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Elucidating the Epigenetic Mechanisms that Modulate Biological Age

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Abstract

In recent years, changes in the epigenome have emerged as a key component in the aging process. DNA methylation, histone acetylation and methylation, and chromatin landscape remodeling are the most well researched of the types of epigenetic modifications. To best elucidate their functions, they should be understood as interacting parts in the context of an integrated epigenetic approach and not as exclusive mechanisms. Each type of modification undergoes some predictable changes with aging but may display variation depending on the individual, cell type, or organism. These epigenetic modifications correlate to changes in phenotypes common with aging and to increased susceptibility to age-related diseases, such as cancer or Alzheimer's Disease. While age may cause these changes, epigenetic modifications also contribute to aging by altering gene expression and interacting with other agents of aging to further the progression. Therefore, the scope of this review looks at epigenetic modifications as an effect and driver of aging.

Keywords: Aging, Epigenetics, DNA Methylation, Histone Modification, Chromatin, Chromatin Remodeling, Chromatin Landscape

1. Introduction

Cellular and molecular damage to cells over time accumulates in a phenomenon called aging, which is partly dependent on the passage of time, or chronological age. Biological age differs from chronological age, as it is the age of a person demonstrated by cellular health and is a more accurate predictor of lifespan and healthspan, the amount of time an individual lives healthily. The rate of aging was previously believed to be predetermined by the genes inherited at birth, but recent research has shown that the environment and the resulting epigenetic changes to the chromosomal landscape determine a significant portion of longevity and health (Kirkwood, 2005; Sen, et al., 2016). Aging is also accompanied by modification of an organism's phenotype, which is connected to the epigenetic modulation of transcription (Kirkwood, 2005; Johansson, et al., 2013). Various other hypotheses and hallmarks of aging have also been proposed, including genomic instability, telomere attrition, and cell senescence (López-Otín, et al., 2013). These hallmarks of aging should not be seen as mutually exclusive, but as an interconnected network of processes influencing each other and contributing to aging as a whole. However, this review will concentrate mainly on epigenetic modifications as the most crucial factor in aging because it controls gene regulation and phenotypic alterations, thus making it an underlying factor that many of the other hallmarks of aging possess.

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Epigenetics refers to changes made to the chromosomal landscape without altering the genetic code directly and includes DNA methylation, histone modification, and chromatin remodeling. While there are other factors that influence epigenetic modification, such as modification of non-coding RNAs, which has also been established as an epigenetic factor more recently, this review will focus on the more established canonical methods of epigenetic modification. The most well studied epigenetic modification is DNA methylation, which refers to the addition of methyl groups to the cytosine in CpG dinucleotides, where a cytosine precedes a guanine in the 5' to 3' direction, and generally represses gene expression through decreasing access to gene regulatory elements, namely promoters and enhancers (Bormann, et al., 2016). Hypomethylation leads to reduced genomic stability and excessive gene expression, increasing the rate of mutations and the probability of age-related health issues, including cancer. Conversely, hypermethylation represses gene expression and may occur at protein-coding genes that carry out basic cell functions, henceforth depleting the cell of said protein which could have catastrophic consequences (Ashapkin, et al., 2017). Histone modification, defined as a post-translational modification (PTM) of histone proteins in chromatin, while less researched than DNA methylation, has also emerged as an important epigenetic factor in the remodeling of the genomic landscape. Amongst the various types of histone modifications, histone acetylation and histone methylation in particular have shown consistent correlations with aging. Both DNA methylation and histone modification are inextricably tied to chromatin remodeling, since DNA methylation correlates with decreased chromatin accessibility while histone modifications can dictate chromatin structure (Johansson, et al., 2013; Kouzarides, 2007).

As the average lifespan increases in developed countries, health in old age becomes an increasingly important concern. While it is not clear the order in which aging hallmarks arise, epigenetic research may be a crucial piece in improving healthspan in older age. The epigenome is alterable unlike the genetic code; therefore, it is theoretically possible to reverse some age-related epigenetic changes to revert a cell to a biologically younger age. Pinpointing the exact epigenetic modifications that affect biological age may aid in the development of pharmaceuticals that target age-related epigenetic modifications to improve healthspan.

