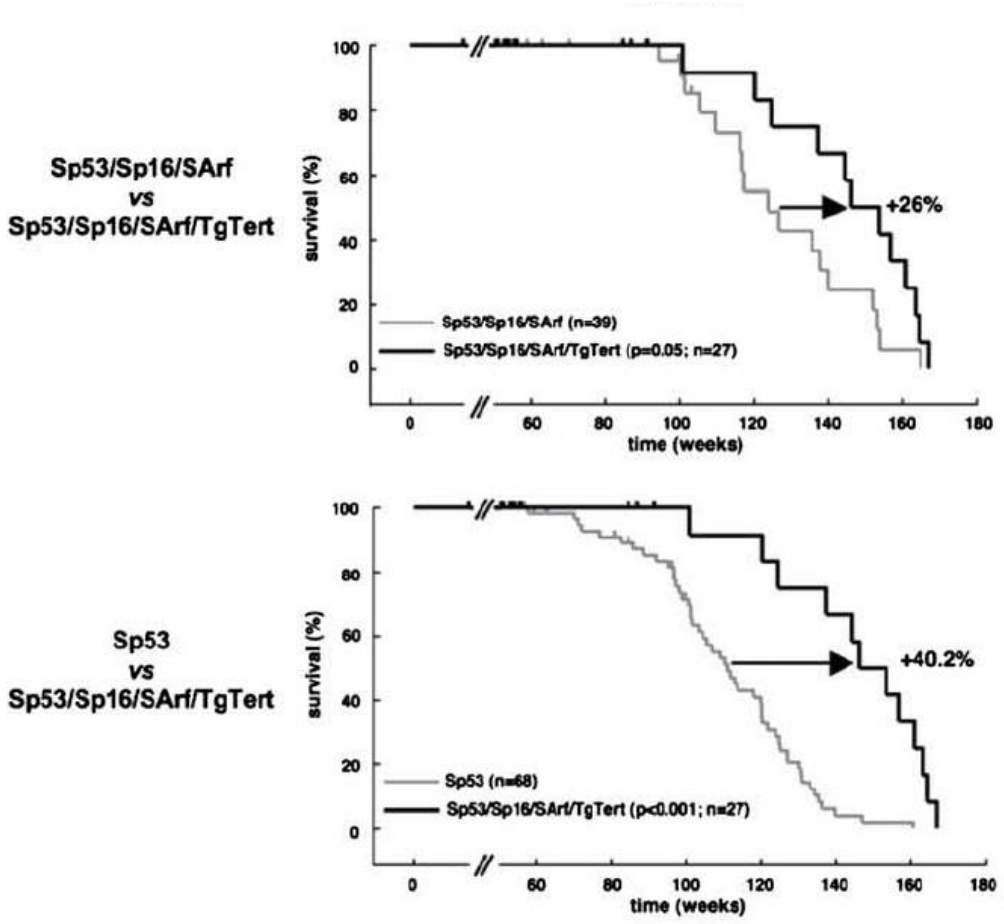




β-galactosidase assay after 60 PD

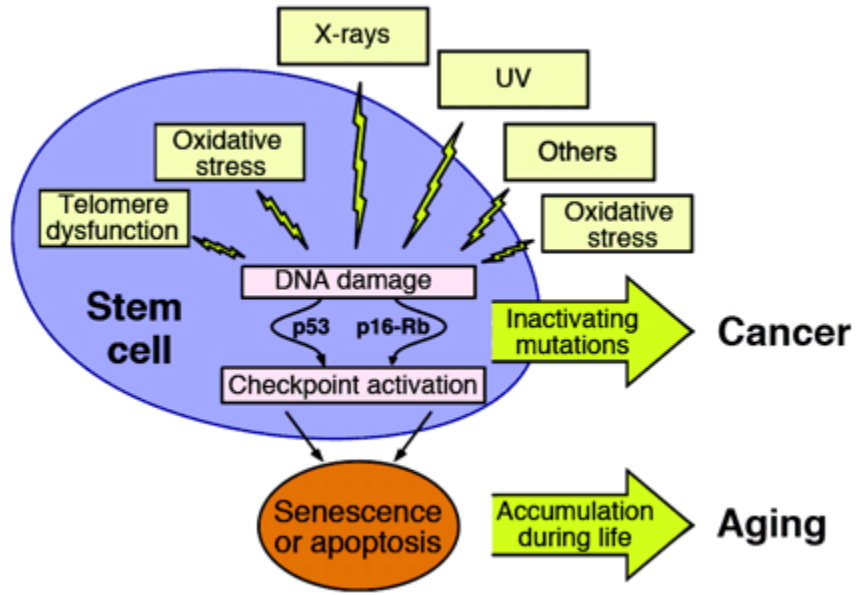
Bodnar et al., Science (1998)

Telomerase Reverse Transcriptase Delays Aging in Cancer-Resistant Mice



Tomas-Loba et al., Cell (2008)

