# Aging: Epigenetic Alterations and Loss of Proteostasis

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**Aging is a physiologic process marked by cellular inability to respond adequately to stresses. Epigenetic changes such as reduced histone bulk, abnormal patterns of histone modification as well as abnormalities in DNA formation are some of the causative factors of aging. Another contributory factor to the aging process is the loss of proteostasis which leads to an unstable set of proteins that are toxic to cells and thus trigger the aging process. With the advancement of biomedical science, many new theories have been proposed to decode this mysterious event in a cell's life.**

## Definition

Aging can be defined as a **diminished response to stress, the escalation of homeostatic imbalance, and an enhanced threat from aging-related pathologies**.

Many theories have been put forward to explain the concept of aging. **Some of the more prominent theories include the following:**

- **Stochastic:** Episodic events that happen throughout a person's lifetime cause random cell damage and accumulate over time, causing aging (eg, free radical

theory, wear and tear theory, error theory, and connective tissue theory)
- **Programmed:** Cells have a limited doubling potential and become unable to replicate afterward, triggering apoptosis or programmed cell death
- **Cellular:** As an increasing proportion of cells gradually reach senescence, a terminal stage at which cells cease to divide, this limits the body's ability to regenerate and to respond to injury or stress
- **System:** The discrete existence of living organisms within the body that obey the second law of thermodynamics or the law of entropy leads to a build-up of chaos and system disintegration
- **Evolutionary senescence:** Aging is the failure of natural selection to affect late-life traits. Mortality increases as fertility decreases, as a way to further the survival of the species

None of these theories enjoys unequivocal support among the scientific community, however, as the general consensus is that each theory explains only one part of a larger picture.

A number of physiological systems are responsible for the process of aging, including the following:

- Genomic instability
- Mitochondrial dysfunction
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis
- Altered intercellular communication
- Cellular senescence
- Deregulated nutrient sensing
- Stem cell exhaustion

Advances in molecular science have identified three main signaling pathways that may disrupt the process of aging (see table below).

| Signaling Pathway | Explanation |
|---|---|
| Dietary restriction | • Based on amino acid sensing serine/threonine kinase mTOR, and the energy status-dependent kinase AMPK<br>• This theory is based on the hypothesis that a diminished dietary intake—that is, below ad libitum levels—increases lifespan |
| Insulin/IGF-1 like signaling pathway (IIS) | • Identified first in *Caenorhabditis elegans* (roundworm) (Panowski and Dillin, 2008)<br>• This theory hypothesizes that decreased IIS activity enables the entry of specific proteins into the nucleus, which then activates a diverse transcriptional profile. This profile is responsible for the extension of the cellular vitality, preservation of functionality, and, therefore, retarded aging |
| Diminution of mitochondrial electron transport chain activity | • Reduction in expression of the mitochondrial genome associated with the electron transport chain (ETC)<br>• Especially affects ETC complexes I, III, IV, and V through iRNA; has been shown to extend the cell's lifespan |

While these pathways may act independently, they all comprise a few key factors that have been shown to be at work in species that enjoy extended lifespans:

- Altered metabolism toward the reinstatement of cellular homeostasis

- Escalated stress response
- Delayed reproduction
- Slowed development

Maintenance of cells' signature protein molecules and genomic stability are two significant traits that can be identified in almost all species that have been relatively successful in slowing down the aging process (see image).

