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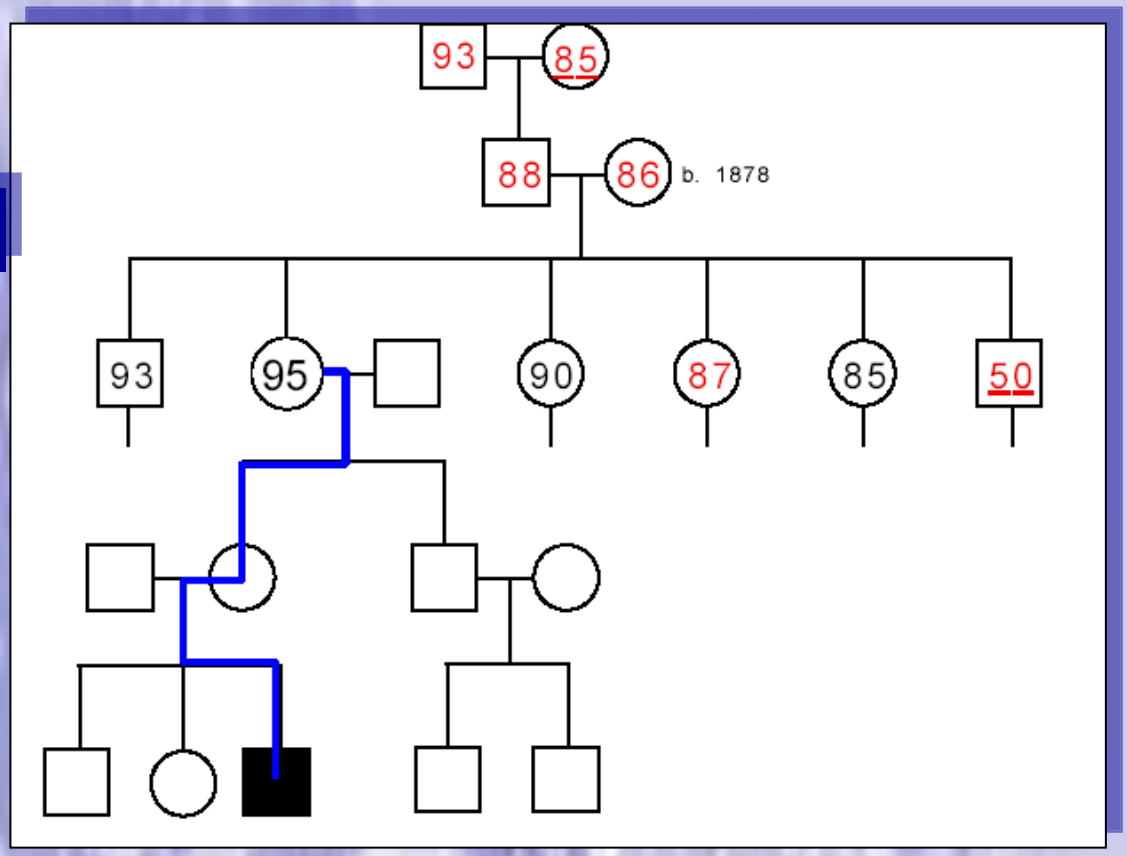
Some believe that aging is determined primarily by genes, while others hypothesize that accumulated cellular damage is the main cause of systemic aging

Aging is a complex process resulting from multiple factors, including genetic and epigenetic molecular markers

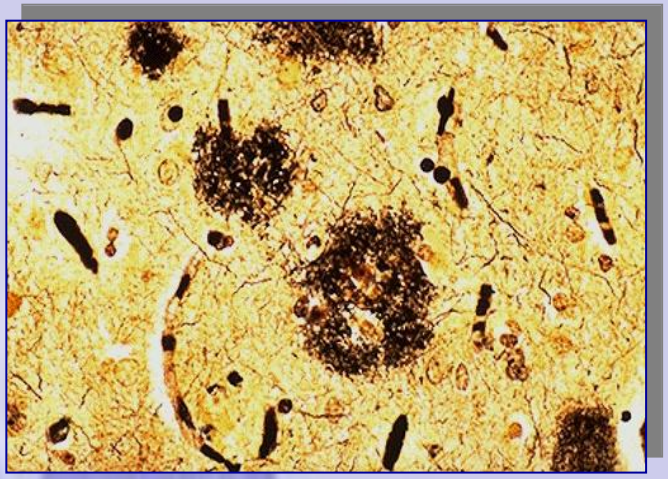
Heritability for aging is about 5%

Biological bases of senescence

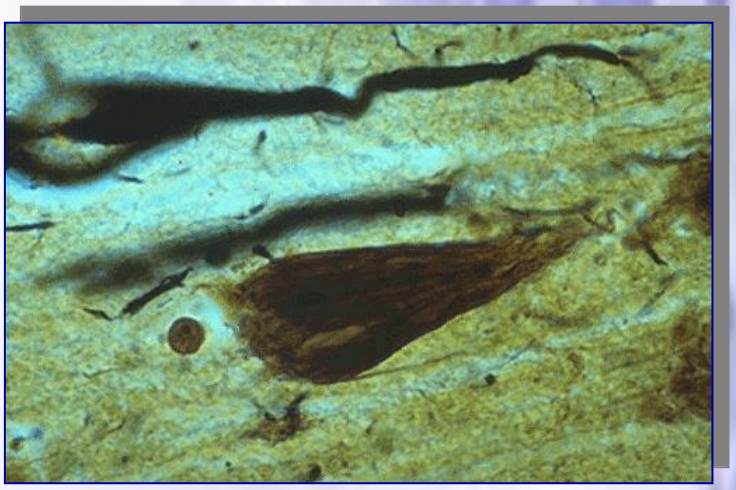
Reverse genetics approach



To study the genetics of very well functioning old people (Heritability gets much higher in over 90s)



Analysis of the genetic background of cellular mechanisms of senescence for candidate genes



AGING

Molecular Theories

Codon restriction - Fidelity/accuracy of mRNA translation is impaired due to inability to decode codons in mRNA.

Error catastrophe - Fidelity of gene expression declines with age, resulting in increased fraction of abnormal proteins.

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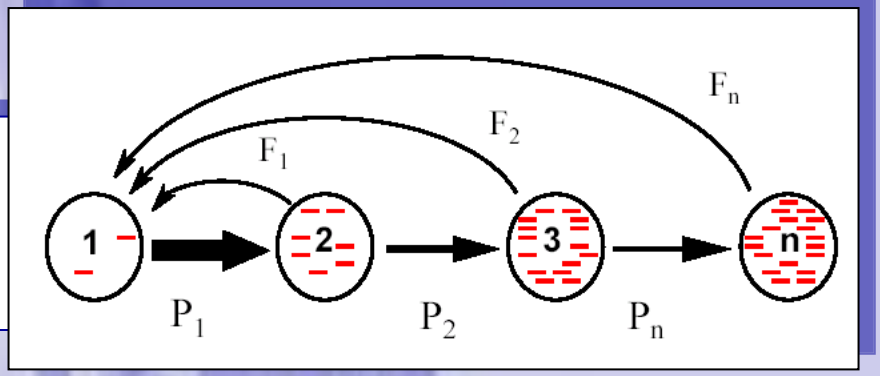
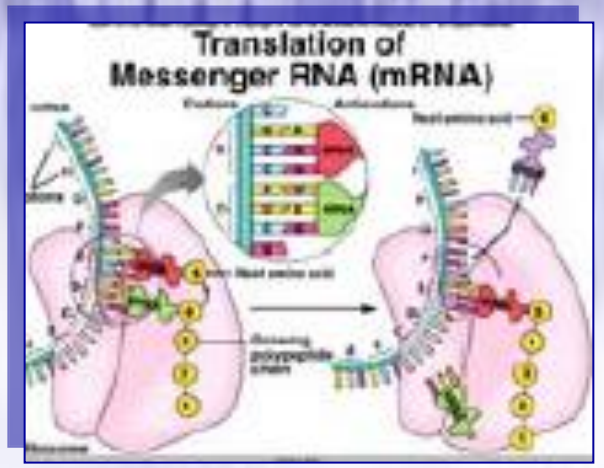
Molecular Theories

Somatic mutation - Accumulation of molecular damage, primarily to DNA/genetic material *

