“This is getting really old . . . ”

The Genetics of Aging

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OBJECTIVES

• Explain how mutations in genes can increase lifespan in various organisms
  
  (**METHUSELAH** gene of *Drosophila*)

• Relate chromosome length with aging
  
  (**TELOMERE SHORTENING**) 

• Understand how alteration of intracellular signaling pathway impacts aging
  
  (**INSULIN-LIKE GROWTH FACTOR**) 

• Relate caloric restriction with aging
  
  (Role of **SIRTUIN** proteins)

• Describe accelerated aging disorders in humans
  
  (**WERNER’S SYNDROME, HUTCHINSON-GILFORD PROGERIA**)
Aging – the decline in survival and fecundity with advancing age, caused by the accumulation of damage to macromolecules, intracellular organelles, cells, tissues, organs.
SOME INTRODUCTORY POINTS

• Natural selection does not select for genes that cause aging or determine lifespan. Rather, aging occurs as a result of the pleiotropic effects of genes that specify other processes [Christensen et al. (2006)].

• Genes that influence longevity are involved in stress response and nutrient sensing, generally, intracellular signaling pathways.

• In the past century, mean life expectancy in Western countries increased from ~50 to 75 – 80.

• Twin studies (human) suggest that 25% of variation in lifespan is caused by genetic differences.

• Manipulation of >100 genes in experimental animal models increases longevity.

• Most of these genes are also present in the human genome.

• Gene manipulations that increase longevity also postpone age-related diseases.
Nematode Worm (C. elegans) as a Model Experimental Organism For the Study of Aging

OLD                                    YOUNG                               MUTANT

2 weeks old                          2 days old                          2 weeks old

Mouse (Mus musculus) as a Model Experimental Organism For the Study of Aging

Yeast (S. cerevisiae) as a Model Experimental Organism for the Study of Aging

From: pringlelab.stanford.edu

Single gene mutations influence mortality rate (blue) and max. lifespan (green).

METHUSELAH GENE OF DROSOPHILA
Survival Curves for WT and methuselah Mutant of Drosophila

*Drosophila* methuselah gene encodes a membrane receptor involved in signaling. Mutation of methuselah makes *Drosophila* more RESISTANT to physiologic stress.

From: ECB, 2nd ed.
Reactive Oxygen Species (ROS) damage DNA, protein, and lipids.

- $\cdot O_2$
- $\cdot OH$
Aging happens because genes that produce deleterious affects late in life are not opposed by natural selection.

TELOMERE SHORTENING AND AGING
Telomeres (yellow) – Special, Protective DNA Sequences at Ends of Chromosomes

Telomeres shorten with age.

From: shirley.wang@wsj.com Copyright ©2010 Dow Jones & Company, Inc.
Telomeres shorten with age.
Telomere shortening leads to cell growth arrest and apoptosis (programmed cell death) as well as mitochondrial dysfunction (and increased ROS production).

INSULIN-LIKE GROWTH FACTOR (IGF-1) SIGNALING PATHWAY AND AGING
Mutation of *age-1* and *daf-2* genes of *C. elegans* extends lifespan.

AGE-1, DAF-2, et al. play roles in Insulin-like growth factor (IGF-1) signaling pathway.
Signal transduction pathways can lead to changes in gene expression.

![Diagram showing signal transduction pathways](image-url)

- Extracellular signal molecule (IGF-1)
- Intracellular signaling pathway
- Cell-surface receptor (DAF-2)

**Fast** (< sec to mins):
- Altered protein function

**Slow** (mins to hrs):
- Altered gene expression
- Altered cytoplasmic machinery
- Altered cell behavior

*Figure 16-23  Essential Cell Biology, 2/e. (© 2004 Garland Science)*
DAF-2, AGE-1, AKT-1 genes of *C. elegans* are involved in insulin-like growth factor signaling.

Mutation of these genes changes patterns of gene expression and increase longevity.

= long-lived mutant of mouse, or human cohort in which DNA variants are associated with exceptional longevity

CALORIC RESTRICTION AND AGING
(SIRTUIN PROTEINS)
Caloric Restriction (CR) extends lifespan of mice (and other organisms).

Mouse (*Mus musculus*) as a Model Experimental Organism For the Study of Aging

*(Same Age Mice - CR vs. *Ad libitum* Fed)*

Caloric Restriction (CR) activates SIR2 proteins (SIRTUINS) and increases longevity. Over-expression of SIR2 also increases lifespan.

Sirtuins are NAD$^+$ dependent deacetylase (HDAC) enzymes that remove acetyl groups from proteins to modulate their function.

From: blog.biotek.com
Chromosomal DNA is complexed with histone proteins to build chromatin which can inhibit gene expression. Chemical modification of histone proteins modulates chromatin structure and can turn expression ON or OFF.

(SIR2) = HDAC

Tightly Wound Chromatin = Decreased Transcription

Relaxed Chromatin = Increased Transcription
SIRT1 is the human equivalent of SIR2. It deacetylates many target proteins, in the nucleus and in the cytoplasm, to modulate their activities. Its activity correlates with increased longevity.

Caloric Restriction (CR) activates Sirt1 which deacetylates and activates PGC-1. PGC-1 increases mitochondrial biogenesis and metabolism and decreases ROS production. This leads to increased longevity and “healthy aging”.

Telomere shortening leads to cell growth arrest and apoptosis (programmed cell death) as well as mitochondrial dysfunction (and increased ROS production).
Does Caloric Restriction Extend Lifespan in Rhesus Monkeys?

Ageing: Mixed results for dieting monkeys

Restricted-Calorie Diet May Not Lead to Longevity

Severe Diet Doesn’t Prolong Life, at Least in Monkeys

Big Calorie Cuts Don't Equal Longer Life, Study Suggests
ACCELERATED AGING DISORDERS

Werner’s Syndrome
Hutchinson-Gilford Progeria
Werner’s Syndrome – A Genetically Based Accelerated Aging Disorder

The \textit{WRN} gene encodes an enzyme involved in DNA replication and DNA repair. Mutation of \textit{WRN} leads to DNA damage and arrest of cell division.
Hutchinson-Gilford Progeria

Mutated gene –LMNA (lamin A) Mutations lead to problems in DNA replication and gene expression.
SUMMARY

• Genes involved in aging (longevity) have other functions in cells, especially roles in stress response and control of metabolism.

• Increased stress resistance correlates with longevity.

• Telomeres shorten with age. Telomere shortening leads to cell growth arrest, and correlates with mitochondrial dysfunction, and increased production of ROS.

• Mutations in genes which encode components of the Insulin Growth Factor signaling pathway are associated with increased longevity in many species.

• Caloric restriction (CR) increases lifespan in many species. CR activates sirtuin proteins which modulate the activity of many target proteins, changing patterns of gene expression, metabolism, mitochondrial function, and leading to increased stress resistance, enhanced energy usage, decreased levels of ROS.

• Human genetic disorders like Werner’s Syndrome and Hutchinson-Gilford Progeria provide clues about cellular aging in humans and suggest that aging correlates with elevated mutation rates, changes in gene expression, and arrest of cell division.
ANTI-AGING AGENTS (?)