

Genetics Of Aging

(Introduction to Biology Course Scientific Report)

Poorvi H C and 2021113004

Computational Natural Sciences, IIIT Hyderabad

Instructor: Dr. Vinod P K

Abstract

The nature of the aging process has been the subject of considerable speculation. Aging is the progressive accumulation of changes with time that are associated with or responsible for the ever-increasing susceptibility to disease and death which accompanies advancing age. There is substantial individual variability in the aging process between men and women. Consistent with this possibility, telomeric regions in humans are highly heterogeneous, and chromosome rearrangements near telomeres are commonly involved in human genetic disease. Understanding the mechanisms of telomere loss will therefore provide important insights into both human cancer and genetic disease.

Keywords: *Genome instability; Telomere attrition; Somatic Fitness; Selection Pressure; Epigenetic alterations*

1. Introduction

The process of aging has been a long drawn research topic. Since the 1950s, constant progressive researches have lead the field to grow. Overcoming limitations of human beings having a long life span, by using small scale model organisms to produce results, we apply them further to larger organisms like humans. Age is used to quantize a persons existence. He/she gains a number gradually every revolution of the earth around the sun. We study age keeping this notation in mind. Aging however is a process of increase in **age**, where there is an accumulation of variational changes over generations which help in determining and studying the underlying biochemical mechanisms behind it.

Our genes control all the processes within our system, so there must exist a genetic explanation to age which we will explore in this review. **The Genetic basis to Aging** is a wide area of research which is progressing on a daily basis. Understanding how our genes control degradation over time as well as the influence of sex chromosomes on the process are the major areas of study.

2. Aging

Aging is the progressive decline in functional and structural integrity and homeostasis, culminating in death. It is a phenomenon that stems from the cumulative malfunctioning of the biological machinery that is vital for the fitness of the soma. Old age is accompanied by a striking increase in diseases that are rare in younger individuals, including cardiovascular disease, cancer, and neuro-degeneration.

Aging is a multi-factorial process that is determined by genetic and environmental factors. The accumulation of molecular errors that compromise adult stem cell functions occurs because of genetic and epigenetic interactions and depends on hereditary, environmental and stochastic factors.

3. Hallmarks of Aging

The complexity of aging is due to the factors,

1. Deregulated nutrient-sensing
2. Genomic instability
3. Telomere attrition
4. Loss of protein homeostasis(proteostasis)
5. Epigenetic alterations
6. Mitochondrial dysfunction
7. Cellular senescence
8. Stem cell exhaustion, and
9. Altered intercellular communication (e.g., inflammation)

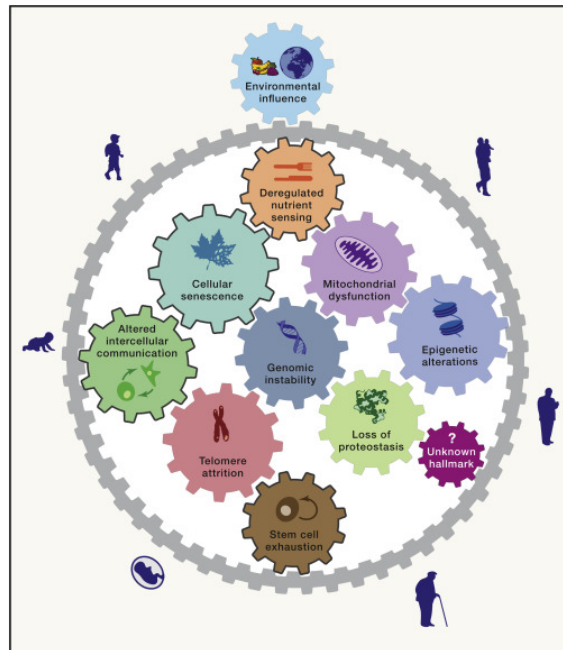


Figure 1. The Aging clock is regulated by interconnected hallmarks (The mechanical analogy illustrates the possibility that perturbations in one hallmark could affect the other)

3.1. Telomeric Attrition

3.1.1. Telomere

The ends of chromosomes in mammals, called **telomeres**, are composed of a 6-bp repeat sequence, **TTAGGG**, which is added on by the enzyme telomerase. In combination with a protein complex called **shelterin**, these telomeric repeat sequences form a cap that protects the ends of chromosomes.