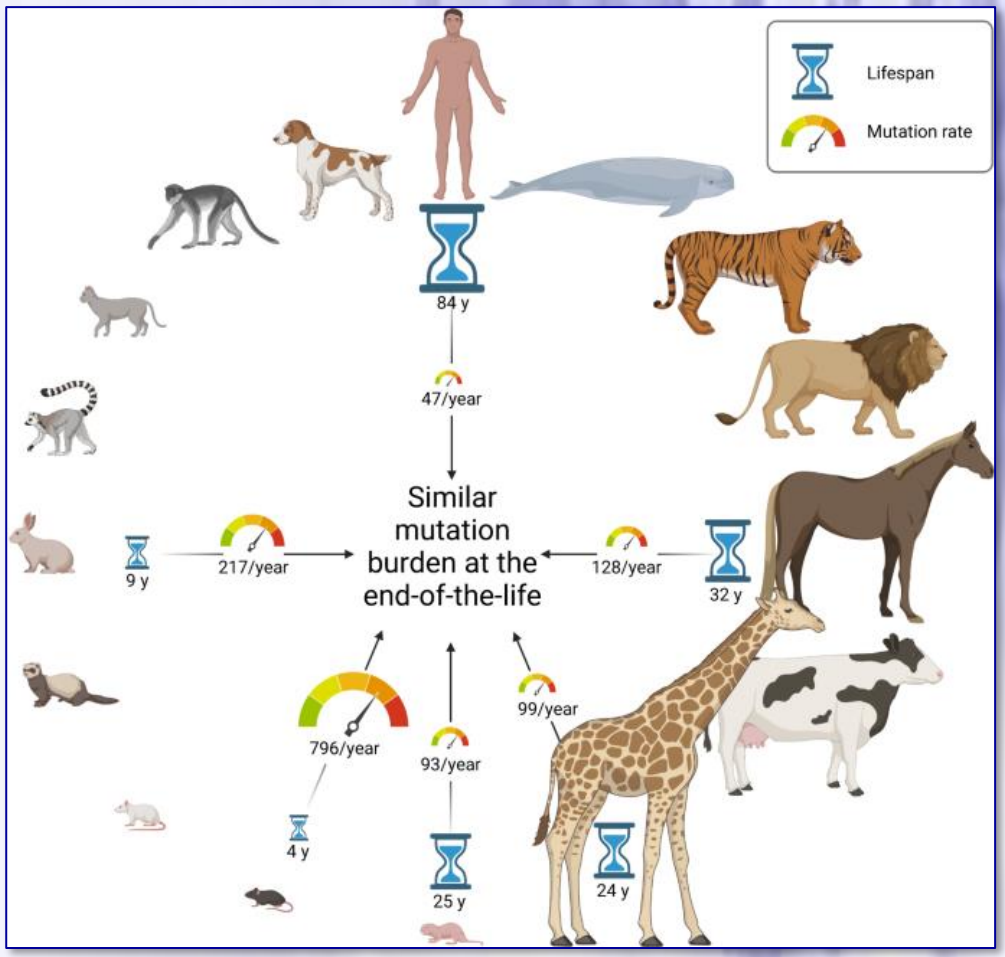


Dysdifferentiation - Gradual accumulation of random molecular damage impairs regulation of gene expression

Gene regulation - Aging caused by changes in gene expression regulating both aging and development

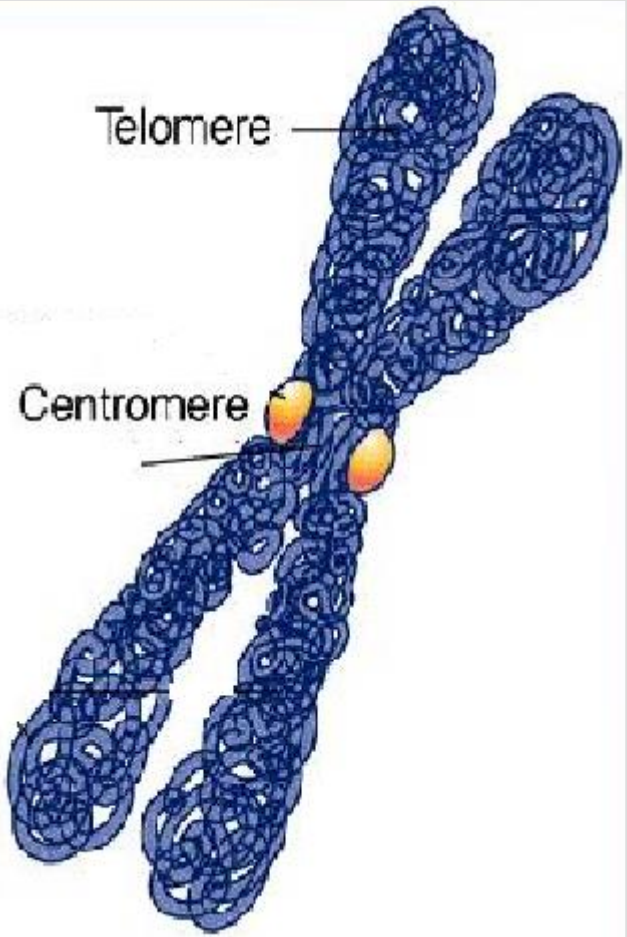


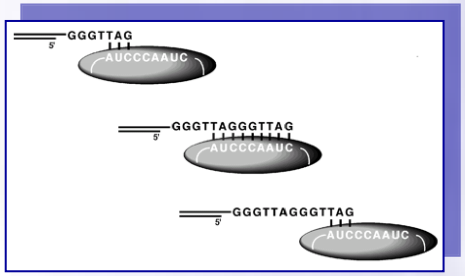
The mutation rate in somatic cells between species is an important factor affecting lifespan, having a strong inverse relationship with lifespan and no obvious correlation with body size



Cellular senescence: telomere shortening

During chromosomal replication, the DNA polymerase cannot complete the replication of the telomere.
Telomerase is needed for this purpose.



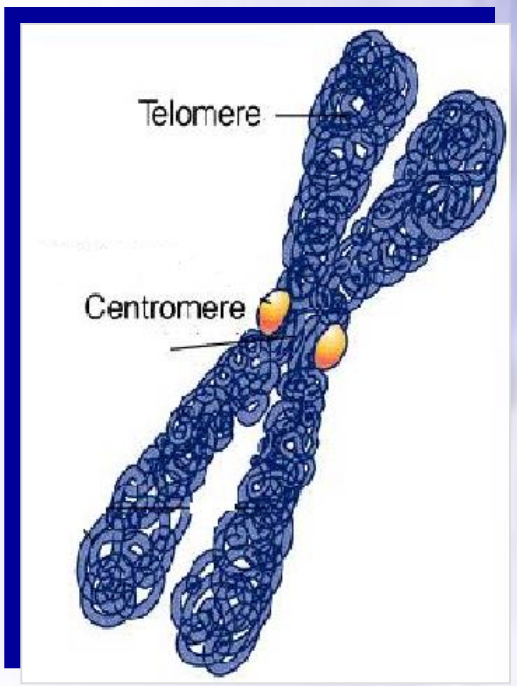


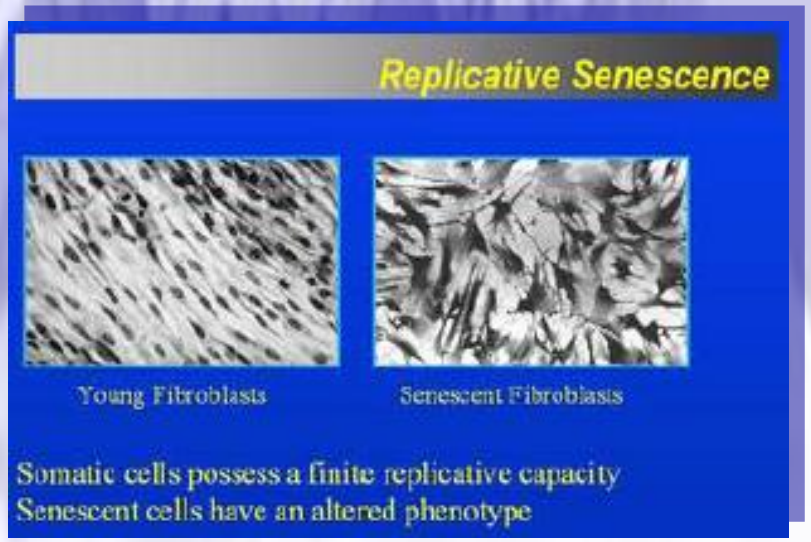
A minimal telomere length is needed for replication