The cellular senescence and antagonistic pleiotropy



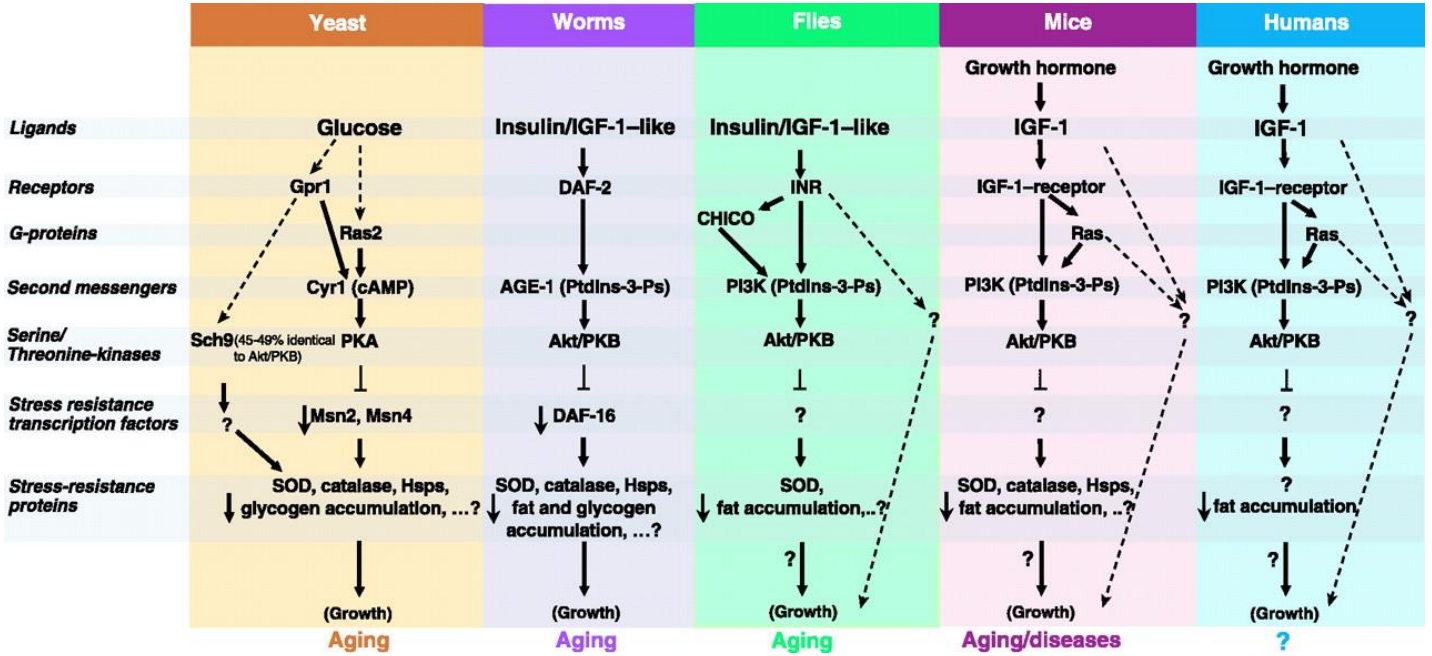
Non-cell autonomous mechanisms of aging

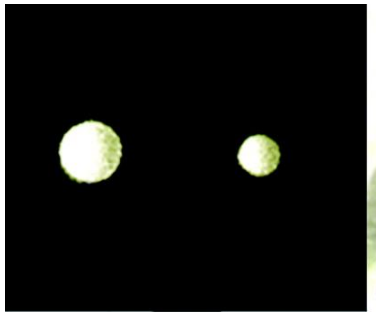
Cell non-autonomous mechanisms are usually coupled with reproduction or energy metabolism.

Endocrine system appears to be the major modulator of aging and lifespan in animal. The degree to which endocrine system influences aging is hormone- and species specific (e.g. estrogen in human has some antiaging effects, prolactins and gonadotropins may promote progression of some aging related diseases).

Pacific salmon: extreme increase of stress hormone cortisol after the first (and only) spawning leads to degeneration of number of glands and organs which in turn causes death by multiple organ failure.

Regulation of aging by endocrine system





sch9

chico

GHR/BP null mice

Longo & Finch, Science (2003)

Caloric restriction

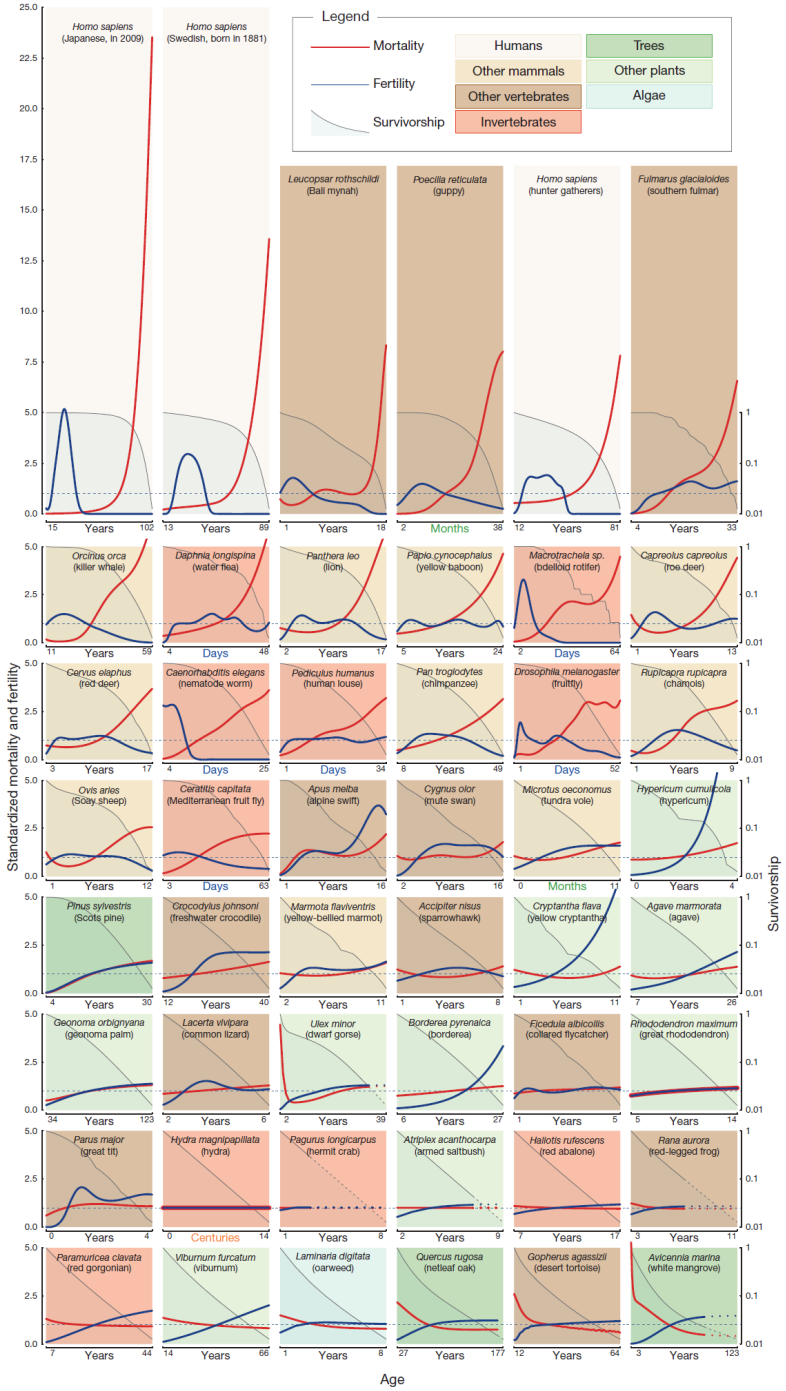
Caloric restriction can in rodents increase life span by 35% and also result in a lower incidence of tumors, kidney disease, vascular calcification and chronic pneumonia.

	Life-span increase		Beneficial health effects	
	Dietary restriction	Mutations/ drugs	Dietary restriction	Mutations/ drugs
Yeast	3-fold	10-fold (with starvation/ DR)	Extended reproductive period	Extended reproductive period, decreased DNA damage/mutations
Worms	2- to 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 neurodegeneration	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

Fig. 1. Experiments on dietary restriction (DR) and genetic or chemical alteration of nutrient-sensing pathways have been performed on a range of model organisms. The results differ widely, and little is known about the long-term effects in humans.

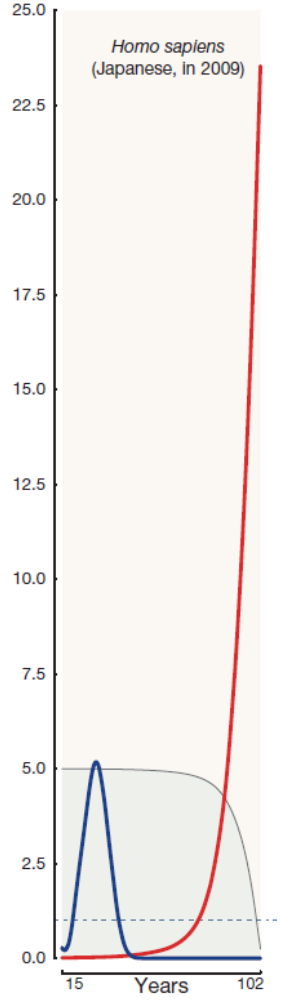
Fontana, Science (2010)

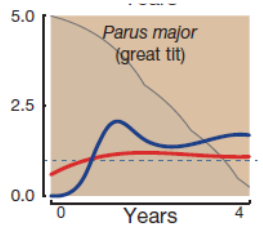
In times of famine, the immediate prospects for successful reproduction and for survival of vulnerable offspring are diminished, while the reward for surviving through to the end of the famine is an opportunity to deliver offspring into the newly abundant but depopulated world that emerges.

