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

Definition of aging can be formulated as “diminished response to stress, escalation of homeostatic imbalance and an enhanced threat from aging-related pathologies.”

Since times immemorial, proposition of many theories to expound aging has been documented in the literature. Some of the prominent theories are mentioned as follows:

- Stochastic theory
None of these theories enjoy unequivocal support. The common consensus among the scientific community is that each theory explores rather a smaller part of the larger picture.

There are various physiological traits identified to describe the process of aging. They can be tabulated as follows:

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

With the advancement of molecular science; three main signaling pathways have been extensively studied in this prospect. They can be summarized as follows:

<table>
<thead>
<tr>
<th>Signaling pathway</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary restriction</td>
<td>Based on amino acid sensing serine/threonine kinase mTOR, and energy status-dependent kinase AMPK; theory of dietary restriction is based on the fact that a diminished dietary intake below “ad libitum” levels culminates in an increase in lifespan.</td>
</tr>
<tr>
<td>Insulin/IGF-1 like signaling pathway (IIS)</td>
<td>Identified first in C.elegans species and characterized by Panowski and Dillin in 2008; this theory hypothesized that decreased IIS activity enables entry of few specific proteins in the nucleus which consequently activate a diverse transcriptional profile. This profile is responsible for the extension of the cellular vitality, preservation of functionality and thus an escape from aging.</td>
</tr>
<tr>
<td>Diminution of activity of mitochondrial electron transport chain</td>
<td>Reduction in expression of the mitochondrial genome associated with electron transport chain (ETC); especially affecting the ETC complexes I, III, IV, and V through iRNA has been shown to result in the extension of the lifespan of the cell.</td>
</tr>
</tbody>
</table>

While these pathways may act independently, they all narrow down to result in few invariable factors which have been preserved remarkably in all species with extended lifespan. The characteristics of species with long lives can be tabulated as follows:

- Altered metabolism towards reinstatement of cellular homeostasis
- Escalated stress response
- Delayed reproduction
- Slowed development

Maintenance of the cell’s signature protein molecules and genomic stability are a few of the significant traits which can be identified in almost all species who have been
relatively successful in evading aging.

Epigenetic Alteration

Epigenetic alterations and loss of proteostasis are the primary hallmarks of aging. Epigenetic factors can influence how genes are expressed at different ages. They stand to epitomize the fact that changes in chromatin state regulate the transcription of genes. Some of the significant nuclear processes affected by epigenetic alterations which have a key role in aging can be tabulated as follows:

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

Epigenetic factors change phenotype without changing the heritable genotype. The key components leading to epigenetic alterations can be summarized as follows:

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

Histone modification
Nucleosome comprising of a string of DNA wrapped around an octamer of histone protein is the basic structural unit of chromatin. The nucleosome is also the basic target of many devastating operations which culminate in cellular aging and death. Histone modifications are post-translational modifications which occur in these proteins to facilitate appropriate chromatin remodeling and associating activities.

Some of the key histone modifications are summarized as follows:

- 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 thus the subsequent gene transcription and translation activity. They also regulate access of regulatory proteins to DNA. Dysregulation of histone modifications thus renders the genome susceptible to modulation by unwanted mechanisms and factors which can have devastating results.

Alteration of DNA methylation patterns

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

Histone modifications and DNA methylation patterns determine two distinct types of chromatin. They are as mentioned below:

<table>
<thead>
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<th>Type of chromatin</th>
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<td><strong>Euchromatin</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Heterochromatin</strong></td>
<td>Is highly condensed chromatin associated with inactivity and decreased transcriptional access to genes. This enclosed chromatin configuration is brought about by hypoacetylation of histones and simultaneous hypermethylation of histones and DNA.</td>
</tr>
</tbody>
</table>
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 an upcoming theory thought to account for the majority of chromatin remodeling and transcriptional gene silencing. The non-coding RNA species are instrumental in the control of diverse vital cellular functions summarized as follows:

- Differentiation
- Apoptosis
- Cell cycle regulation
- Tumor suppression

The important types of non-coding RNAs can be mentioned as follows:

- 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 manifest multiple progeroid symptoms by the age of 2 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.

Loss of Proteostasis

Maintenance of cellular proteome, the unique subset of proteins in every cell, is remarkably similar in long-lived animals.