Many of the studies on epigenetics and its role in aging have been done in model organisms such as budding yeast (*Saccharomyces cerevisiae*) and the fruit fly (*Drosophila melanogaster*), which have short generations and high reproduction rates, providing ideal conditions for researchers to track target genes and phenotypes related to aging over many generations. These organisms also possess some highly conserved cellular processes, allowing us to make inferences about aging in humans (Kaeberlein, et al., 2007). To elucidate the importance of epigenetic mechanisms in the process of aging, this review highlights patterns of DNA methylation, histone modification, and chromatin remodeling as it relates to other hallmarks of aging, providing a holistic perspective on epigenetic modifications and their roles in aging. This holistic review will bring to light the extensive interplay between different epigenetic modifications, allowing scientists to easily identify the key questions in the field and investigate them experimentally.

2. DNA Methylation

As aging progresses, a global pattern of hypomethylation occurs, but specific CpG sites show hypermethylation (Day, et al., 2013). Aging is accompanied by an increase in heterogeneity between methylomes and amongst cells of the same tissue over time due to random errors in DNA methylation that may arise during replication (Winnefeld and Lyko., 2012; Bormann, et al., 2016; Ashapkin, et al., 2017). The increasing differences between individual methylomes account for many of the phenotypic differences that arise in identical twins as they progress through life, and the increasing heterogeneity within tissues increases risk of organ failure (Tan, et al., 2016; Ashapkin, et al., 2017). Studies in *D. melanogaster* and *C. elegans* have contributed to our understanding of the correlation of DNA methylation and aging, however, the type of DNA methylation that occurs in *D. melanogaster* and

C. elegans differs from the traditional mammalian (5mC) methylation (Booth and Brunet, 2016; Greer and Shi, 2012). Therefore, while model organisms can provide insight into the global correlations of DNA methylation and aging, DNA methylation must be studied as well in mammalian cells to provide insight into the cellular mechanisms behind epigenetic patterns and aging.

Tracking DNA methylation at CpG sites has been established as a reliable way to measure chronological age, more so than other well studied age predictors such as telomere length (Hannum, et al., 2012; Horvath, 2013; Jylhävä, et al., 2017). Although there are individual variations in patterns of DNA methylation, some methylation sites are highly conserved among mammalian species, demonstrating a clear link between aging and specific genes (Li, et al., 2022). The ELOVL2 gene, which is associated with the synthesis of long fatty acid chains primarily in the liver, has been identified as the strongest correlative gene between methylation and age (Li, et al., 2022; Spólnicka, et al., 2018; Garagnani, et al., 2012). As chronological age increases, the ELOVL2 gene becomes hypermethylated, decreasing gene expression (Garagnani, et al., 2012). Other CpG sites with methylation patterns highly correlated to age have been found to play a role in cancer and Alzheimer's Disease, among other common symptoms of aging and decline in health (Spólnicka, et al., 2018). Some CpG sites have shown strong positive correlation between DNA methylation and age in certain regions of the brain (Hernandez, et al., 2011).

When methyl groups bind to CpG dinucleotides, the new methylated form of cytosine called 5-methylcytosine (5mC) (Figure 1) inhibits binding of transcriptional activators or promotes binding of transcriptional repressors to repress gene expression (Watt and Molloy, 1988; Booth and Brunet, 2016). CpG sites are often located at the promoter regions of housekeeping genes, therefore regulating gene expression of essential proteins (Day, et al., 2013). However, methylation correlated with aging most dramatically occurs not in the promoter regions, but in the enhancer regions, which are also sites important to regulating gene expression (Johansson, et al., 2013). Furthermore, methylation at noncoding sites has emerged in recent years as a significant factor in genome stability (Winnefeld and Lyko, 2012). It is thought that hypomethylation of noncoding DNA sites decreases chromatin density and allows insertion of transposable elements, thereby increasing genomic instability and mutations prevalence (Pal and Tyler, 2016). Therefore, breast and other types of tissue that typically indicate a higher biological age according to DNA methylation patterns also demonstrate a higher incidence of cancer and tumors (Horvath, 2013).