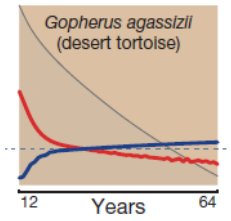


Diversity of ageing across the tree of life

Owen R. Jones[1,2]*, Alexander Scheuerlein[3]*, Roberto Salguero-Gómez[3,4], Carlo Giovanni Camarda[5], Ralf Schaible[3], Brenda B. Casper[6], Johan P. Dahlgren[1,2], Johan Ehrlén[7], María B. García[8], Eric S. Menges[9], Pedro F. Quintana-Ascencio[10], Hal Caswell[2,3,11,12], Annette Baudisch[3] & James W. Vaupel[1,3,13]







Naked mole-rat

- The longest living rodent (over 30 years, average for other species 4 years)
- Decrese in mortality and constant fertility with age; physiologicaly young at advanced age
- Unusual resitence to cancer
- Tissues accumulate high-molecular weight hyaluronan
- Cells with KO of hyaluronan synthase become susceptibel to malignant transforamtion

Tian et al, Nature (2013)

Are there immortal animals?

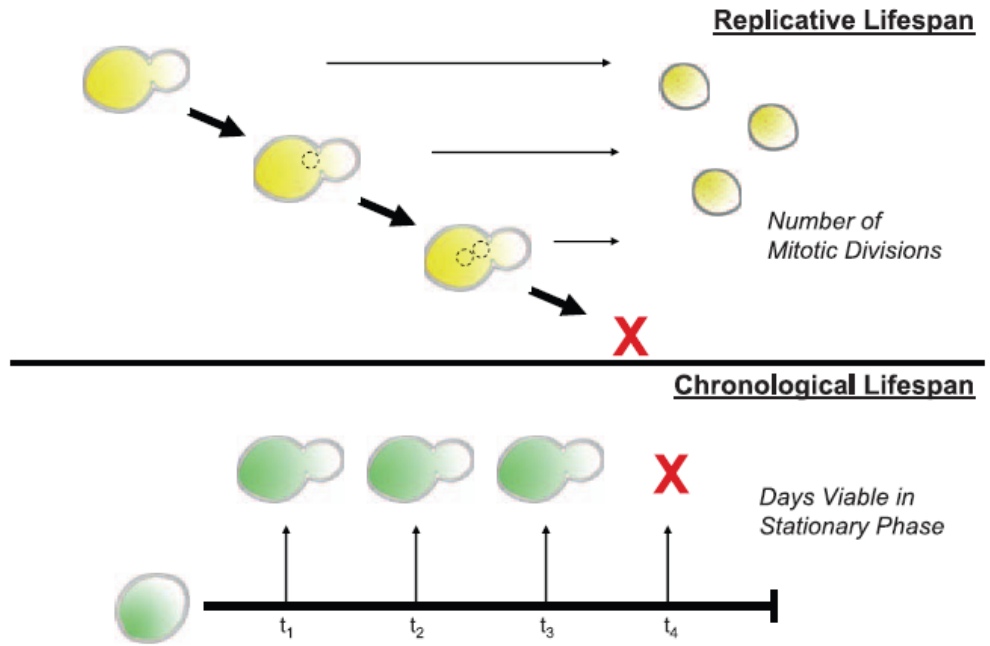
Greenland shark – an individual tha could be up to 512 old

Niellsen et al, Science (2016)

Unicellular organisms: aging in yeast

Yeast replicative lifespan: number of cell divisions an individual cell can undergo before dying.

Yeast chronological lifespan: a length of time a population of cells remains viable in non dividing state after nutrient deprivation.

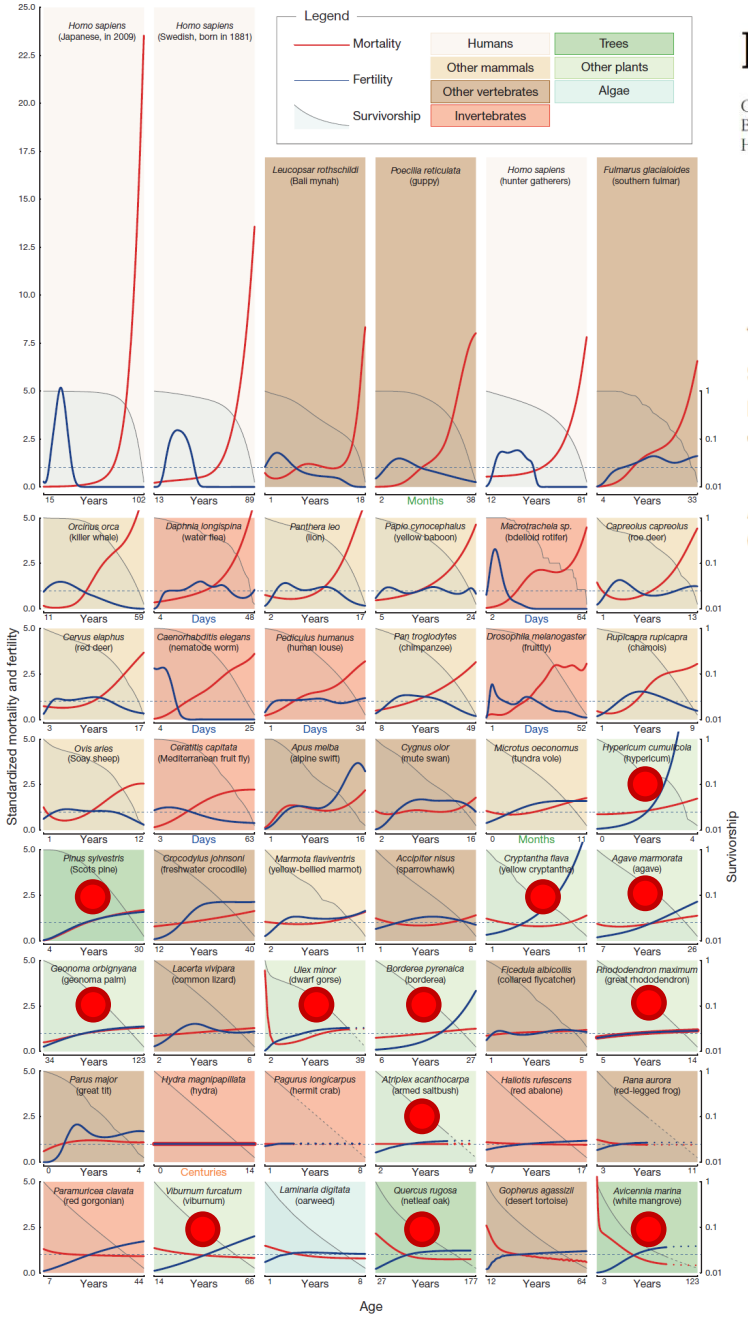


doi:10.1371/journal.pgen.0030084.g001

Figure 1. Schematic for Yeast Replicative and Chronological Aging

(A) RLS in yeast is measured by the number of mitotic divisions that can arise from a single mother cell. Replicative viability is calculated as the mean number of daughters produced from mothers of a particular strain background before senescence.