There is a multitude of ways in which the vital cellular protein machinery could be tampered with. Some of the relevant ones can be mentioned as follows:

- Misfolding of proteins
- Aggregation errors
- Translational errors
- Covalent modifications such as oxidation
- Polymorphism
- Cellular stress

The resultant abnormal protein aggregates secondary to proteotoxic stressors can induce a vicious cycle of damage, wherein they lead to the production of more damaged and cytotoxic abnormal protein molecules. Cataclysmic results are brought about by these unstable molecules, which ultimately lead 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. Indeed, older cells are documented to possess more abnormal, misfolded proteins and proteins bearing the brunt of the oxidative damage, such as increased cross-linking and aggregated proteins, diminished the catalytic activity of enzyme proteins, oxidized methionine, glycation, and carbonylation.

A complex security network to ensure proper production, regulation and timely destruction of cellular proteins exist. Homeostasis of proteins in a cell is vital for the proper functioning of a cell. This network is christened as the “proteostasis network”. The various sub-components of the proteostasis network 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 following significant pathways as summarized below:

<table>
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<td>Translation rate control</td>
<td>Modulation of the rate of protein synthesis has the potential to alter proteostasis. There is strong evidence to suggest that diminished translation rate culminates in a delay in aging in many species.</td>
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<tr>
<td>Protein folding</td>
<td>Molecular chaperones assist proteins in folding and assembling themselves in a specific manner. Dysregulation of this crucial step may result in protein misfolding and ultimately cellular senescence.</td>
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<td>Stress response</td>
<td>Chaperones and other upstream transcription factors prevent a 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 the determination of longevity of a cell’s life.</td>
</tr>
<tr>
<td>Heat-shock response</td>
<td>The heat shock response co-ordinates the response to thermal stress and is a determining component in a cell’s lifespan extension pathway.</td>
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<tr>
<td>Protein trafficking</td>
<td>Delivery of proteins to their appropriate destination is crucial to the longevity of a cell’s lifespan.</td>
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</tbody>
</table>
Unfolded protein response (UPR) | 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 aging.

Protein degradation | Terminally misfolded, abnormal proteins are scavenged through a specialized system mediated by ubiquitin, proteasomes, and lysosomes. Mismanagement of 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. 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, chaperone-mediated autophagy is linked to the role of lysosomes in premature aging.

### Diseases of Protein Misfolding

Involvement of disparate toxic proteins and the late age of onset are the hallmark features of these diseases. Through an alteration in proteostasis machinery, signaling pathways similar to those which regulate aging have a hand in the etiopathogenesis of these diseases. Neurons are specifically susceptible to such changes. The most elaborately studied diseases of protein misfolding are thus the neurodegenerative diseases. **The significant ones are as mentioned below:**

- 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 successful aging and normal 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. Scientists now aim to accomplish successful aging, which is defined as little or no age-related decrement in physiological and cognitive functioning.

Successful aging can be accomplished by 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. Recently, psychosocial elements were added to the definition of successful aging.

**The main elements of successful aging can be tabulated as follows:**

- 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 measure successful aging by the following:

- Accomplishments
- Financial security
- Integration into the neighborhood
- Physical appearance and grooming
- Productivity and contribution to the society and the local community
- Sense of humor
- Having a purpose
- Spirituality

Summary

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

There are many theories proposed to elucidate aging, but none is superior to the other. At the same time, all theories most likely converge on a few important cellular pathways which 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 defined.

Epigenetic alterations and the loss of proteostasis are 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 which have a deep impact on the key regulatory pathways of the cell cycle, its maintenance and aging.

Proteostasis symbolizes protein quality control. It is mediated through a complex network of regulatory factors which control the optimum functioning of the protein subset of the cell. Proteostasis is a multifaceted process organized with diverse checks at many points right from protein synthesis to protein degradation. Loss of proteostasis culminates in aging and age-related disorders.

Review Questions

The correct answers can be found below the references.

1. Which disease is associated with a loss of proteostasis?
   A. Parkin’s disease
   B. Harolington’s disease
   C. Harvey’s disease
   D. Huntington’s disease

2. Which of the following statements is true?
   A. Hyperacetylation of histones and hypermethylation of both histones and DNA is seen in heterochromatin.
   B. Hyperacetylation of histones and hypomethylation of both histones and DNA is seen in heterochromatin.
C. Hyperacetylation of histones and hypomethylation of both histones and DNA is seen in Euchromatin.
D. Hypoacetylation of histones and hypermethylation of both histones and DNA is seen in Euchromatin.

3. Which of the following statements is false?

A. DNA methylation modifications have been linked to Alzheimer’s disease.
B. Chaperones and other upstream transcription factors prevent the formation of folding-sensitive proteins in times of stress which can disrupt proteostasis.
C. A diminished dietary intake below “ad libitum” levels culminates in an increase in lifespan.
D. The ubiquitin-proteasome system is largely responsible for protein trafficking and endoplasmic reticulum stress response.

References


**Correct answers:** 1D, 2C, 3D

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