Cellular senescence: telomere shortening

Most somatic cells in humans do not express telomerase Therefore the number of cell cycles is limited by length of the telomere

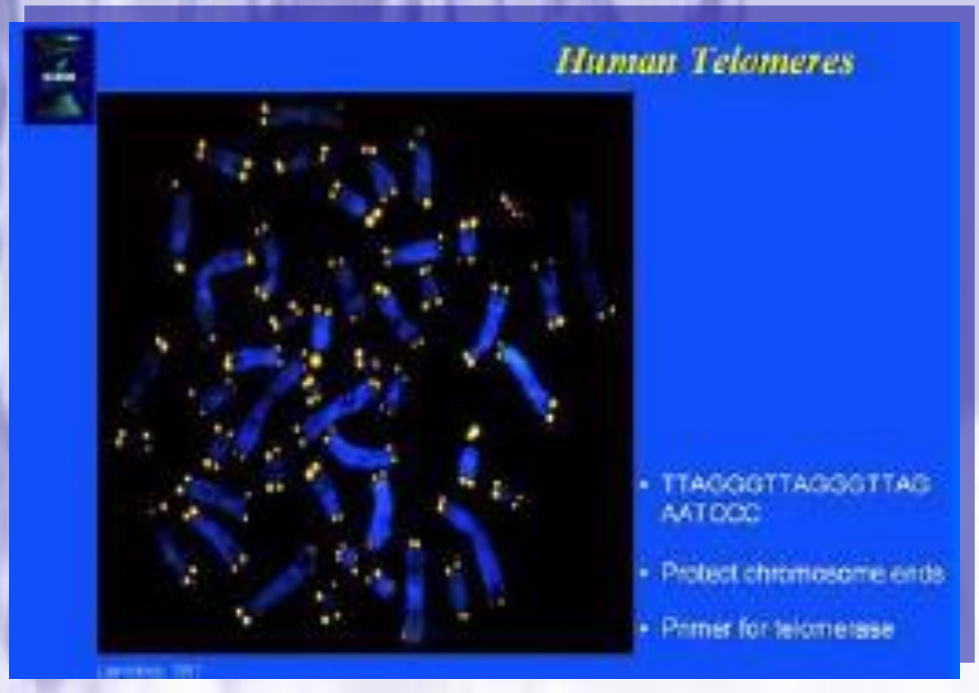
replicative senescence





Cellular senescence: telomere shortening

Individual differences in telomeres length are genetically determined with a 78% heritability



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Cellular Theories

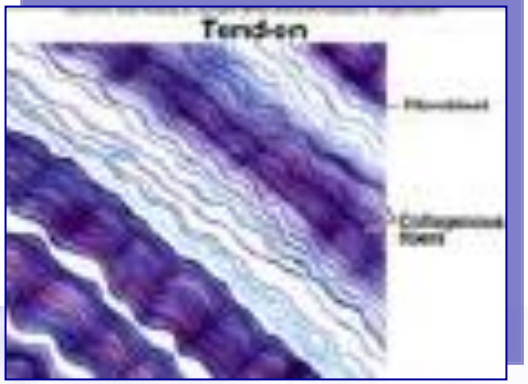
Glycoxidation Theory of Aging

Advanced Glycosylation End products (AGEs)

- The Glycosylation (oxidation). Theory of Aging suggests that cross-links generated in proteins and nucleic acids by nonenzymatic glycosylation may contribute to age-related declines in the functioning of cells and tissues.

- Non-enzymatic addition of glucose to proteins may gradually slow down the protein function.

- Non-enzymatic addition of glucose to nucleic acids may gradually damage DNA of aging



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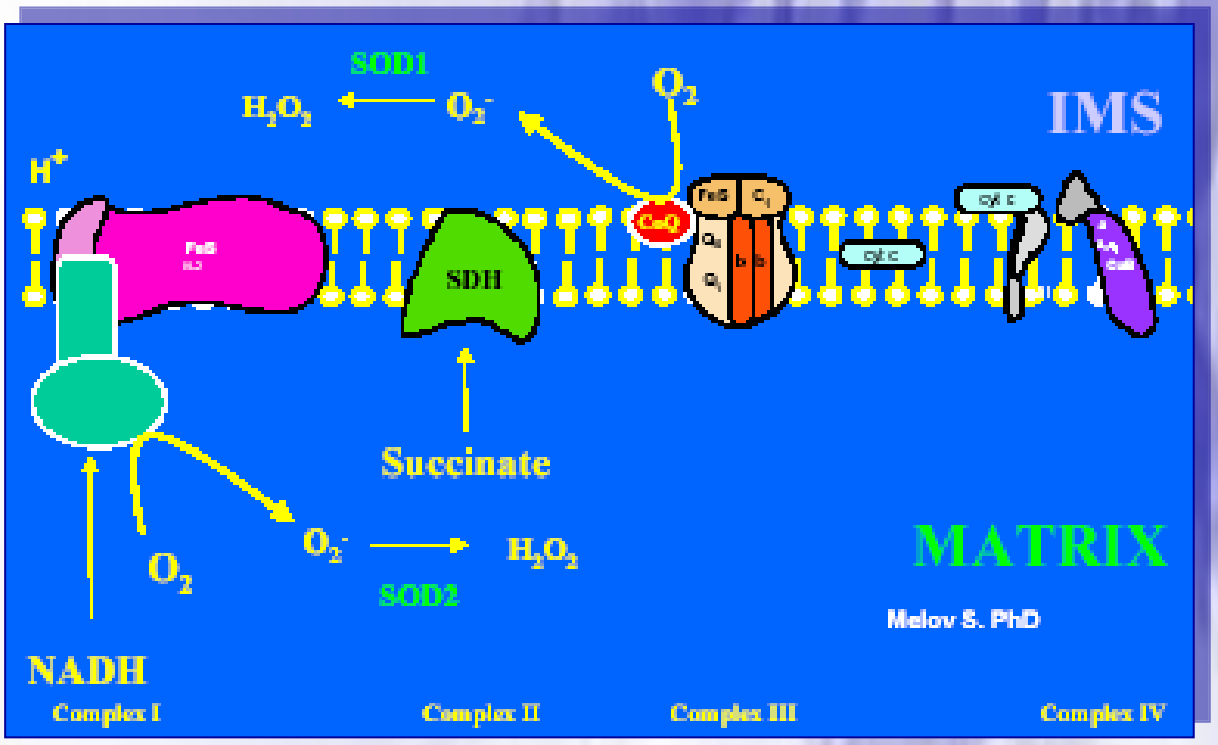
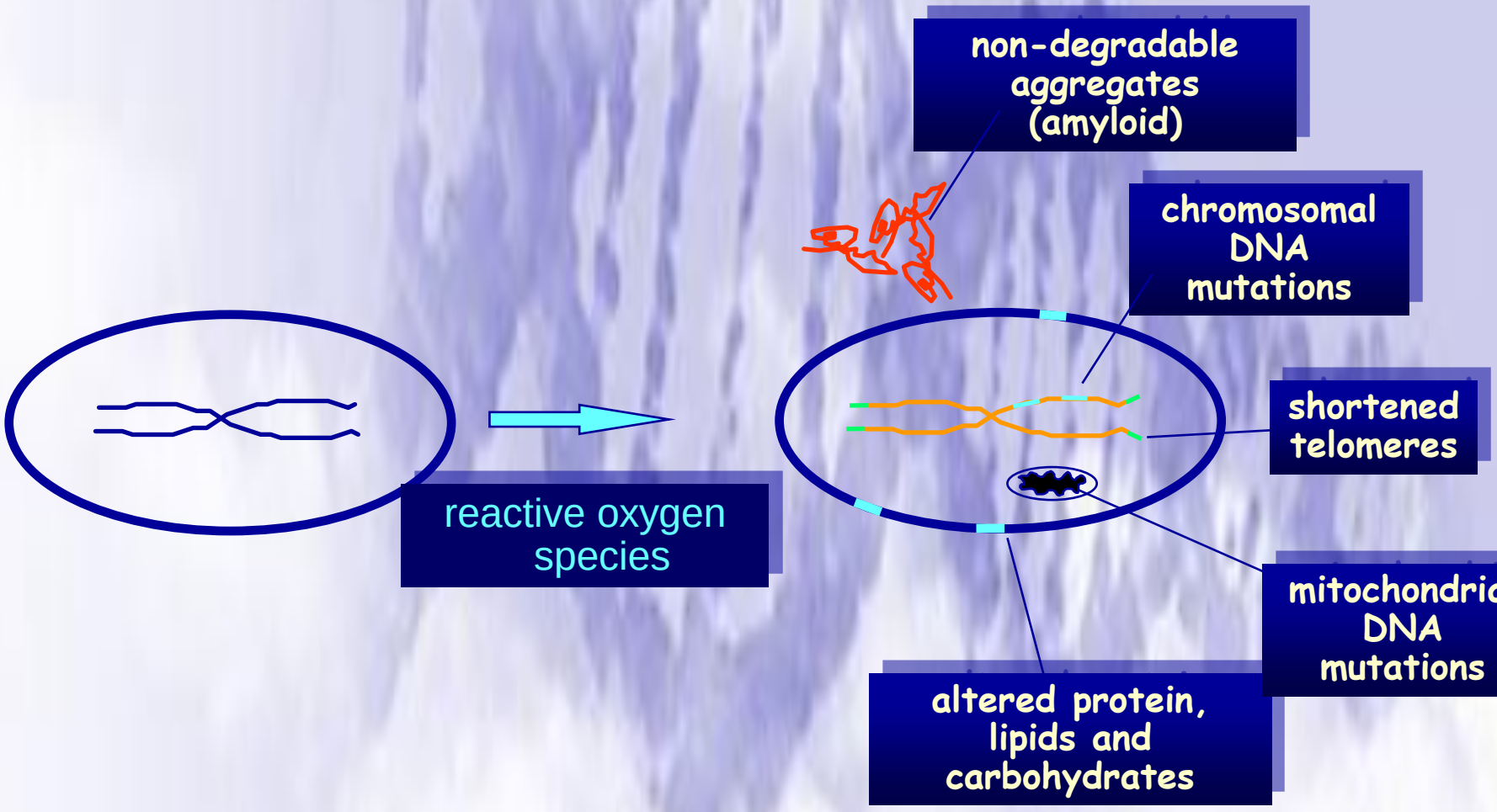
Cellular Theories