## Epigenetic Alteration

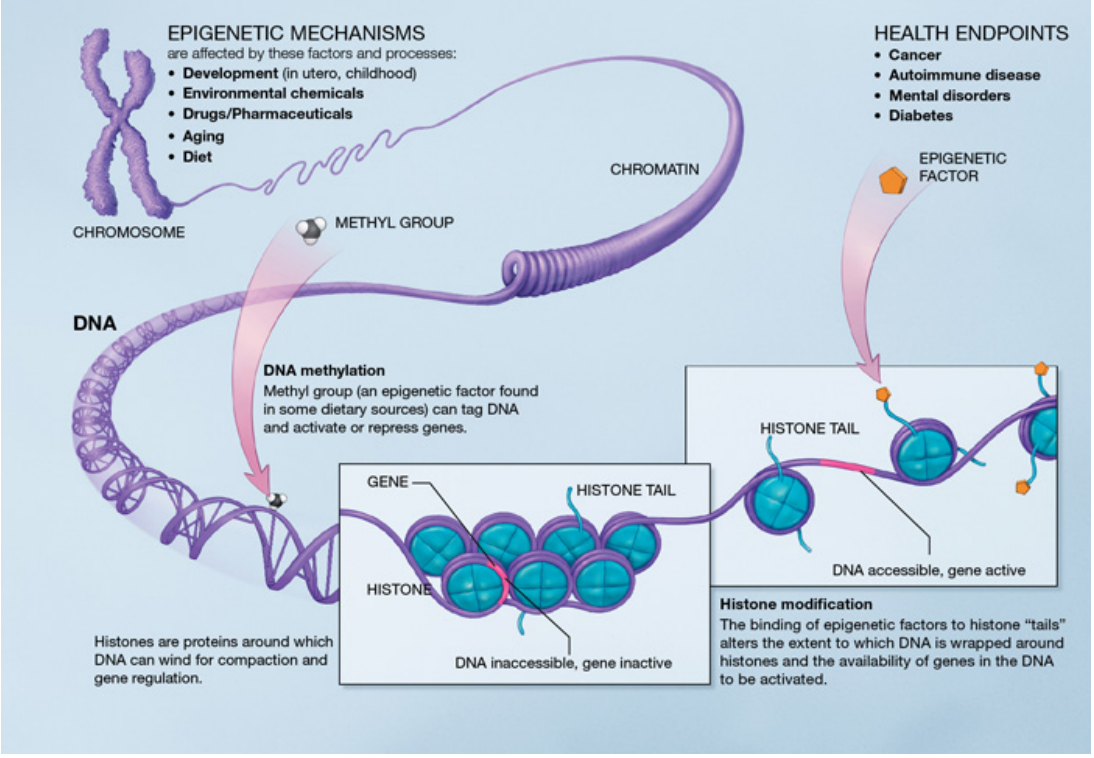


Image: Epigenetic mechanisms. B:y National Institutes of Health. License: Public domain.

Epigenetic alterations and loss of proteostasis are the primary hallmarks of aging. Epigenetic factors can influence how genes are expressed at different ages. Changes in chromatin state regulate the transcription of genes.

**Some of the significant nuclear processes affected by epigenetic alterations that have a key role in aging include the following:**

- DNA replication and repair
- Gene transcription and silencing
- Cell cycle progression
- Telomere and centromere structure and function

Epigenetic factors change the phenotype without changing the heritable genotype. **The key components leading to epigenetic alterations include:**

- Histone modifications
- Alteration of DNA methylation patterns
- Chromatin remodeling

## Histone Modification

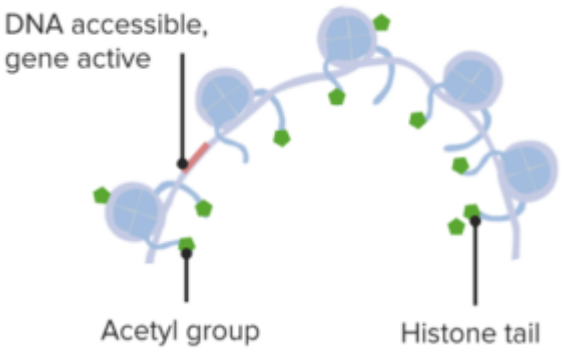


Image: Histone modification. By: Lecturio.

Nucleosome comprising a string of DNA wrapped around an octamer of histone protein is the basic structural unit of chromatin (see image). The nucleosome is also the basic target of destructive processes that culminate in cellular aging and death. Histone modifications are post-translational modifications that occur in these proteins to facilitate appropriate chromatin remodeling and associated activities.

**Key histone modifications include the following:**

- Lysine and arginine methylation
- Lysine acetylation
- Serine and threonine phosphorylation
- ADP-ribosylation of glutamic acids
- Proline isomerization
- Lysine sumoylation and ubiquitylation

These histone modifications control the accessibility of DNA and therefore the resulting gene transcription and translation activity. They also regulate the access of regulatory proteins to DNA. Dysregulation of histone modifications thereby renders the genome susceptible to modulation by unwanted mechanisms and factors, which can have significant negative results.

## Alteration of DNA Methylation Patterns

**DNA methyltransferase enzymes regulate nucleosomal DNA's methylation.** DNA methylation is an established means of modulating transcriptional restriction or activating many vital genes. Methylation of subtelomeric chromatin, transposons, and pericentric chromatin prevents translocation and recombination across the genome. Notably, these are also the hubs of repetitive sequences.