(B) CLS is measured by the length of time cells in a stationary culture can remain viable. Viability is calculated by the fraction of the culture able to reenter the cell cycle after an extended state of quiescence.



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Journal of Ecology 2013, **101**, 596–606 doi: 10.1111/1365-2745.12084

SPECIAL FEATURE

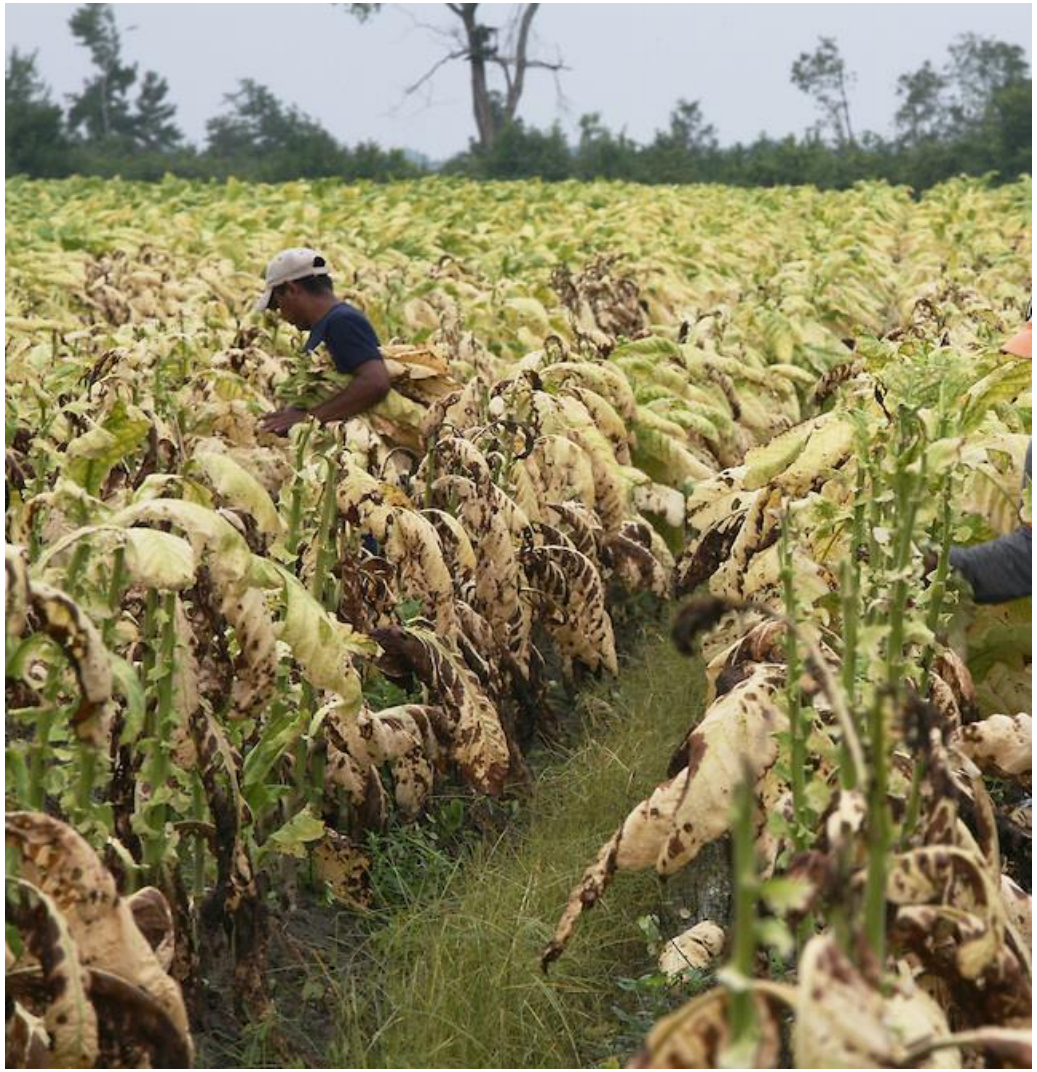
NEW PERSPECTIVES IN WHOLE-PLANT SENESCENCE

The pace and shape of senescence in angiosperms

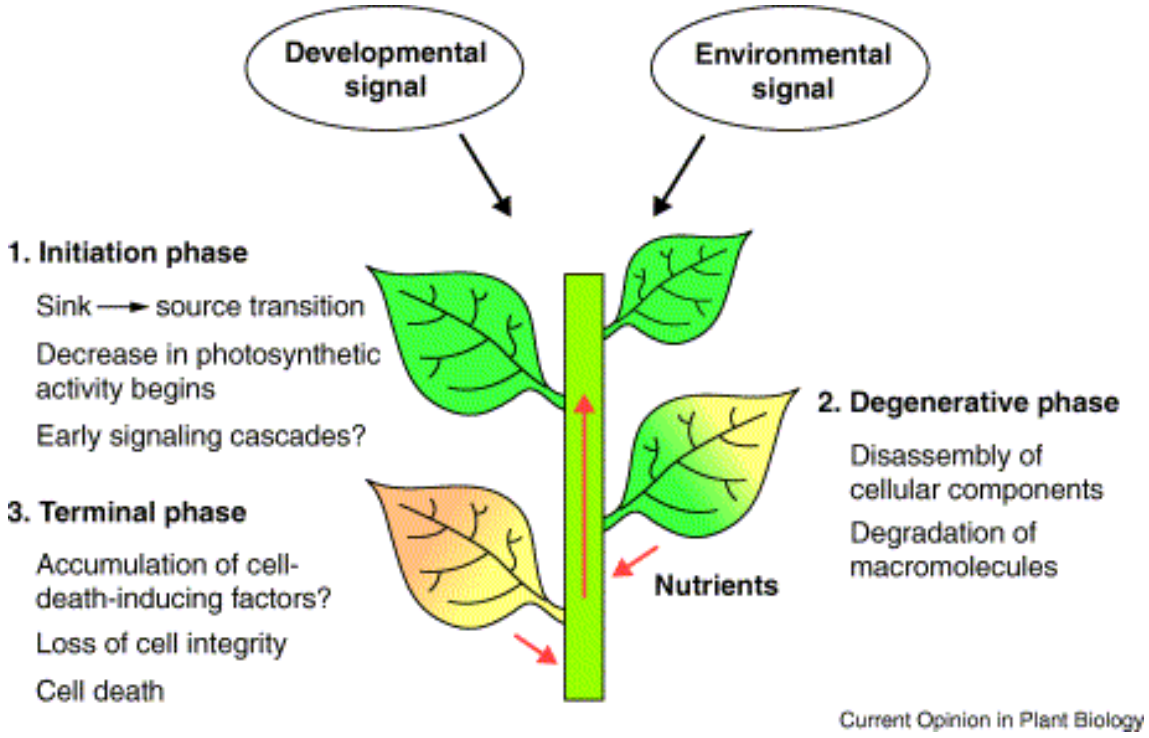
Annette Baudisch[1]*, Roberto Salguero-Gómez[1,2], Owen R. Jones[1,3,4], Tomasz Wrycza[1], Cyril Mbeau-Ache[5], Miguel Franco[5] and Fernando Colchero[1,3,6]

Out of 290 angiosperm plants, 93% show negligible or negative senescence.