Free radical - Oxidative metabolism produces highly reactive free radicals that subsequently damage protein and DNA.



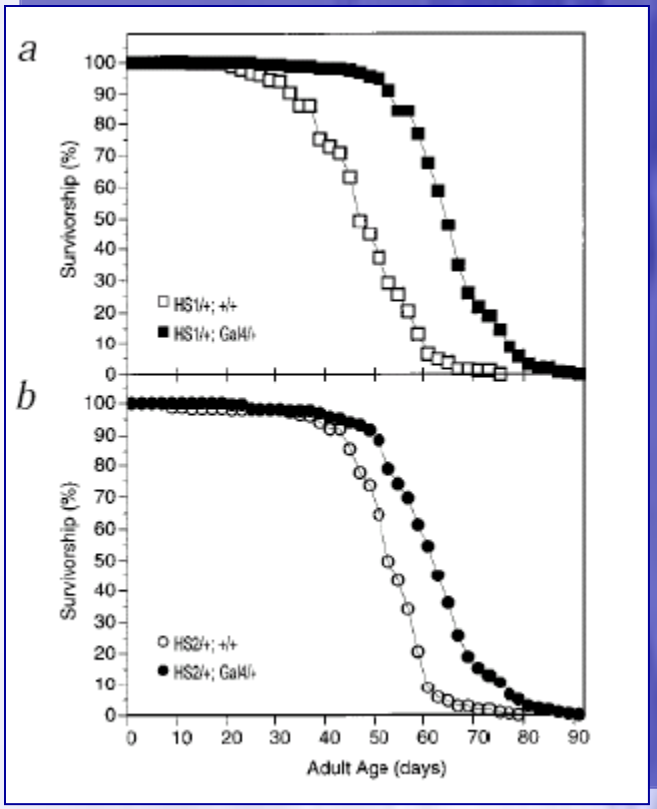
accumulation of mtDNA mutations

ROS-dependent ageing processes



Extension of *Drosophila* lifespan by overexpression of human *SOD1* in motorneurons

Tony L. Parkes[1], Andrew J. Elia[2], Dale Dickinson[1], Arthur J. Hilliker[1], John P. Phillips[1] & Gabrielle L. Boulianne[2]



