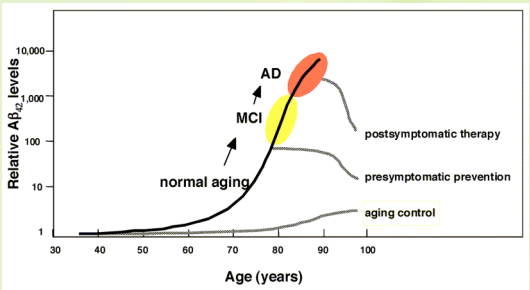
The aging phenotype: cellular aspects

A&S300-002 Jim Lund

Cell loss

- Reduced cell number.
  - Cell death:
    - programmed cell death (apoptosis) due to mutation or injury
    - unprogrammed cell death (necrosis) due to damage.
  - Reduced rate of cell replacement due to loss of stem cells.
  - Some cell populations are not replaced (neurons)
- Fibrosis of the tissue. Lost cells replaced by extracellular material reducing tissue function.

Alzheimer's disease



Relationship between age, Amyloid Beta ($A\beta$)42 accumulation, normal aging, Mild cognitive impairment (MCI), and Alzheimer's disease (AD). Typically, the $A\beta$42 levels in the brains of AD patients are 1,000–10,000–fold higher than in the brains of normal controls.

Cell loss can lead directly to disease

- Parkinson's disease
  - Loss of dopamine neurons in the substantia nigra.
- Alzheimer's disease
  - Tangles and plaques cause cell death.

Stem cells

- Stem cells required for maintenance of many tissues.
  - Immune system
  - Skin
  - GI epithelium
- In some cases, stem cell numbers decline.
- Stem cells lose proliferation potential, so lost cells are not replaced.

Cellular changes

- Damaged protein levels increase.
- Protein turnover declines.
- DNA damage
  - Somatic DNA accumulates mutation.
  - Mitochondrial DNA damage.
- Telomere shortening.
- Lipofuscin deposits in cells.
- Mitochondria function declines.
- Gene expression changes.
  - Response to cellular stresses.

Changes in senescent cells

Table 1. Altered characteristics of senescent hepatocytes.

Parameter	Changes with aging
Transcription	Decline
Translation	Decline
Proteolysis	Decline
Responsiveness to hormones	Decline
Lipofuscin	Increase
Abnormal nuclei	Increase
Chromosomal abnormalities	Increase

Data derived from Makarides (4) and Dice (5).

Youssef and Badr, 1999

DNA damage due to replication errors

- Mitochondria: DNA polymerase λ, 1 error in 10^{-5} bases.
- Nucleus: DNA polymerase I, 1 error in 10^{-9} bases.
- Mitochondrial DNA replication is more error prone than nuclear DNA replication.

Mitochondrial DNA damage

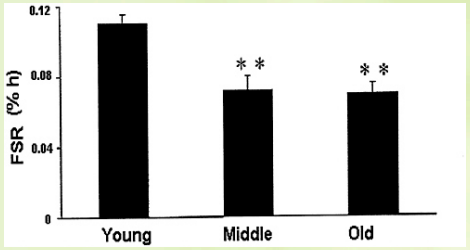
- Mitochondrial DNA lives in a harsher environment than nuclear DNA and has much higher rates of damage.
- mDNA mutation levels rise.
- mDNA accumulates deletions.
- Problem worsened by replication advantage of mutated mitochondria (muscle especially).
- Causes loss of mitochondria function.
  - Cellular energy production declines.

Protein turnover

- Progressive decrease in the creation of new protein.
- Reduction in the rate of protein degradation.
- Inaccessible protein deposits.

Result: damaged proteins in cells increase as we age

Muscle mitochondrial protein synthesis decline



A decline in fractional muscle mitochondrial protein synthesis occurred with age. Approximately a 40 percent decline occurred by middle age ($P < 0.01$), but there was no further decline with advancing age.
** Indicates significant difference from young age.
Source: Rooyackers et al., 1996

Advanced **G**lycosylation **E**nd-products: **AGEs**

- An oxidative reaction of glucose with protein damages protein and creates protein-protein crosslinks.
- A Maillard reaction of free amino groups on proteins and glucose.

Pentosidine, a glycosylation product increases with age

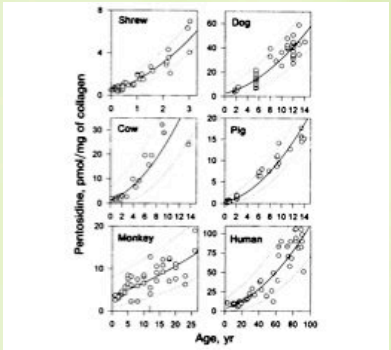
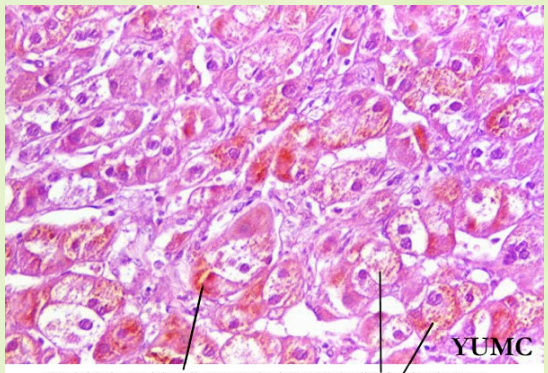


FIG. 1. Pentosidine level in skin collagen as a function of age in different animal species. The regression line and 95% confidence interval of predicted values are shown. Regression equations are given in Table 2.