Leaf senescence

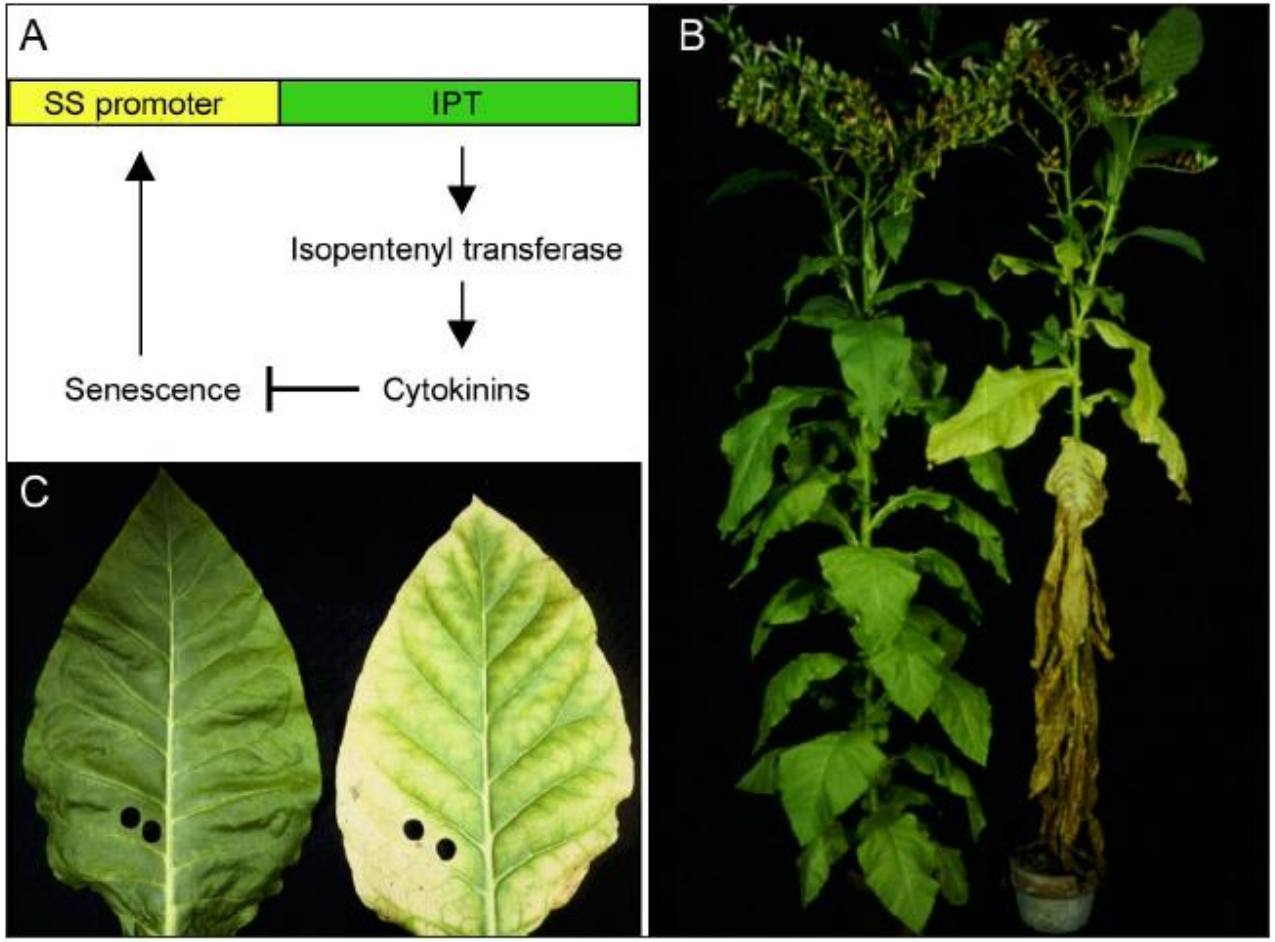


Leaf senescence is a programm



These degenerative activities occur concomitantly with a massive remobilization of the hydrolized molecules to the growing parts of plants, such as young leaves, developing seeds, and fruits.

Reversing leaf senescence



Gan & Amasino, Science (1995)

Leaf senescence vs organismal aging

The term senescence is used in a specialized way by plant scientists: it is highly regulated physiological process that allows nutrient remobilization and ends up in the death of cell, organ or plant, but it is not by itself aging (leaf senescence in trees is a recurrent process).

Perenial plants: some of the longest living organisms on this planet

Perennials: plants that live for more than two years

Life forms in perennials:

1. woody perennials
2. herbaceous perennials
3. clonal, creeping perennials (clover, prairie grass)

bristlecone pine ~5000 years
(germinated 3050 BC)

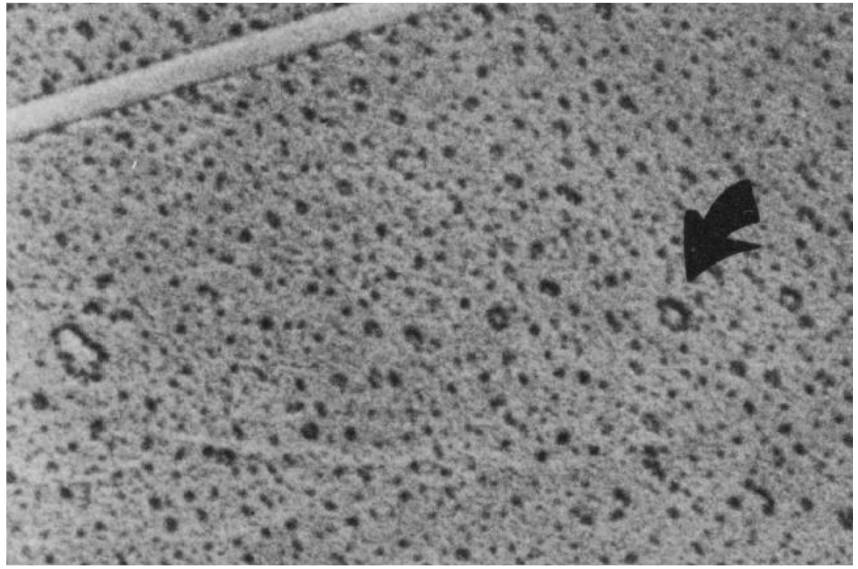
Borderea pyrenaica
~300 years

Larrea tridentata
~11000 years

Munne-Bosch, Crit Rev Plant Sci (2007)

The „King clone"