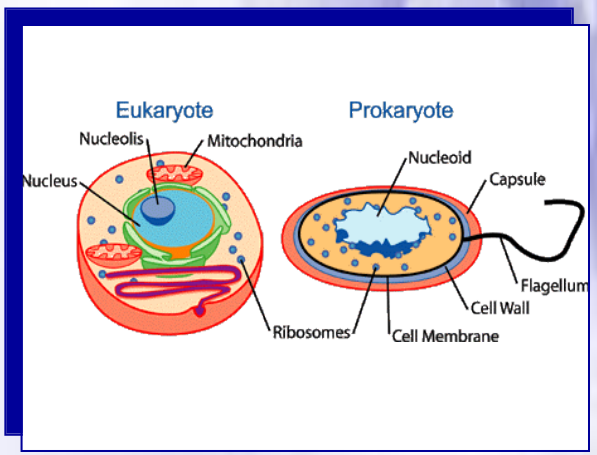
Nature Genetics 1998

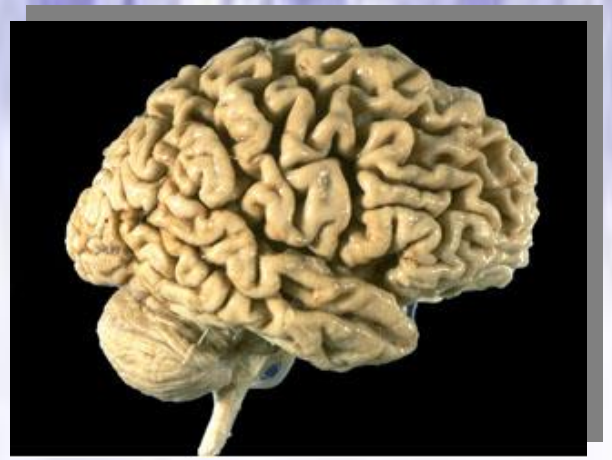
Biological bases of senescence

Early aging

Senescence

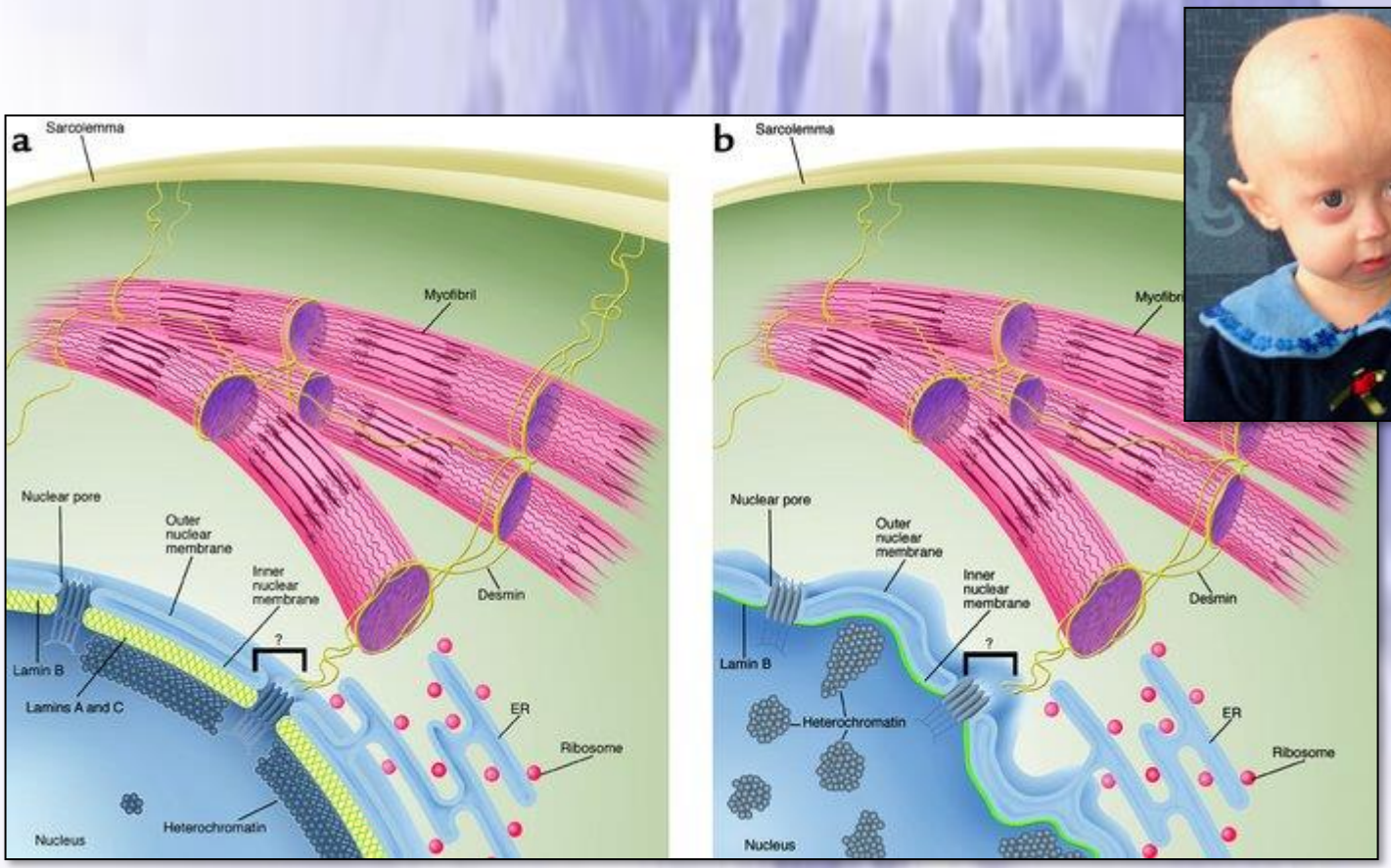
Late onset diseases

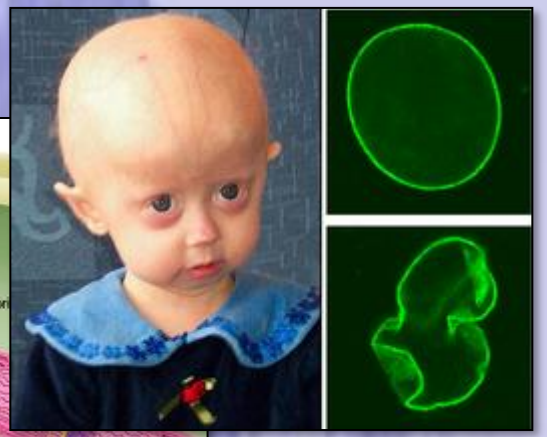




Single gene mutation (progerias)

Lamin A is one of the main components of the nuclear matrix, and mutations manifest as premature aging via epigenetic changes, histone H4 acetylation at lysine 16 (H4K16ac) [10], tri-methylation of H3 lysine 9 (H3H3K9me3) [11], and tri-methylation of lysine 27 on H3 (H3K27me3) on heterochromatin protein 1 (HP1)

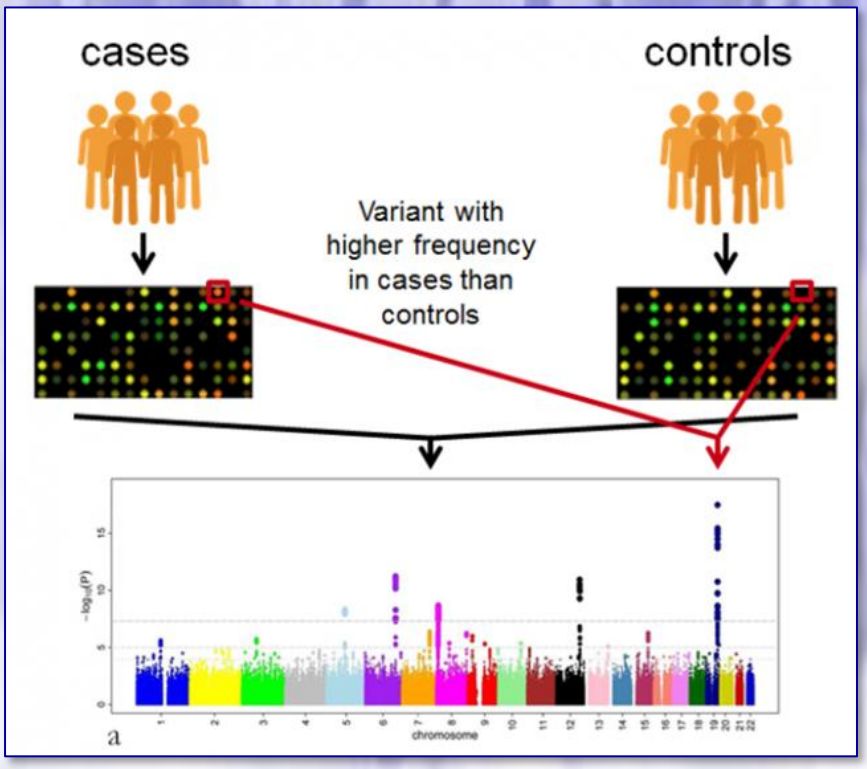




GWAS

27 aging-related gene SNP have been found, many close to the gene encoding apolipoprotein E (APOE).

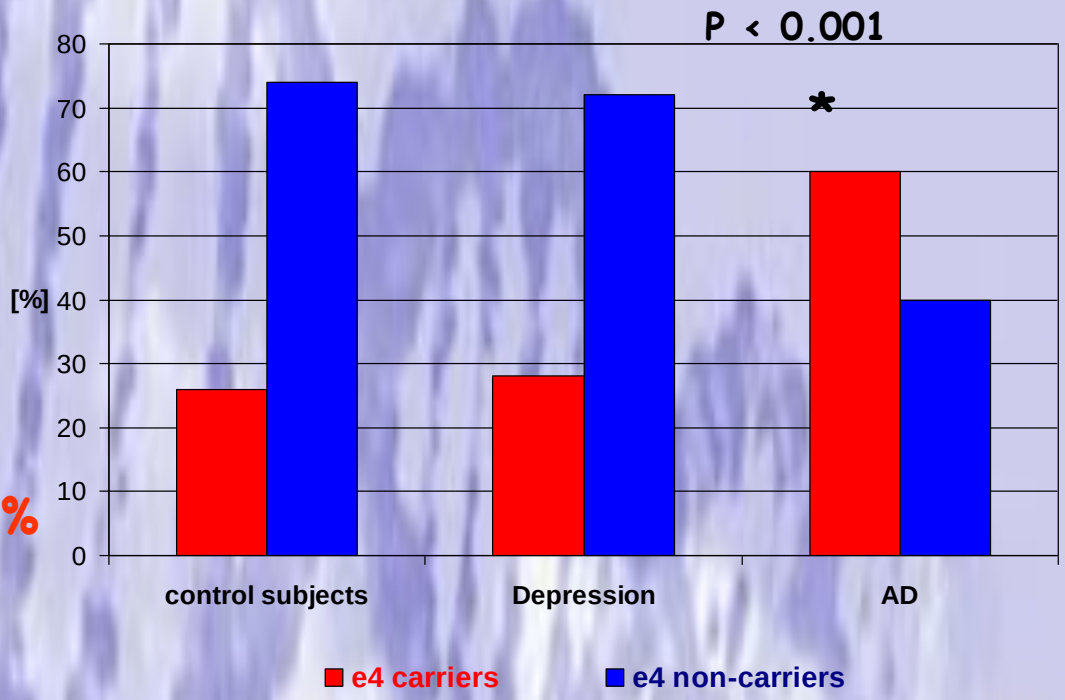
APOE levels are upregulated in cell aging models, driving cellular senescence by regulating the stability of heterochromatin.



