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Chapter 4: Epigenetics and the aging process: Rewriting the story of life

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Abstract

Epigenetic regulation plays a pivotal role in the aging process, influencing how genes are expressed without altering the underlying DNA sequence. Aging is associated with characteristic changes in epigenetic markers, including DNA methylation, histone modifications, and chromatin remodeling, which collectively impact gene expression, genomic stability, and cellular function. These alterations contribute to the progressive decline in tissue homeostasis and the development of age-related diseases. Recent research has identified epigenetic clocks — biomarkers based on DNA methylation patterns — that can accurately predict biological age and highlight the reversible nature of some aging processes. Understanding how epigenetic mechanisms drive aging offers promising opportunities for therapeutic interventions aimed at slowing aging, restoring tissue function, and extending healthy lifespan.

Keywords: Epigenetics, DNA Methylation, Histone Modification, Chromatin Remodeling, Epigenetic Drift, Epigenetic Clock

4.1. Introduction

microRNAs (miRNAs) and epigenetic regulation play critical roles in the aging process. These are part of the body's intricate system for controlling how genes are expressed, and their deregulation is strongly associated with aging and age-related diseases. miRNAs regulate longevity genes, promote senescence, inflammation, and age-related diseases. Epigenetic changes alter gene expression patterns, reduce repair, increase instability, disrupt stem cell function. And the feedback loop mutual regulation between miRNAs and epigenetic enzymes worsens with age.

4.2. Epigenetic factors

Functional relevant changes in the genome that do not involve a change in the nucleotide sequence are often defined as “Epigenetics”, e.g., DNA methylation or histone modification. These changes in DNA methylation and/or histone modification alter the availability of DNA to the binding of proteins which can either induce or repress gene transcription (Paital and Ramalingam, 2018; Shekhidem et al., 2018; Subaramaniyam et al., 2023).

4.3. The epigenetic process

There are three categories of signals that reach a finale in the establishment of a stably heritable epigenetic state: a signal that we propose to call the ‘‘Epigenator,’’ which originate from the environment and an intracellular pathways are triggered; an ‘‘Epigenetic Initiator’’ signal, which response to the Epigenator and to define the specific location of the epigenetic chromatin environment it is necessary; and an ‘‘Epigenetic Maintainer’’ signal, which assist the chromatin environment in the first and subsequent generations (Berger et al., 2009; Ilango et al., 2020).

4.4. Epigenator

By changes in the environment of the cell, the epigenetic phenotype is triggered. The Epigenator signal would be a part of everything occurring upstream of the first event on the chromosome, including an environmental cue or niche and the subsequent signaling pathways leading to the Initiator. Once an Epigenator signal is received, it is converted to an intracellular Epigenator pathway culminating in the ‘‘activation’’ of the Initiator. The Epigenator signaling pathway could be a protein-protein interaction or a modification-based event that unleashes the latent activity of the Initiator. The Epigenator signal will be transient, remaining in the cell long enough to trigger the epigenetic phenotype but not necessary for subsequent events (Berger et al., 2009).

4.5. Epigenetic initiator

The Epigenetic Initiator translates the Epigenator signal to mediate the establishment of a local chromatin context at an exact location. Following by the epigenator signal, the priming of the Initiator, the Initiator will define the location on a chromosome where the epigenetic chromatin state is to be established. The Initiator could be a noncoding RNA, a DNA-binding protein, or any other entity that can define the coordinates of the chromatin structure to be assembled. Hence, some form of sequence recognition must be a feature of this signal. The Initiator will be a signal that requires self-reinforcement and self-renewal through positive feedback mechanisms. One operational characteristic of the Epigenetic Initiator is that it may be sufficient to initiate an epigenetic phenotype when introduced into a cell. Also, unlike the

Epigenator, the Initiator may not dissipate after its action but rather may persist with the Maintainer (Berger et al., 2009).

4.6. Epigenetic maintainer

The Epigenetic maintainer sustains the epigenetic chromatin state but is not sufficient to initiate it. This signal involves many different pathways, including DNA methylation, histone modifications, histone variants, nucleosome positioning, and others. The Epigenetic maintainers have the common property that they do not have absolute DNA sequence specificity. Hence, they could operate at any chromosomal location to which they are recruited by an Initiator. Epigenetic maintainers may function by carrying an epigenetic signal through the cell cycle or could maintain epigenetic landscapes in terminally differentiated cell types (Berger et al., 2009).

Heritable changes regulated by epigenetic alterations critical for the evolution of all human cancer types. As abnormal patterns of DNA methylation, disrupted patterns of histone post-translational modifications (PTM's), and changes in chromatin composition and organization can be observed in the "epigenetic alterations". By disrupting the epigenetic machinery the changes in the epigenome occur largely. In many human cancers signaling gene (oncogenes) mutations are often dominant and drive the formation of cancers. Eg: ras. An abnormality in the epigenome, which may affect gene expression patterns and genomic stability, has frequent mutations in genes that encode for the components of epigenetic machinery (Baylin et al., 2019).