Lipofuscin

- Lipofuscin (LF) is a conglomerate of lipids, metals, organic molecules, and biomolecules that commonly fluoresces at 360 to 470 nm.
- LF granules have been found in every eukaryote examined, and always accumulate within cells as the organism ages, and usually as cellular integrity is challenged.
  - Called "the aging pigment."

Lipofuscin



Insoluble brownish-yellow granular intracellular lipofuscin pigment
Fig. 2: Lipofuscin ("wear-and-tear") pigment accumulation of adrenal gland

Image: Yonsei University College of Medicine

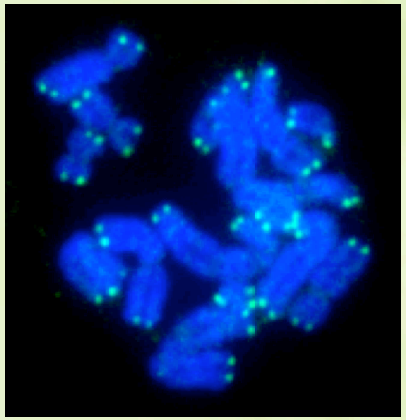
Telomeres: Ends of linear chromosomes

Repetitive DNA sequence
(TTAGGG in vertebrates)

Specialized proteins at telomere

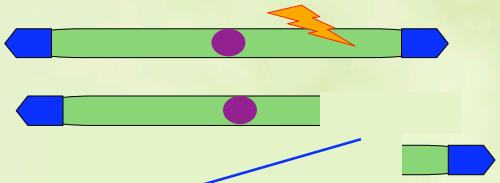
Form a 'capped' end structure

Telomeres 'cap' chromosome ends



Why are telomeres important?

- Prevent runaway cell replication (cancer)
- Allow cells to distinguish chromosomes ends from broken DNA

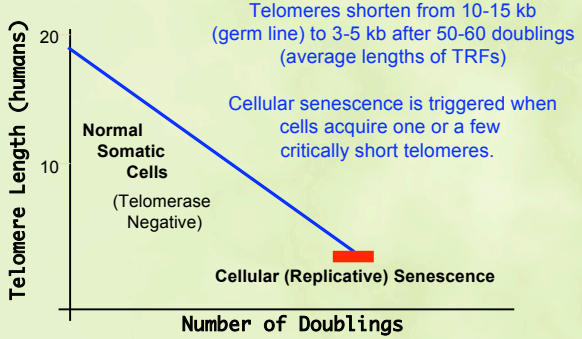


Stop cell cycle!
Repair or die!!

Homologous recombination
(error free, but need nearby homologue)

Non-homologous end joining
(any time, but error-prone)

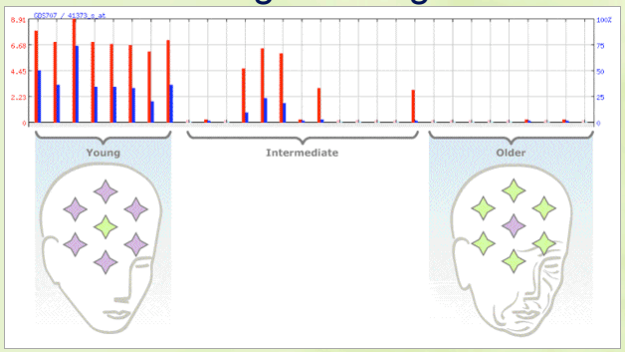
Telomere also provide a means for "counting" cell division: telomeres shorten with each cycle



Telomeres shorten from 10-15 kb (germ line) to 3-5 kb after 50-60 doublings (average lengths of TRFs)

Cellular senescence is triggered when cells acquire one or a few critically short telomeres.

Expression levels of some genes change with age



MAP1B expression. Red is expression level, blue is percentile rank of this gene.

Antioxidant enzymaltic levels

Table 4. Liver catalase in animals of various ages.

Species	Young[a,b]	Old[a,b]	Reference
Male Fischer	100 (3)	63 (24)	(*61*)
344 rats	100 (5)	48 (26)	(*62*)
	100 (6)	60 (26)	(*63*)
	100 (6)	61 (24)	(*64*)
	100 (6)	48 (29)	(*64*)
Female CSWV mice	100 (11)	71 (18)	(*52*)
Female OFi mice	100 (11)	66 (24)	(*53*)

[a]Results are expressed as percent of specific activity in young animals within the same study. [b]Numbers in parentheses are age of animals in months.

Youssef and Badr, 1999