Apolipoprotein E (Chr. 19)

- three alleles (e2, e3, e4)
- APOE e4 associated with AD

Corder et al., Science, 1993

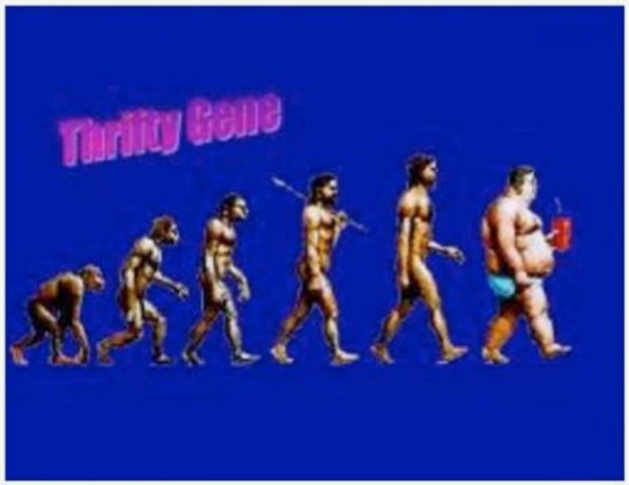


Papassotiropoulos et al.
Dement Geriatr Cogn Disord, 1999

- OR in e4 homozygotes: ~ 8
- Influence on age-of-onset
- Sensitivity and specificity ~ 60%
- little or no predictive validity

Centenarians had a very low frequency of APOEe4 allele and increased frequency of the allele APOEe2

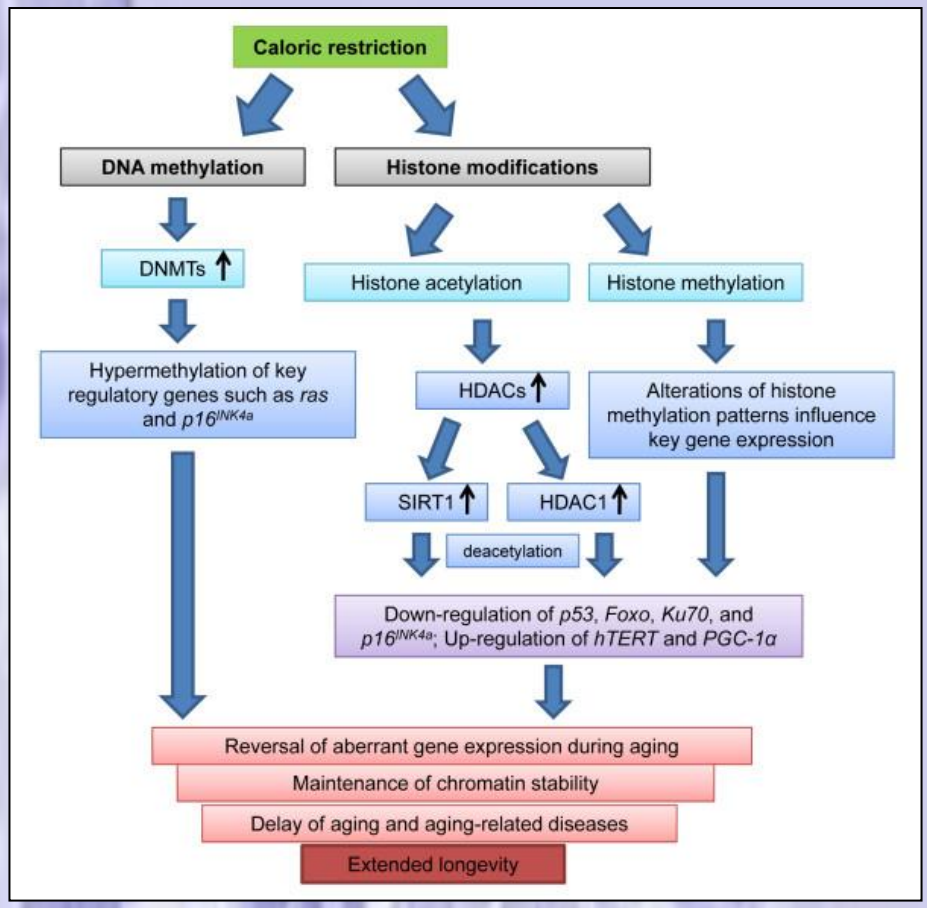
The frequency of the APOEe4 allele is higher in countries where food supply is scarce. This allele is linked to elevated cholesterol blood levels
It is a "thrifty" allele.



As human lifespan lengthened and cognitive and cardiovascular health became more important, the APOEe3 allele spread, while the APOEe4 allele was maintained in all populations by balancing selection. The exposure of people carrying APOEe4 to the new affluent environmental conditions (Western diet and longer lifespans) could have rendered them susceptible to CVDs and AD

Calorie restriction extends the lifespan of Saccharomyces cerevisiae, C. elegans, normal and progeria mouse models, and non-human primate rhesus monkeys, and is the most effective lifespan-extending intervention across species

Restricting the amount of branched chain amino acids (BCAAs), such as leucine, in the diet prolongs the lifespan of $Lmna^{G609G/G609G}$ and $Lmna^{-/-}$ mice.



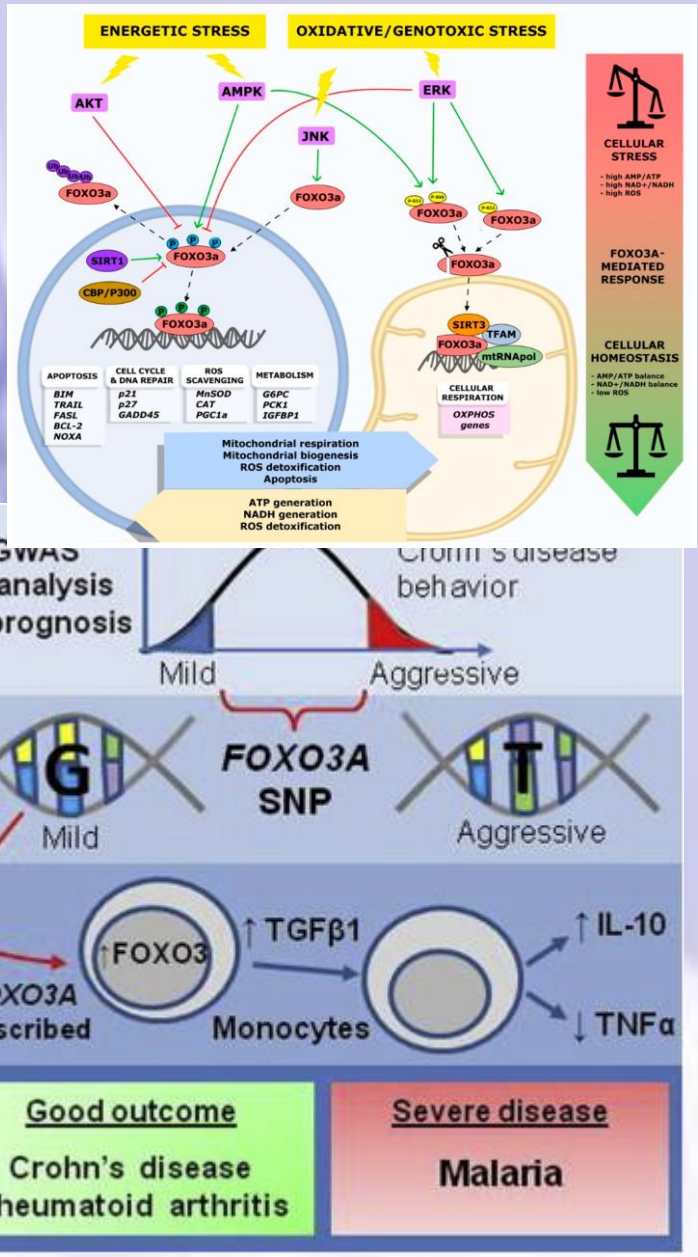
Association Studies

FOXO3A, which is part of the nutrient sensing pathway linked to insulin and insulin growth factor(IGF)-1, balances the cell response to oxidative stress and nutrient availability.