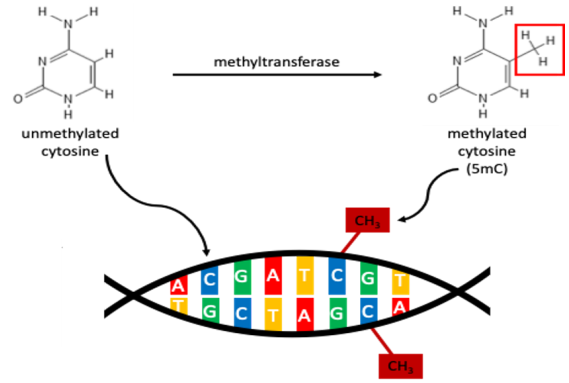

Figure 1. Structure and Mechanism of DNA Methylation. DNA is methylated by methyltransferases which adds a methyl group onto the 5' carbon at CpG sites.

DNA methylation data shows modest correlation with other hallmarks of aging and lifespan: cell senescence, the cessation of cellular division, and telomere attrition, the shortening of the DNA sequence at the ends of chromosomes (López-Otín, et al., 2013). Cellular senescence correlates with changes in DNA methylation at certain loci, which may indicate some degree of interplay between the molecular mechanisms, although the nature of the relationship is not clear (Koch, et al., 2013). However, some hallmarks of aging demonstrate a degree of exclusivity from DNA methylation, such as telomere attrition, as epigenetic age increases even in the presence of telomerase, an enzyme that lengthens telomeres (Kabacik, et al., 2018). The greatest correlation between another hallmark of aging and DNA methylation is seen between stem cell exhaustion and patterns of DNA methylation, as DNA methylation is crucial in maintaining the undifferentiated state of stem cells (Li, et al., 2022).

These correlations between DNA methylation patterns and hallmarks of aging need to be further investigated experimentally to determine the exact degree of molecular mechanism interplay between the processes.

3. Histone Modification

Histone proteins can undergo many types of PTMs, such as phosphorylation, acetylation, and methylation. However, histone acetylation and methylation are by far the most researched (Sterner and Burger, 2000). It is challenging to track histone modification, as it is generally fluid and dynamic in nature and shows less of an overall pattern as it does specific alterations at certain gene loci (Sen, et al., 2016). Research in *D. melanogaster, C. elegans,* and *S. cerevisiae* has demonstrated that histone modifications, or histone marks, regulate gene expression through affecting the density of chromatin packaging, either promoting or inhibiting transcription depending on the site of the mark (Booth and Brunet, 2016; Kouzarides, 2007). However, not all mechanisms of histone modification are conserved between model organisms and mammals, increasing the demand for thorough histone modification research in mammalian cell cultures (Dang, et al., 2009). This section of the review covers known histone acetylation and methylation events that are correlated to aging.

3.1 Histone Acetylation

Histone acetylation loosens chromatin folding due to the acetyl group neutralizing the charge of lysine residues in histone side chains, leading to transcriptional derepression (Kouzarides, 2007). Enzymes called histone deacetylases, of which include sirtuins, deacetylate histones (Houtkooper, et al., 2012). A loss of sirtuins has been linked with aging in both *S. cerevisiae* and humans, due to the loss of telomere silencing as histone acetylation increases (Dang, et al., 2009; Michishita, et al., 2008). Global histone deacetylation correlates with increased longevity in *S. cerevisiae* through suppression of oxidative stress responses, as chronic oxidative stress is known to play a role in cell damage, death, and aging (Eisenberg, et al., 2009). Research in *S. cerevisiae* has also shown that acetylation of lysine 56 on histone H3 (H3K56) at the promoters of histone genes decreases with age, corresponding to decreased gene expression and loss of core histones (Dang, et al., 2009). Conversely, acetylation of lysine 16 on histone H4 (H4K16) in telomeres increases with age, correlating to the loss of silencing in these regions and a shortening of the cell's replicative lifespan, or premature cell senescence (Dang, et al., 2009). Premature cell senescence is associated with the loss of telomere silencing and telomere dysfunction (Michishita, et al., 2008), once again demonstrating interplay of histone acetylation and other hallmarks of aging.