Larrea tridentata ~11700 years old clone in Mojave desert



Vasek, Am J Bot (1980)

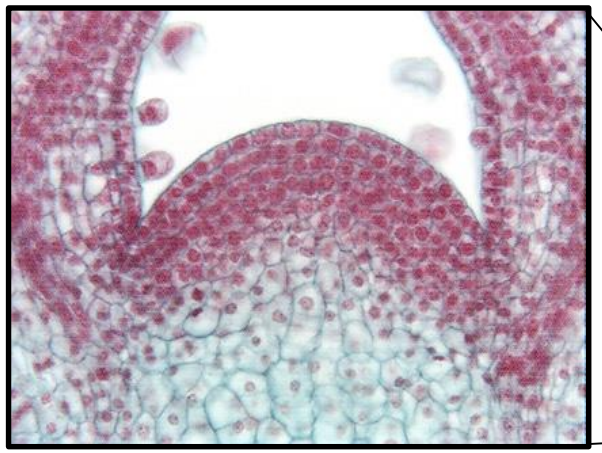
Aging is a fate that probably awaits all living organisms: it is just that plants are organized so that they are not there when it happens. - *Howard Thomas*

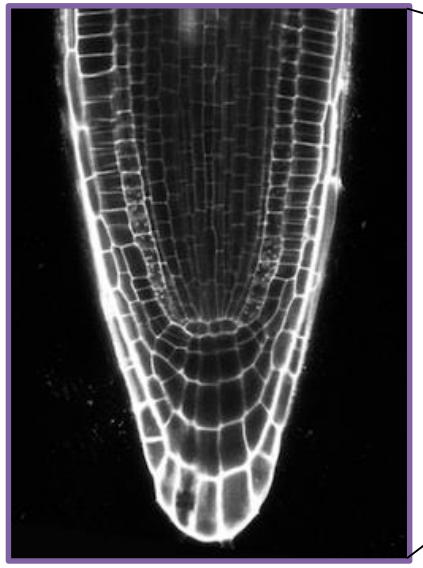
What makes plants special?

- Indeterminate growth
- Modular development
- No separation of germline from soma

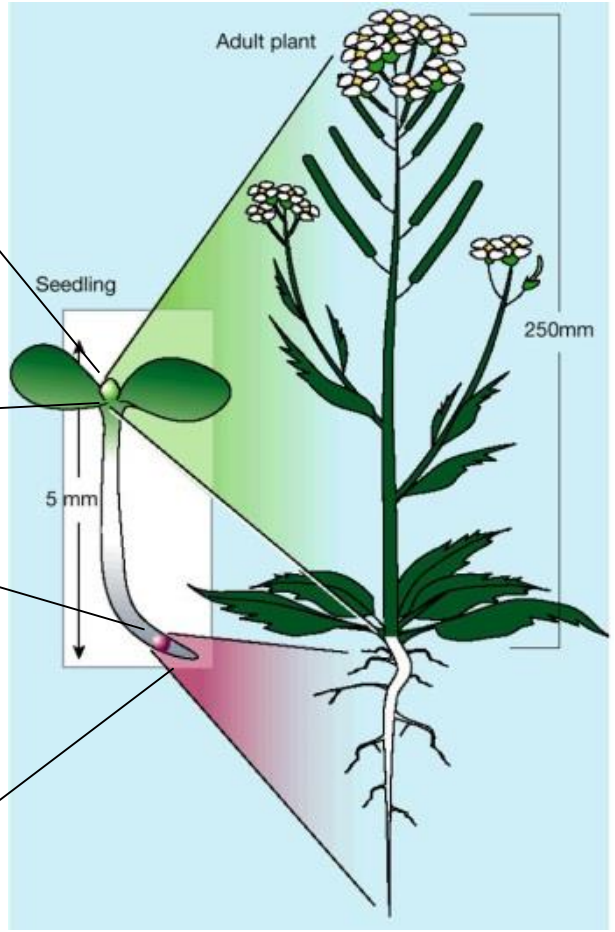
Plant growth is driven by cell division in meristems