3.1.2. Telomeric influence on aging

Due to insufficient telomerase expression, telomeres shorten gradually with each cell division in human somatic cells, which limits the number of times they can divide.

Double-strand breaks (DSBs) in DNA form as a result of exposure to exogenous agents such as radiation and certain chemicals, as well as through endogenous processes, including DNA replication and repair. DSBs near telomeres are especially prone to chromosome rearrangements, because telomeric regions are deficient in DSB repair. DSBs near telomeres can result in **chromosome instability** in mouse embryonic stem cells, suggesting that telomere loss can contribute to heritable chromosome rearrangements. Consistent with this possibility, telomeric regions in humans are highly heterogeneous, and chromosome rearrangements near telomeres are commonly involved in human genetic disease.

A correlation has been proposed between telomere shortening and somatic stem cell decline during aging. Furthermore, oxidative stress and inflammation, two major postulated causal factors of aging, are known to accelerate telomere shortening, suggesting that telomere length may be an important **biomarker of aging** because it reflects the cumulative burden of oxidative stress and inflammation.

Mammalian telomeric DNA is composed of the TTAGGG repeat sequence with a short single-stranded 3 prime overhang at its end. The single-stranded 3 prime overhang is tucked back into a proximal complementary telomeric sequence to form the t-loop, which essentially hides and protects the free end. **Telomerase** is a **reverse transcriptase** that carries an RNA template that aligns with the end of the existing telomere to add additional telomeric repeat sequences. The regulation of access of telomerase to the telomere determines telomere length, which ranges from **2 to 20 kb** on different human chromosomes.

This occurs because the lagging strand is not completely replicated due to the presence of the RNA primer, which does not start at the very end of the chromosome. As a result, telomere shortening occurs with each round of DNA replication.

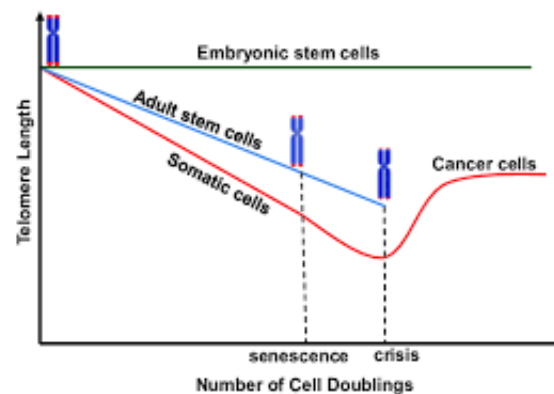


Figure 2. Comparison of stage of life of a cell VS length of telomere.

3.2. Nutrient-Sensing Pathways

The vertebrate-specific growth hormone (GH) acts in the pituitary gland to control the **insulin/IGF pathway** and mediated at least in part by insulin/IGF signaling. Loss-of-function mutations in transcription factors necessary for pituitary development, lead to deficiency in GH production and result in a extension of lifespan.

In addition to GH, other circulating vertebrate-specific hormones and peptides have been linked to aging, including **leptin**, **ghrelin**, and **fibroblast growth factor 21** (FGF21).

For example, Increased levels of FGF21 can systemically extend lifespan in part by inhibiting GH and insulin/IGF signaling. Decreased levels of **calcitonin gene-related peptide (CGRP)** can extend lifespan. Hormones and peptides act in a non-cell-autonomous manner to systemically modify physiology and influence lifespan.

3.3. Senescent Cells and Inflammaging

Vertebrate-specific hallmarks of aging, such as cellular **senescence** and **Inflammaging** (a chronic state of inflammation that is characteristic of old age) have recently been targeted to

extend health span. Senescent cells contribute to inflammaging by secreting **cytokines** during aging. This is consistent with the observation that senolytics (drugs that specifically kill senescent cells) have beneficial effects on age-related diseases.

Inflammation can also occur due to immune system decline (immuno-senescence) and reactivation of endogenous transposons.