FOXO3A acts as a transcription factor on multiple homeostatic genes in response to decreased insulin/IGF-1 signaling. The SNP rs2802292 allele is associated with longevity across many populations

FOXO3 rs2802292 G-allele has protective effects on several age-related diseases, inparticular CVDs cancer and bone fractures

Nutrient Sensing

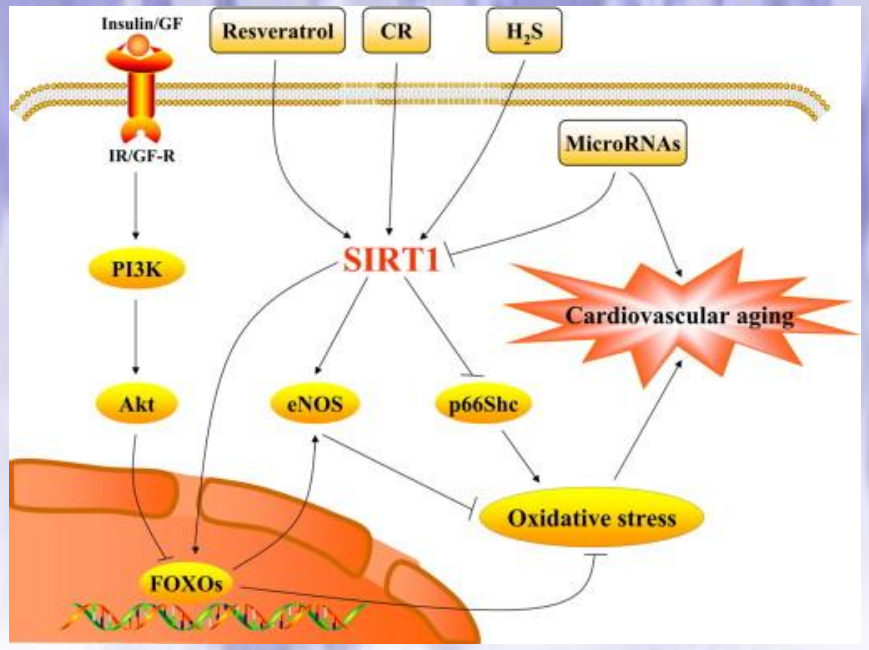


Sirtuins

Nutrient Sensing

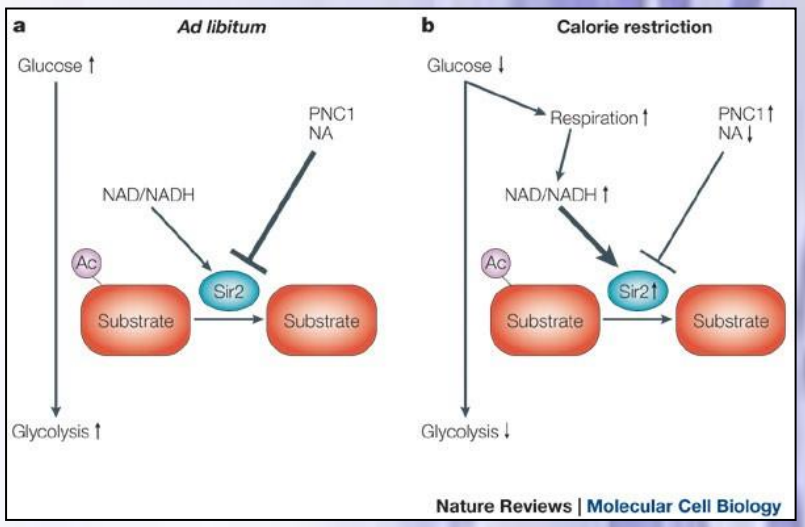
Association Studies

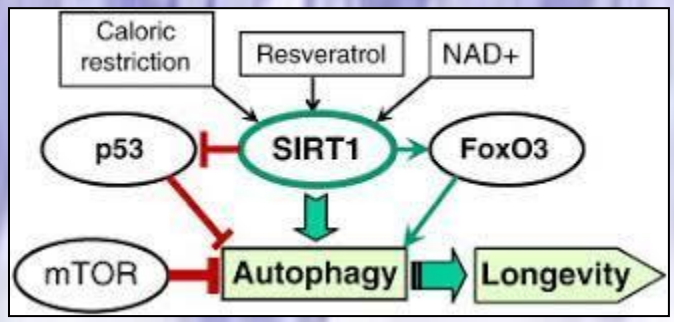
- Le **sirtuine** sono proteine ad attività enzimatica; operano come istone deacetilasi o mono-ribosiltransferasi.
- Le sirtuine mediano fenomeni quali l'invecchiamento, la regolazione della trascrizione, l'apoptosi, la resistenza allo stress e influiscono peraltro sull'efficienza energetica e la vigilanza durante le situazioni a basso introito calorico (restrizione calorica)



Sirtuins

There are seven sirtuins in mice and humans, and, under Caloric Restriction, SIRT1 expression is upregulated.



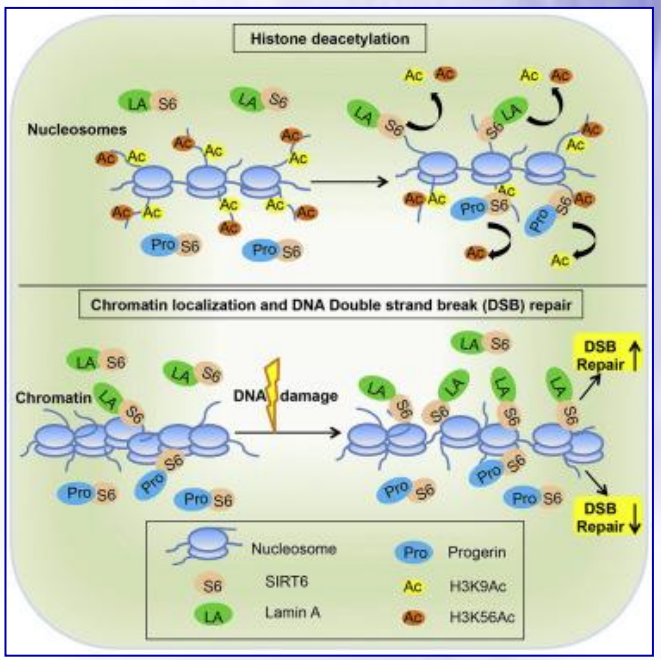


Association Studies

Sirtuin 6 gene (SIRT6) allele contains two linked substitutions (N308K/A313S) enriched in Ashkenazi Jewish centenarians

Lamin A/C interacts with SIRT1, 6, and 7 and affects their intracellular activity and stability, thereby regulating aging

This allele enhances the stimulation of DNA double strand break repair and displays a stronger interaction with Lamin A/C (LMNA)

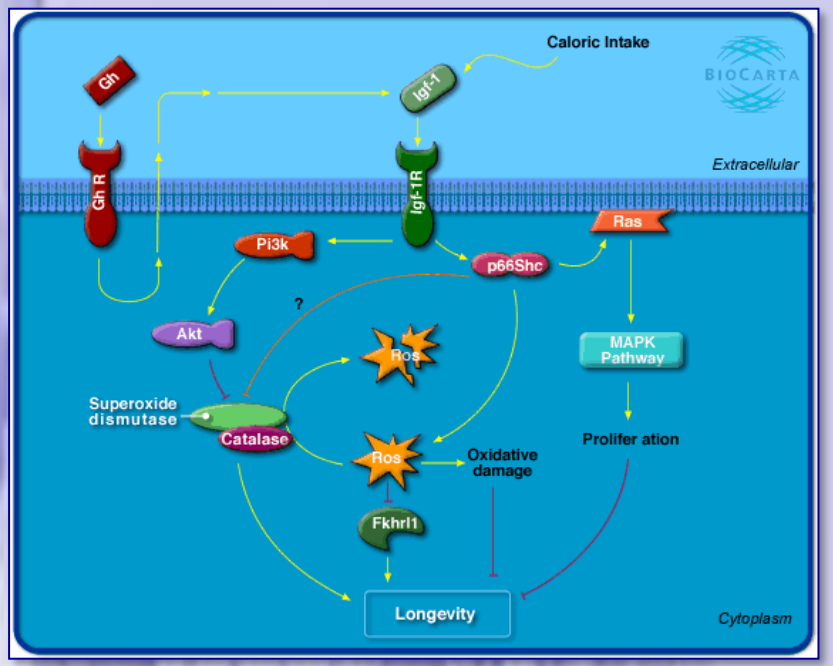


The mutation rate in somatic cells between species is an important factor affecting lifespan, having a strong inverse relationship with lifespan and no obvious correlation with body size