shoot apical meristem

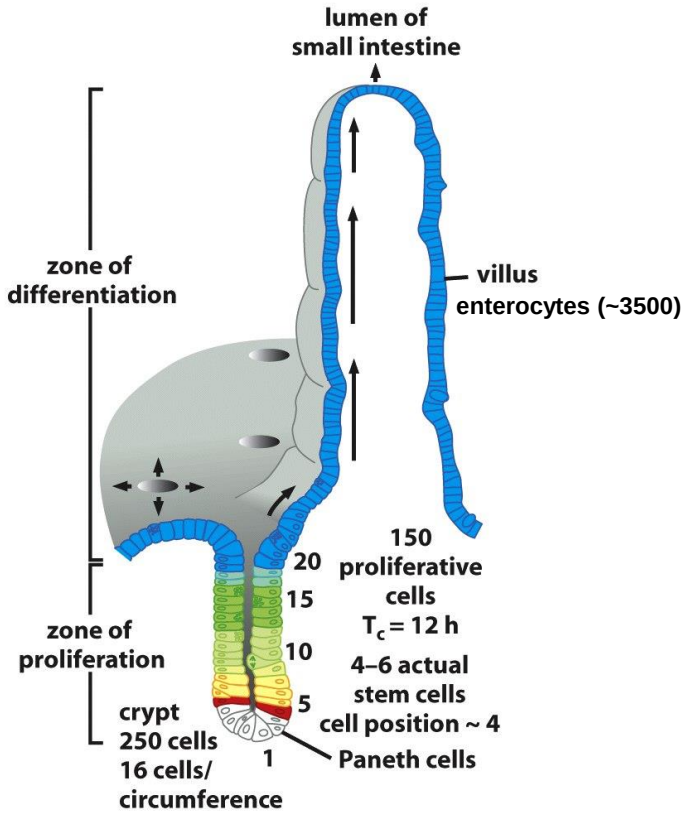




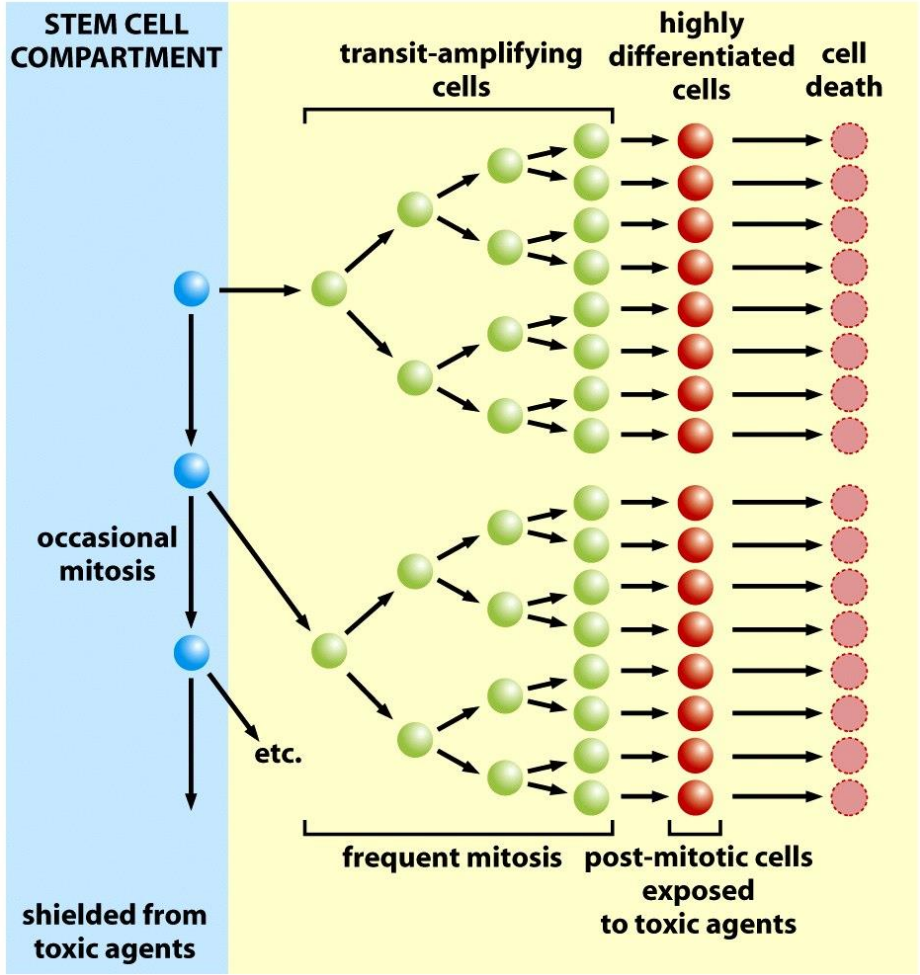
root meristem



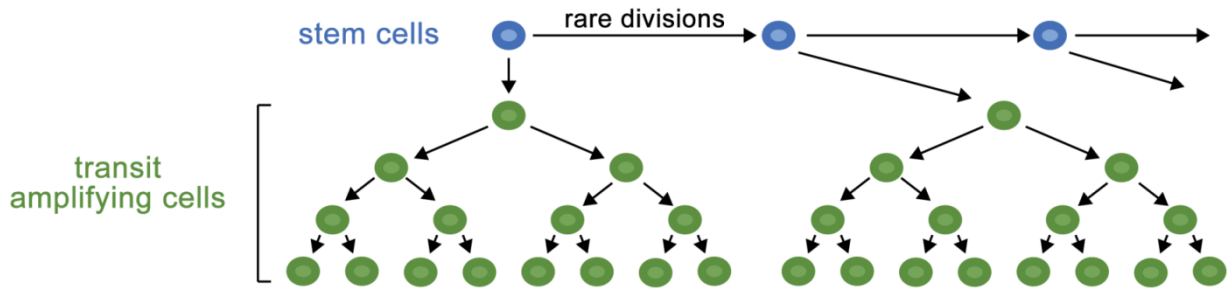
Tissue organization and protection of the stem cell genome

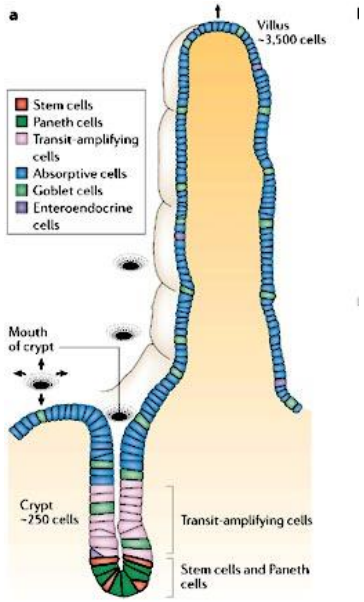


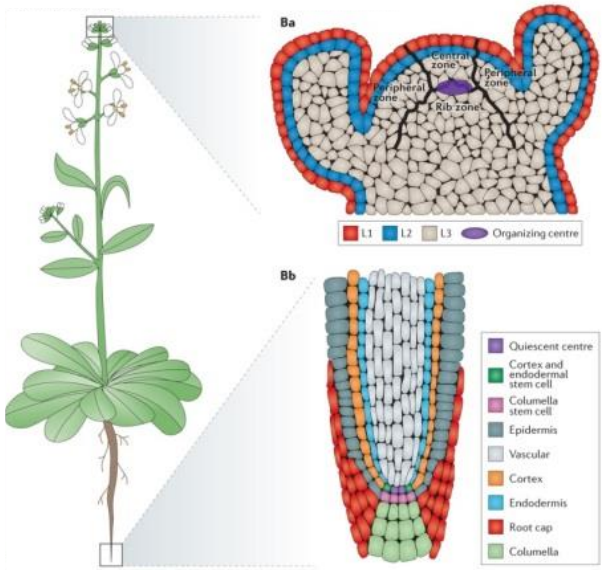
Organization of stem cells in gastrointestinal crypts of the small intestine



Stratification of plant meristems may decrese mutation by protecting stem cells from excessive proliferation







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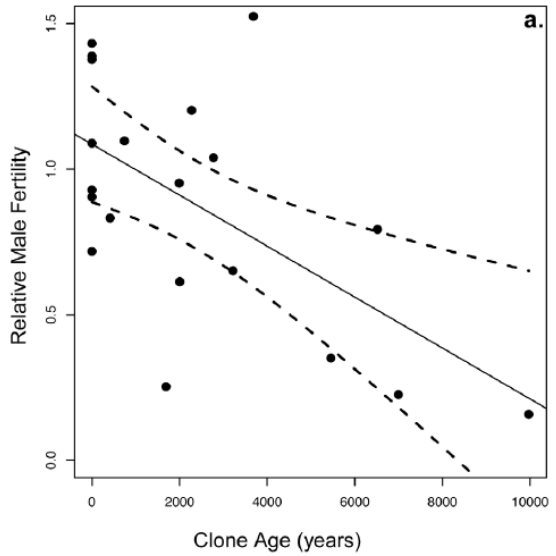
PLOS BIOLOGY