The hallmarks of aging are highly interconnected, and mutation in one gene likely influences several hallmarks. Notably, hallmarks that are responding to the environment, such as nutrient sensing, may act as hubs to impact many pathways at once.

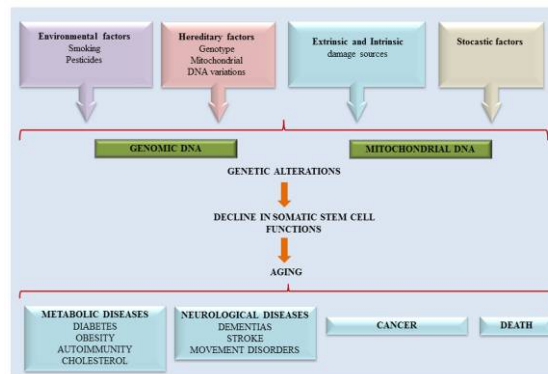


Figure 3. The environmental conditions, individual genotype (genomic and mitochondrial DNA) and stochastic factors can induce genetic and epigenetic alterations that cause a decline in somatic stem cell function that can be the origin of metabolic, degenerative diseases, cancer and aging in the individuals.

3.4. Measure of Somatic Fitness

According to the latest discoveries, Within members of the human species, **mean telomere length in leukocytes** is an index of somatic fitness. What's more, shorter mean leukocyte telomere length is associated with obesity, insulin resistance, and cigarette smoking. As telomere length is heritable, and obesity and cigarette smoking are largely environmental, acting in combination, genes and the environment may not only shorten leukocyte telomere length but also reduce the human life span.

3.5. Theories of Aging

There are two main groups of biological aging theories: **the senescent theory of aging** and **the programmed theory of aging**.

The senescent theory builds on the belief that damage, random errors, and drift occur for different reasons as we age, which eventually leads to less capacity for maintenance and resilience. The subtheories are:

1. **Disposable soma:** faults accumulate in somatic cells as they get worn out across life.
2. **Reactive oxidative species (ROS) theory of aging:** free radicals and oxidative damage across the lifespan cause damage.
3. **Mutation accumulation:** somatic DNA mutations accumulate in cells and tissues that cause errors, and
4. **Rate of living theory:** increased energy metabolism escalates the production of free radicals that in turn accelerate organismal senescence and reduce lifespan.

The programmed theory of aging suggests that aging is tightly regulated, similar to a biological clock,

1. **Hayflick limit:** was shown that the number of times a cell can divide is finite and preset in the cell's DNA.

2. **The central aging clock** was proposed in 1975 as a 'hypothalamic clock' or with the pineal gland as a central clock regulator.

3. Developmental processes and growth, embryonic development, and aging are driven by the same molecular mechanisms.

3.6. Relation of Sex on Aging

In general, women live longer than men, consistent with lower biological ages as assessed by **molecular biomarkers** but there is a paradox. Women are frailer and have worse health at the end of life. While men still perform better on physical examinations.

As telomere length is equivalent in newborn boys and girls, the sex-related difference in leukocyte telomere length appears to arise from variables that affect telomere attrition during **extrauterine life**. These variables may include **ovarian steroid hormones**, particularly estrogen, and **selection pressure** between two somatic cell types.

3.6.1. Oxidative Stress and Inflammation

Oxidative Stress and Inflammation figure centrally in several hypotheses of aging and life span. **Oxidative stress** accelerates telomere erosion during somatic cell replication, and inflammation increases leukocyte turnover rate. Estrogen, a powerful **antioxidant** in most tissues and an **anti-inflammatory agent**, probably attenuates leukocyte telomere erosion in women.

3.6.2. Sex-chromosomal linked mechanisms

As men and women are born with different sets of chromosomes, the double X version in women versus the XY in men, there are apparent phenotypic differences because of this. Men are thus more susceptible to X-linked recessive diseases, for example hemophilia, and there may be many more age-related traits driven by X-chromosomal variation. The effects may be more pronounced due to increased **genomic instability** as we age.

Other sex-specific genetic factors may contribute to the programmed theory of aging. For example, mitochondrial inheritance (and selection) takes place through the maternal line, as the cytoplasmic contents are derived from the mother's egg.