In regulating many of the hallmarks of cancer there is a central influence of epigenetics and it has garnered the interest and focus of scientists, clinicians, and the pharmaceutical industry with the aim of controlling and resetting the cancer epigenome. These efforts have yielded a vast array of investigational small molecules that target epigenetic writers, readers, erasers, and chromatin remodelers. They have also fueled studies aimed at delineating the role of epigenetic regulators in human diseases unrelated to cancer. DNA hypomethylating agents (DNA methyltransferase inhibitors (DNMTi) and histone deacetylase (HDAC) inhibitors are the most clinically advanced epigenetic therapies in oncology (Dawson, 2017).

4.7. MiRNA in ageing

Micro RNAs (miRNA) are the expression of the short non-coding part of DNA which usually of 22 nucleotide long. Many miRNA are found to be directly or indirectly regulate the ageing associated events in cells (Iswariya et al., 2019). For example, miR-15a, miR-16 and miR-29 are under expressed when HDAC1, HDAC2 and HDAC3 transcripts are up-regulated. The later genes are accountable for histone modifications. Finally, it may be linked to the events of telomere shortening and

ageing. Immune-compromisation and inflammation events are also controlled by miRNA (Jung and Suh, 2012). The deregulated protein synthesis process is also controlled by miRNAs (Pincus et al., 2011). So, it is evident that miRNA regulate the longevity in organisms. For example, miRNA lin-4 that acts as a longevity promoting factor, and its target miRNA lin-14 that acts as a lifespan antagonizing factor together believed to control the lifespan *C. elegans* (Pincus et al., 2011).

On the contrary, mir-71, -238 and -246 mutants shortens the longevity and over expressing miR-71 or miR-246 reverse the process, strongly argue about their significant role in ageing, Indicating that these miRNAs function to promote longevity (Jung and Suh, 2012). Expression of nearly 200 miRNAs in *C. elegans* is modulated in life stages and about 100 of them are conserved in humans (Smith-Vikos and Slack, 2012). Many miRNA are found to regulate pathway as DAF-2 does, PTEN, Insulin/IGF signaling, DAF-12 signaling and TOR signaling that are controlling factors of ageing events. Similarly miR-1, miR-21, miR-122 and miR-375 are able to regulate many neural disorders that are common for ageing (Smith-Vikos and Slack, 2012). Therefore, miRNA are important in regulating ageing and longevity in human and non0human animals. Therefore, more focused research on miRNA regulating ageing associated events such as DNA damage and metabolic pathways by miRNA such as miRNA 21, 102, 374 and 504 needs to be done. Inflammation is common in ageing and related pathways are also regulated by miRNA such as 29C, 290, 293 and 499. MicroRNA137 and 143 control gene that regulates ageing. Senescence is regulated by miRNA 106a. So, targeting the role of miRNA on ageing would open a new window to slow down the ageing events.

MicroRNAs are small, non-coding RNA molecules (~22 nucleotides) that regulate gene expression by binding to messenger RNAs (mRNAs) and preventing them from being translated into proteins. Some miRNAs regulate longevity genes and suppress genes involved in stress response, DNA repair, or metabolism—processes that are essential for healthy aging. On the other hand, certain miRNAs promote senescence genes (e.g., miR-34a, miR-21) and are overexpressed in aging tissues and are known to promote cellular senescence. Some miRNAs regulate inflammatory pathways, contributing to “inflammaging” (chronic, low-grade inflammation associated with age). Abnormal miRNA expression is linked to diseases for neurodegeneration like Alzheimer’s, Parkinson’s, and age-related cancers.

Epigenetic regulation involves changes in gene expression without altering the DNA sequence. The main mechanisms include DNA methylation, histone modification, non-coding RNAs (like miRNAs). DNA methylation clock: With age, global DNA methylation patterns change. Some regions become hypermethylated

(silenced), while others are hypomethylated (activated inappropriately). These changes are so consistent they're used in the epigenetic clock to estimate biological age. Histone changes: Alterations in histone acetylation/methylation can lead to relaxed or condensed chromatin, affecting gene access and expression, often in ways that promote aging.

Loss of epigenetic control leads to inappropriate gene expression, genomic instability, and impaired tissue function. Stem cell aging or epigenetic drift affects the regenerative potential of stem cells. Finally, the miRNA–epigenetic feedback loop epigenetics regulate each other. miRNAs regulate the enzymes that control DNA methylation and histone modification (like DNMTs, HDACs). Epigenetic modifications control miRNA genes, influencing which miRNAs are expressed. This feedback loop becomes disrupted with age, amplifying aging-related changes in gene expression.

Conclusion

Epigenetic regulation plays a pivotal role in the aging process by influencing how genes are expressed without altering the underlying DNA sequence. Over time, age-associated changes in epigenetic mechanisms—such as DNA methylation, histone modifications, and non-coding RNA activity—lead to disrupted gene expression, loss of cellular identity, impaired tissue function, and increased susceptibility to age-related diseases. One of the most compelling discoveries in this field is the concept of the "epigenetic clock," which accurately reflects biological age based on specific DNA methylation patterns. This highlights not only the significance of epigenetics in aging but also its potential as a biomarker for health and longevity. Importantly, unlike genetic mutations, epigenetic changes are potentially reversible, offering promising opportunities for therapeutic interventions aimed at slowing aging, restoring youthful gene expression patterns, and improving health span. In conclusion, understanding the epigenetic regulation of aging deepens our insight into the molecular basis of aging and opens exciting new paths for promoting healthy aging and combating age-related decline.

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