Aging in a Long-Lived Clonal Tree

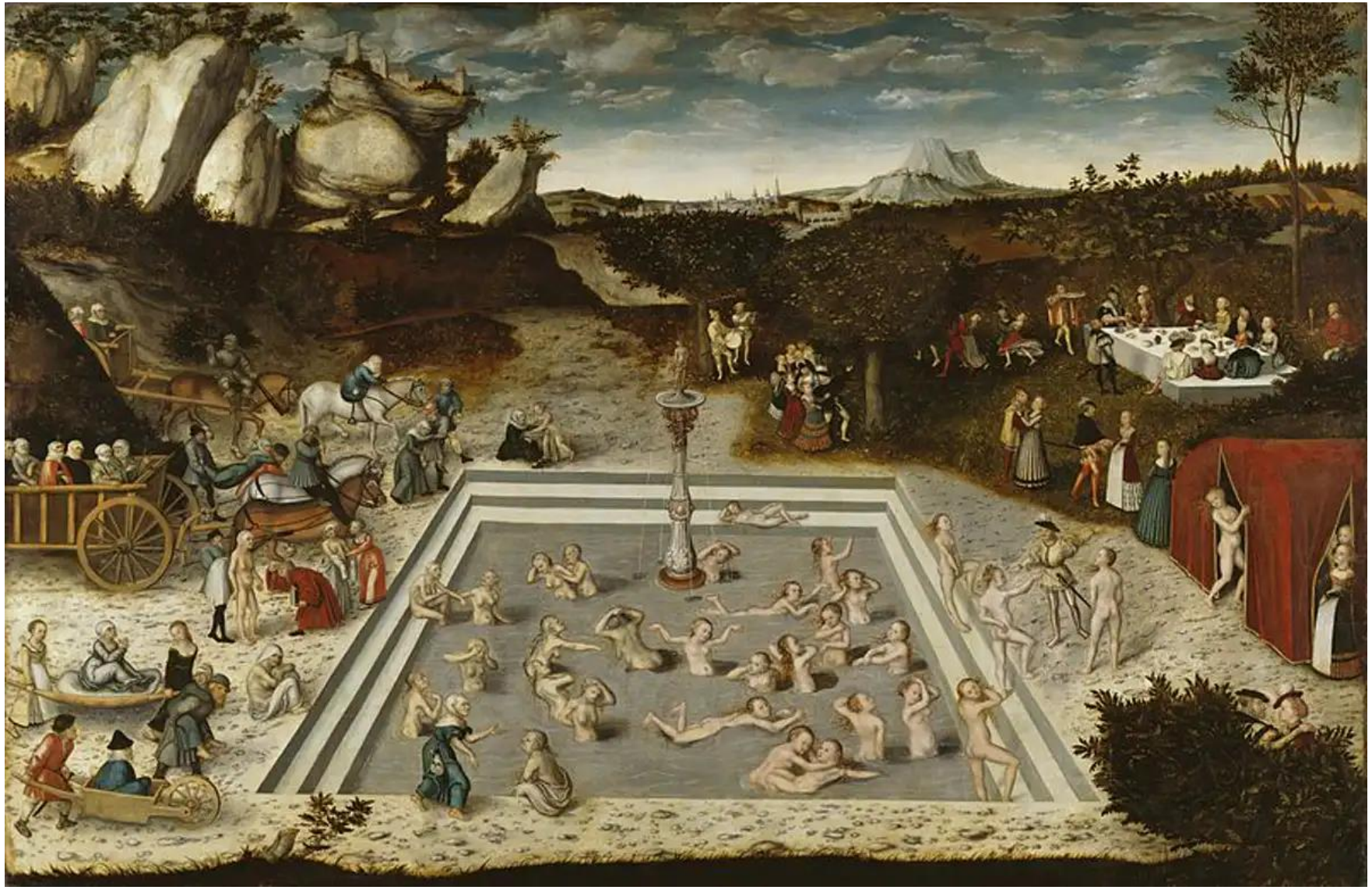
Dilara Ally[1,2]*, Kermit Ritland[3], Sarah P. Otto[2]

trembling aspen



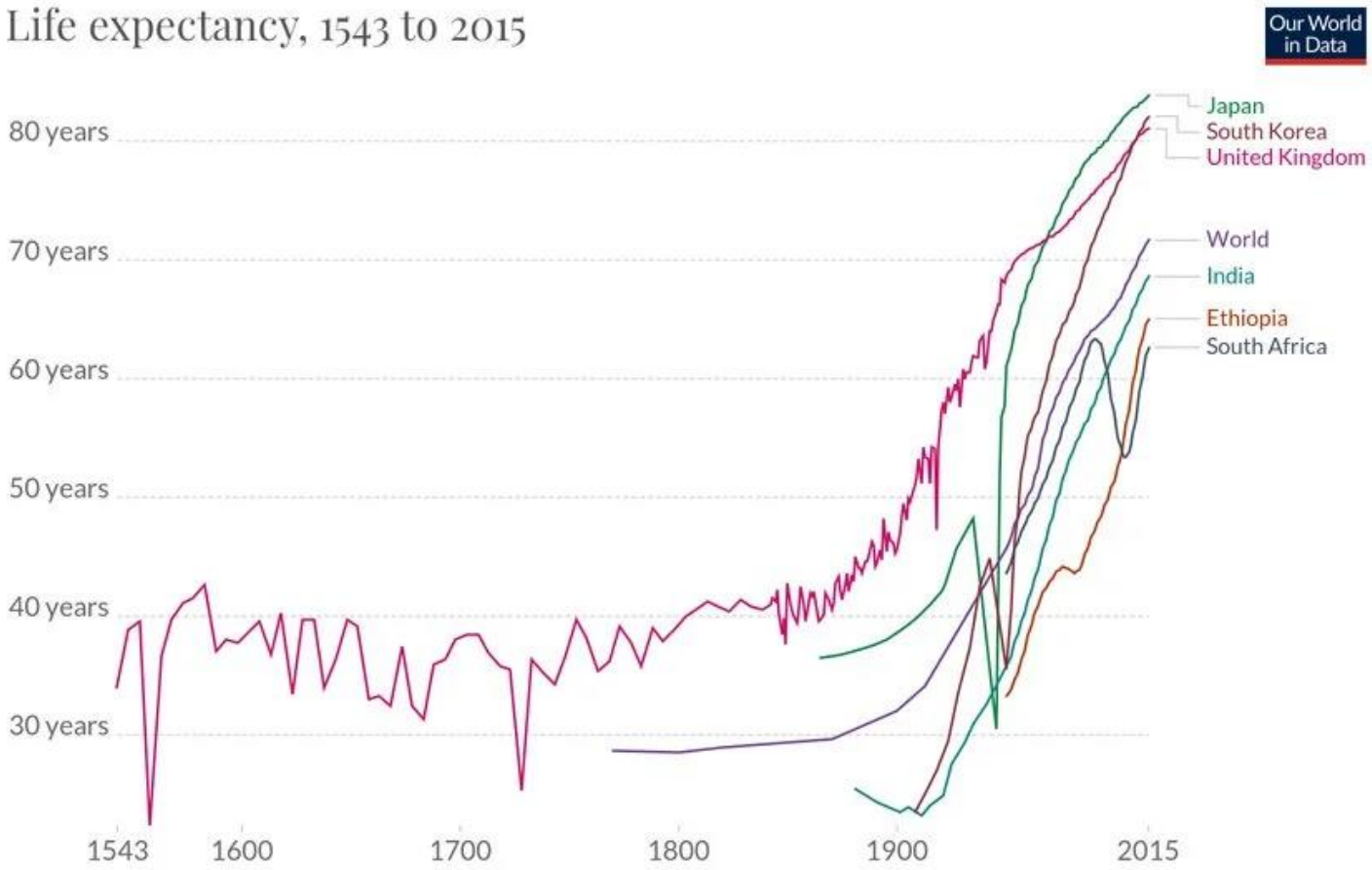
There may not be a universal cause of aging valid for all organisms.

Can we cure aging?



The Fountain of Youth, a 1546 painting by Lucas Cranach the Elder.

Life expectancy, 1543 to 2015



Source: Riley (2005), Clio Infra (2015), and UN Population Division (2019)
Note: Shown is period life expectancy at birth, the average number of years a newborn would live if the pattern of mortality in the given year were to stay the same throughout its life.