3.6.3. Selection Pressure

One of the X chromosomes of each somatic cell of the developing female embryo is stochastically inactivated during the early phases of embryonic life—a process that silences roughly 75% of the genes on the affected chromosome. Newborn girls, therefore, exhibit a balanced somatic cell mosaicism, in that half of their cells have an active paternal X chromosome and the other half an active maternal X chromosome. Somatic cell mosaicism is skewed in elderly women, so that the majority of their somatic cells exhibit either an active paternal or an active maternal X chromosome. This intriguing and ostensibly **epigenetic** phenomenon may be explained by selection pressure during the woman's lifespan. A man, in contrast, possesses only one somatic cell type with respect to the X chromosome and is hence disadvantaged as compared with a woman in terms of somatic cell selection.

Altogether, women's augmented anti-oxidative and anti-inflammatory capacity, boosted by the advantage of somatic cell selection, bespeaks a better somatic fitness, expressed in the longer life span and leukocyte telomere length of women than men.

4. Future Advancements / Potential research opportunities

The striking success of research on the genetic modulation of life spans in model organisms has not yet been matched by investigations of the maintenance of structure and function in various organs (i.e., health span).

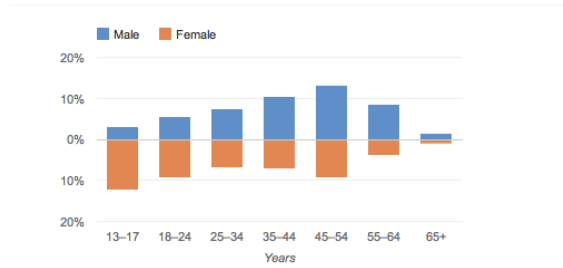


Figure 4. Distribution of male-female individuals of a given age range.

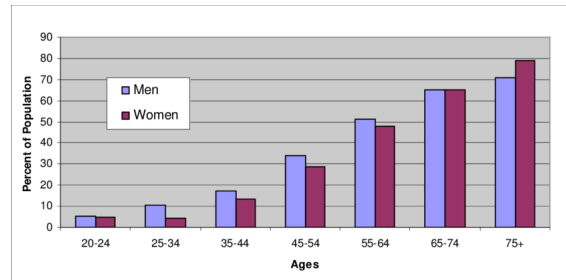


Figure 5. Prevalence of **cardiovascular disorders** in people of different genders and ages. (age related disorder)

More work is needed in worms, flies, and even in mice, where such studies are more advanced. We also require much more sensitive and specific assays for a range of human physiological functions during aging. Epigenetic drifts in gene expression have been shown to be among the reasons identical human twins differ as they age. Are such epigenetic variegations mainly due to environmental influences?, such questions need to be answered and more deep research is needed in these areas.

There is overwhelming support for the fact that whenever sex is analyzed in biological research on aging, it demonstrates significant sex differences, whether it is human cohorts or animals. However, most pre-clinical and clinical studies have been performed in male subjects, animals, or cell lines, limiting our understanding of the impact of sex on the given research question.

To overcome these issues, the National Institutes of Health now expects that sex as a biological variable to be factored into research designs, analyses, and reporting in vertebrate animal and human studies. A suggestion could be that all biomedical journals should adhere to common practice and guidelines requiring authors to report sex-specific effects of their findings and put that into a research context whenever applicable.

5. Conclusion

In this review, we have tried to disentangle the complex interactions between biological aging and sexual dimorphism and have provided evidence from the perspective of current theories thereof. Many of the biological and functional markers of aging under study, as well as for age-related diseases, are consistent with both the programmed theory of aging and the senescent theory at the same time.

Both chromosomal-linked mechanisms and hormones may explain the observed sexual disparities. Hence, there is no clear pattern of association within these interactions; rather, many intertwined mechanisms are in action.

It is clear that cellular and molecular mechanisms of aging are better maintained in women, although after menopause, women seem to catch up and, to some extent, reach the same levels of aging as men.

Aging as a phenomenon is a well studied and researched topic, it has immense scope and a standard problem while studying age is faced because human life span is way too long to obtain

any conclusive results. So most of the experiments are conducted on small scale animals with small lifespans, and there results are magnified to accommodate animals with larger lifespans.

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