3.2 Histone Methylation

Histone methylation is the addition of methyl groups to arginine, histidine, or lysine residues in histone side chains. Compared to DNA methylation or histone acetylation, histone methylation often results in more versatile effects. Furthermore, multiple histone methylation marks can occur simultaneously on the same histone, which produces a different effect on chromatin remodeling and gene expression than when a mark occurs alone (Greer and Shi, 2012). The effect of methylation may also differ depending on the amino acid methylated (Greer and Shi, 2012).

Lysine methylations, such as trimethylation of histone H3 at lysine 4 (H3K4me3) and lysine 27 (H3K27me3), are modifications that significantly influence transcription and gene expression as aging progresses (Sen, et al., 2016). H3K4me3 is traditionally associated with transcriptional activation, while H3K27me3 is associated with transcriptional repression (Rothbart and Strahl, 2014). Changes in these marks with age can vary widely between cell types and organisms. For example, global H3K27me3 increases in quiescent adult skeletal muscle stem cells yet decreases in somatic *C. elegans* cells with age (Liu, et al., 2013; Maures, et al., 2011). In murine hematopoietic stem cells, H3K27me3 levels mostly increase with age, but some loci show decreased levels of methylation (Sun, et al., 2014). Similarly, studies in *C. elegans* and *D.*

melanogaster show varying patterns of H3K4me3 with age depending on cell type (Booth and Brunet, 2016). Nonetheless, the causal relationship of histone methylation and aging is clear. The ability to methylate and demethylate is a crucial process that decreases with age, where overexpression of enzymes that add methyl groups (methyltransferases) or strip them away (demethylases) has resulted in increased longevity in model organisms, and many of these pathways are highly conserved (Maures, et al., 2011; Greer and Shi, 2012).

It is hypothesized that DNA methylation influences patterns of histone methylation, indicating an interaction between these two types of epigenetic modifications to repress gene expression (Fuks, 2005). However, it is yet unclear which modification occurs first, and further research of this phenomenon may lead to a deeper understanding of the order and progress of aging (Bartke, et al., 2010).

4. Chromatin Landscape Remodeling

Chromatin is wrapped around proteins called histones, forming units of nucleosomes. These nucleosomes can be packaged tightly in a state called heterochromatin, which represses transcription, or packaged loosely in a state called euchromatin, which enables transcription. The genome may display various states of chromatin density depending on loci and the phase of the cell cycle. The heterochromatin loss model of aging presents the loss of tightly packed DNA as a cause of aging due to the increase in genome instability (López-Otín, et al., 2013). Research in *C. elegans* and *D. melanogaster* has demonstrated that maintaining heterochromatin is a conserved process important for muscle strength and longevity (Larson, et al., 2012). Furthermore, heterochromatin was seen to decrease in aging cells and in cells of individuals with Hutchinson-Gilford progeria syndrome (HGPS), a premature aging disease (Greer and Shi, 2012).

Changes in the chromatin landscape associated with aging can be attributed to patterns of DNA methylation and histone modification throughout the genome (Bannister and Kouzarides, 2011). For example, H3K27me3, a mark that induces heterochromatin, is lost on the inactive X chromosome in HGPS cells (Shumaker, et al., 2006). Additionally, studies have shown that high levels of CpG methylation coincide with heterochromatic regions and repressed gene expression (Fuks, 2005).