Histone modifications and DNA methylation patterns determine two distinct types of chromatin (see table below).

| Type of Chromatin | Explanation |
|---|---|
| Euchromatin | Hyperacetylation of histones and hypomethylation of both histones and DNA results in the formation of gene-opulent, biochemically active, transcriptionally effective domains of loosely held chromatin. |

| | |
|---|---|
| Heterochromatin | Highly condensed chromatin is associated with inactivity and decreased transcriptional access to genes. This enclosed chromatin configuration is brought about by the hypoacetylation of histones and the simultaneous hypermethylation of histones and DNA. |

DNA methylation modifications have been linked to Alzheimer's disease.

## Chromatin Remodeling

Decreasing levels of heterochromatin are associated with aging. Epigenetic chromatin remodeling is caused by environmental stimuli. Modulation of non-coding RNA species is believed to account for the majority of chromatin remodeling and transcriptional gene silencing (see image).

**Non-coding RNA species that are instrumental in the control of diverse vital cellular functions include the following:**

- Differentiation
- Apoptosis
- Cell cycle regulation
- Tumor suppression

**The important types of non-coding RNAs are:**

- Small interfering RNAs
- Micro-RNAs
- Piwi-associated RNAs

Epigenetic alterations have been implicated in premature aging syndromes such as **Hutchinson-Gilford progeria syndrome (HGPS)**. Patients with HGPS exhibit multiple progeroid symptoms by the age of three years. They possess defects in gene encoding A-type laminins and have associated loss of heterochromatin from the nuclear periphery. Evidence suggests that defects in the structural nuclear proteins alter epigenetic control of the genome, resulting in genomic instability.

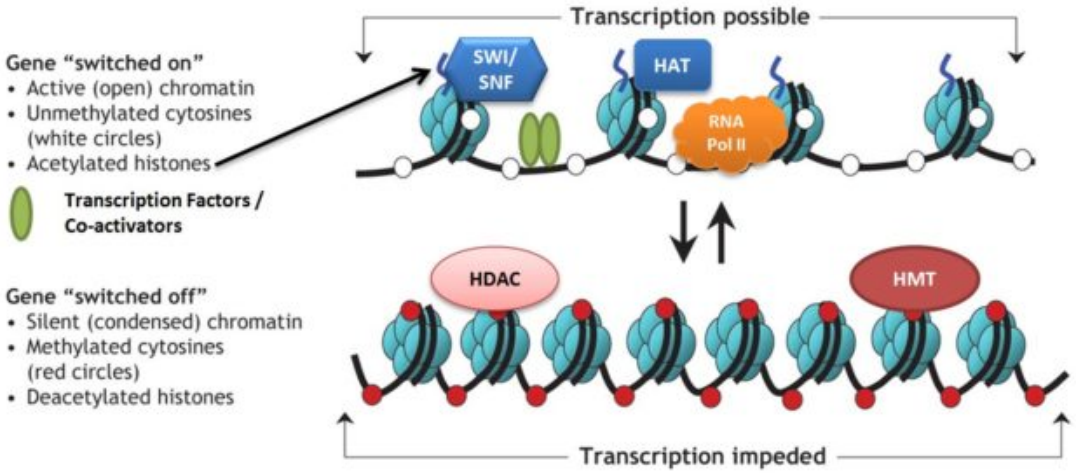


Image: Chromatin remodeling complexes in the dynamic regulation of transcription. License: CC BY 3.0

# Loss of Proteostasis

Maintenance of cellular proteome, the unique subset of proteins in every cell, is remarkably similar in species with long lifespans.

**Vital cellular protein machinery can be altered in a number of ways, including:**

- Misfolding of proteins
- Aggregation errors
- Translational errors
- Covalent modifications (eg, oxidation)
- Polymorphism
- Cellular stress

The resultant abnormal protein, which aggregates secondary to proteotoxic stressors, can induce a vicious cycle of damage. This process leads to the production of more damaged and cytotoxic abnormal protein molecules. Significant damage is caused by these unstable molecules, which ultimately leads to the destabilization of the cell protein's homeostasis.

This loss of proteostasis culminates in the malfunctioning of various cellular sub-components and, ultimately, deterioration in the cell's function and vigor. Older cells possess more abnormal, misfolded proteins and proteins that bear the brunt of the oxidative damage, such as increased cross-linking and aggregated proteins, diminished catalytic activity of enzyme proteins, oxidized methionine, glycation, and carbonylation.