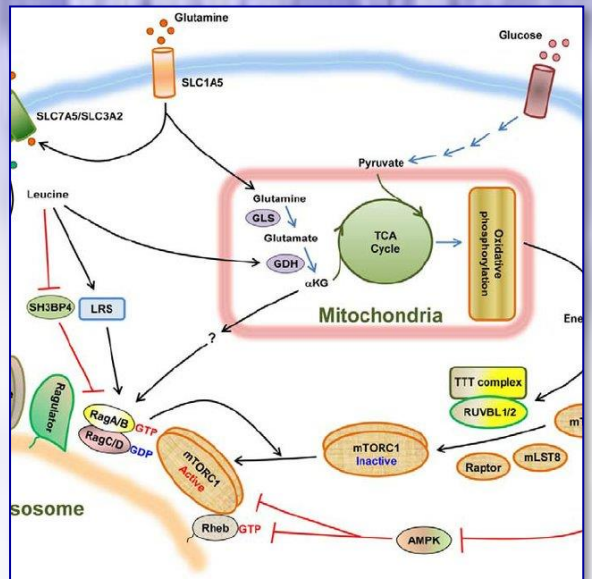
Aging-Related Genes and Signaling Pathways

Nutrient Sensing

In C. elegans, mutations in daf-2 gene, which encodes an insulin-like receptor and regulates the insulin/insulin-like growth factor 1 (IGF-1) pathway, have been found to significantly prolong lifespan.

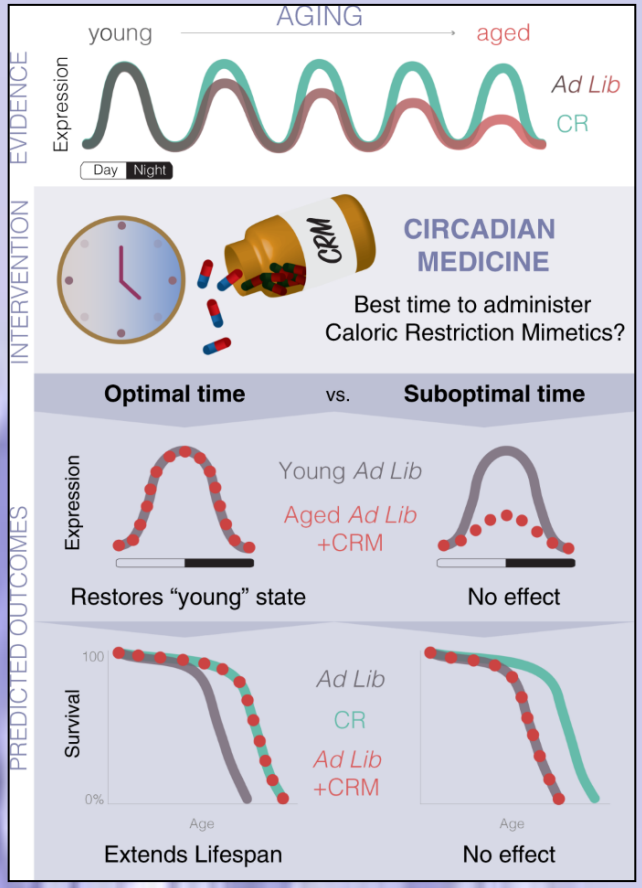


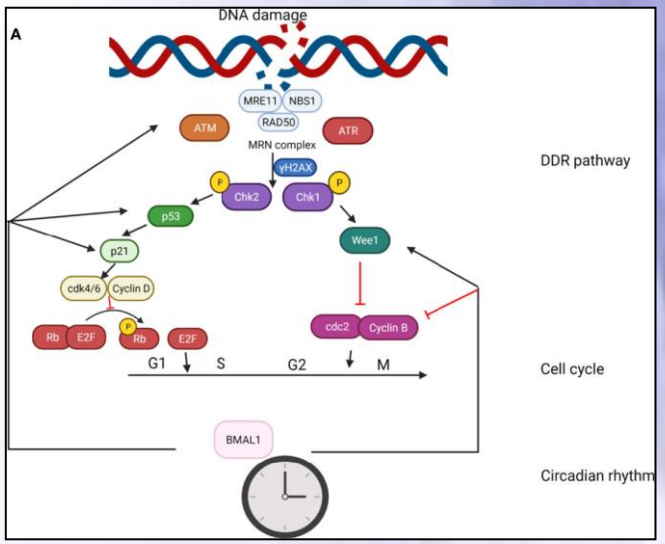
The target of rapamycin (mTOR) signaling pathway is important for perceiving stress signals and nutrient sensing, Genetically inhibiting the insulin/IGF and mTOR pathways extend mouse lifespan.



Circadian Rhythm

low-calorie diet can improve the circadian rhythm of somatic and stem cells, inhibiting the aging process

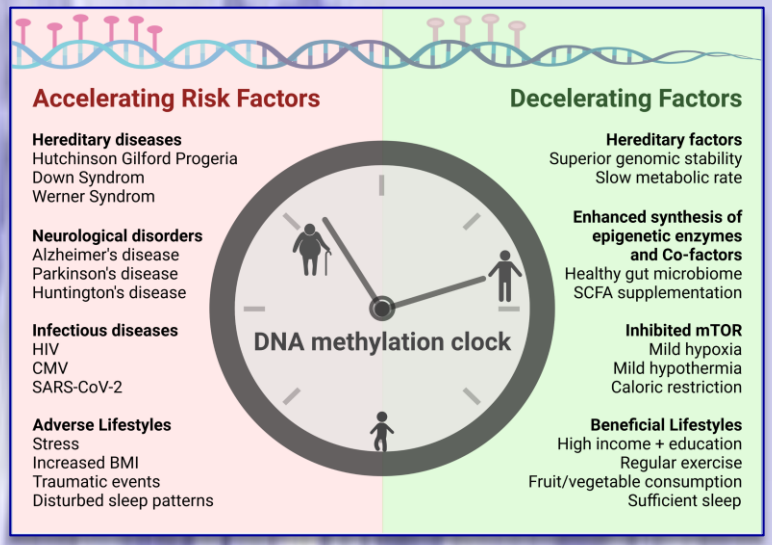


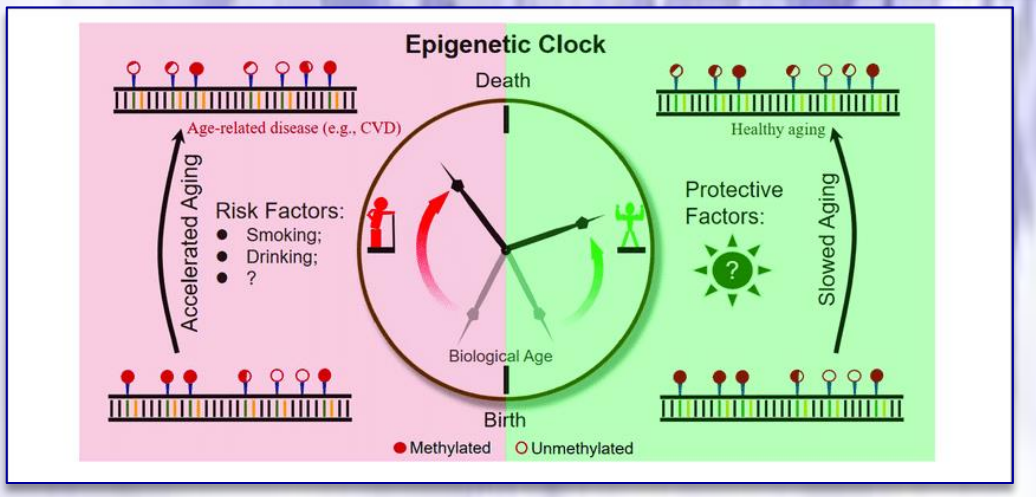


The absence of the core clock transcription factor Bmal1 leads to multiple aging-like pathologies in mice

Age-associated epigenetics perform a more important role than classical genetics in determining which genes in the body are expressed, and this affects susceptibility to disease as aging progresses

DNA methylation (50 methylcytosine (5mC)) levels are clearly correlated with age and can be used to predict the chronological age Thus, this has been termed the "epigenetic clock"





GRAZIE A TUTTI !!