Histone methylation may also indirectly contribute to the loss of heterochromatin through the loss of nucleosomes (Booth and Brunet, 2016). The H3K27me3 modification downregulates genes that code for histones and has been linked to the loss of core histones with age (Liu, et al., 2013). This may cause the loss of nucleosome occupancy and the loss of chromatin density, possibly resulting in genomic instability, insertions of transposable elements, and an increase in genomic mutations (Liu, et al., 2013). As mutations accumulate, the susceptibility to age-related diseases increases, leading to decreased health- and lifespan.

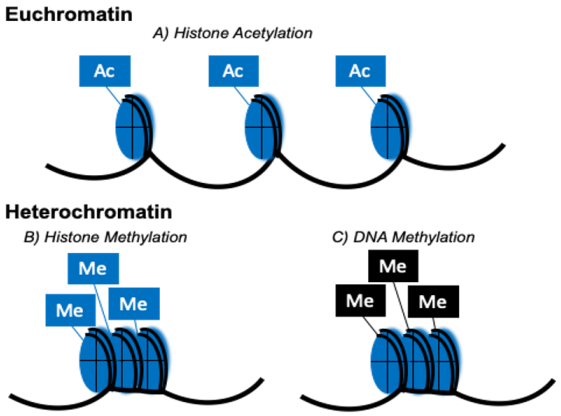

Figure 2. Chromatin Types and the Effects on the Chromatin Landscape. Euchromatin is when DNA is open due to histone acetylation and ready for use via transcription or replication. Heterochromatin is when DNA is tightly wound and inaccessible to proteins important for transcription and replication processes. This DNA tightening is due to histone and DNA methylation.

Similarly, as DNA becomes globally hypomethylated with aging, chromatin becomes less tightly packed (Figure 2), resulting in genomic instability and transposon activation. When heterochromatin unravels into euchromatin, enzymes have easier access to the DNA and gene expression becomes less regulated. Uncontrolled gene expression may lead to the conversion of healthy cells to cancer cells, which is indicative of

accelerated biological age (Horvath, 2013). Epigenetic alterations also result in the loss of heterochromatin at transposable elements, increasing the probability of transposition and consequently mutations that occur due to transposition and result in DNA damage.

Increased histone acetylation also contributes to aging by increasing genomic instability and telomere dysfunction through loss of heterochromatin (Figure 2). Telomeres are ideally maintained permanently in the heterochromatic state outside of DNA replication to maintain genomic integrity, and failure to maintain this state promotes cellular aging (Bannister and Kouzarides, 2011; Michishita, et al., 2008). For example, the loss of SIRT6, a protein that deacetylates lysine 9 histone H3 (H3K9) at telomeres, which results in increased H3K9 acetylation and thus loss of telomeric chromatin density, leads to premature cell senescence (Michishita, et al., 2008). Also, the natural decrease in telomere length with successive cell replications causes DNA damage signaling, which negatively impacts histone expression. The loss of histones, in turn, decreases chromatin density and perpetuates a state of genomic instability (O'Sullivan, et al., 2010). This state of genomic instability can be further perpetuated through DNA methylation and histone modification (Sen, et al., 2016). Thus, epigenetic modifications and other hallmarks of aging may work synergistically to contribute to the molecular causes of aging.

5. Conclusion

Epigenetic modifications demonstrate correlation with various other hallmarks of aging and shape the chromatin landscape of the genome, regulating gene expression and altering phenotypes. While large strides have been made in the field of DNA methylation and its implications on aging, information on histone modification is comparatively lacking. The fluidity of histone modification may offer an easier path toward forced chromatin remodeling and suppression of age-related ailments than may DNA methylation alone, and the coexistence of some histone marks may be a property to take advantage of in the development of targeted pharmaceuticals. Further research is needed to understand the true relationship between each hallmark of aging and where they show correlation or causation to better comprehend the initiation of cellular decline and to extend healthspan as lifespan increases.

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