A complex security network to ensure the proper production, regulation, and timely destruction of cellular proteins exists. Homeostasis of proteins in a cell is vital to the proper functioning of a cell. This network is called the "proteostasis network."
**Its various sub-components can be summarized as follows:**

- Regulators of protein synthesis
- Protein translation moderators
- Protein folding controllers
- Protein trafficking regulators
- Protein secretion monitors
- Protein degradation controllers

**Alteration and subsequent loss of proteostasis can be modulated by a detrimental change in the significant pathways outlined in the table below.**

| Pathway Affected | Explanation |
|---|---|
| Translation rate control | Modulation of the rate of protein synthesis has the potential to alter proteostasis. There is strong evidence to suggest that a diminished translation rate delays aging in many species. |
| Protein folding | Molecular chaperones assist proteins in folding and assembling themselves in a specific order. Dysregulation of this crucial step may result in protein misfolding and, ultimately, cellular senescence. |
| Stress response | Chaperones and other upstream transcription factors prevent the formation of folding-sensitive proteins in times of stress, which can disrupt proteostasis. These molecules mediate their actions through diverse cascades, which have been implicated in determining the length of a cell's life. |

| | |
|---|---|
| Heat-shock response | This response coordinates the response to thermal stress and is a determining component in a cell's lifespan extension pathway. |
| Protein trafficking | Delivery of proteins to their appropriate destination is crucial to the longevity of a cell's lifespan. |
| Unfolded protein response | The endoplasmic reticulum (ER) has its own customized stress response and handles errors in protein trafficking through the secretory pathway. The ability of a cell to regulate the ER stress response diminishes with age. |
| Protein degradation | Terminally misfolded, abnormal proteins are scavenged through a specialized system mediated by ubiquitin, proteasomes, and lysosomes. Mismanagement of the proteolytic breakdown of these irrevocably damaged molecules can result in cellular damage and a decline in cellular proteostasis. |
| Proteasomal degradation | The ubiquitin-proteasome system is largely responsible for the scavenging of misfolded proteins. At present, age-dependent changes in this pathway are being extensively studied. |
| Hypoxia response | Transcription factors activated as a response to low oxygen conditions are known to modulate aging. |
| Autophagy | Macroautophagy, or chaperone-mediated autophagy, is linked to the role of lysosomes in premature aging. |

## Diseases of Protein Misfolding

The involvement of disparate toxic proteins and the late age of onset are the hallmark features of diseases of protein misfolding. Through an alteration in proteostasis machinery, signaling pathways similar to those that regulate aging have a hand in the etiopathogenesis of these diseases. Neurons are especially susceptible to such changes. The most studied diseases of protein misfolding are the neurodegenerative diseases, including:

- Parkinson's disease
- Huntington's disease
- Alzheimer's disease

Cataracts can also be thought of as a disease of the elderly secondary to mismanaged proteostasis.

## What is Successful Aging?

To differentiate between normal aging and successful aging, we first need to define these two terms. Normal aging is defined as the normal decline in physical, social, and cognitive functioning with age. Successful aging, on the other hand, is defined as little or no age-related decrement in physiological and cognitive functioning, which scientists are now attempting to bring about.

Successful aging can also be defined as the absence or avoidance of disease, and the risk factors for disease; by the maintenance of physical and cognitive functioning; and by maintaining autonomy and social integration. Certain psychosocial elements have also recently been added to the definition of successful aging.

**The main elements of successful aging include the following:**

- An increase in life expectancy
- Life satisfaction, happiness, and contentment
- Preserved cognitive functioning
- Personal growth and learning new things
- Independent physical functioning
- Perceived autonomy, control, independence, adaptability, coping, self-esteem, and sense of self

**The general population tends to measure successful aging by the following factors:**

- Accomplishments
- Financial security
- Integration into the neighborhood/community
- Attention to physical appearance and grooming
- Productivity and contribution to society and their local community
- Sense of humor
- Having a “purpose” in life
- Spirituality

## Summary

Aging can be defined as a diminished response to stress, the escalation of homeostatic imbalance, and an enhanced threat from aging-related pathologies.

Although many theories have been put forward to explain the process of aging, none of these theories enjoys unequivocal support among the scientific community. At the same time, there is agreement that a few important cellular pathways act in a coordinated fashion to evade aging.

With the advancement of biomedical science, genetics, and molecular biology, many new biomolecular traits of aging have been identified.

Epigenetic alterations and the loss of proteostasis are the primary hallmarks of cellular damage. Epigenetic alterations influence gene structure, function, and organization. Histone alterations, DNA methylation, and chromatin remodeling are the elemental epigenetic modifications; these have a significant impact on the key regulatory pathways of the cell cycle, as well as its maintenance and aging.

Proteostasis symbolizes protein quality control. It is mediated through a complex network of regulatory factors that control the optimum functioning of the protein subset of the cell. Proteostasis is a multifaceted process that is organized along diverse checkpoints, from protein synthesis to protein degradation. Loss of proteostasis results in aging and age-related disorders.

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