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Advances in the Epigenetic Mechanisms of Aging

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Abstract. Aging is a process in which cells, tissues, and organs undergo systematic changes over time, leading to age-related diseases and ultimately death. Cellular aging is a transient state of growth arrest that occurs in response to various types of injury or stress. The abnormal accumulation of senescent cells in tissues can impair tissue regeneration, create a pro-inflammatory environment, and contribute to the onset and progression of various age-related diseases, including cancer. The decline in cell proliferation caused by cellular aging is one of the fundamental causes of organ aging and functional deterioration. In recent years, numerous studies on aging have been conducted, resulting in significant advancements in cell biology, genetics, and signal transduction. This review discusses the basic characteristics of aging, the relationship between histone methylation and acetylation and aging, the progress in research on non-coding RNAs and cellular aging, and the link between aging and related diseases. This article aims to provide valuable academic references for newcomers to the field.

Keywords: Aging, Histone Methylation, Histone Acetylation, Non-coding RNA.

1. Introduction

Aging is a fundamental biological process. It is of urgent importance for humans to study it because doing so provides insights into the basic functions of organisms. Cellular senescence, a more specific aspect of aging, helps explain the aging process. A deeper understanding of cellular mechanisms can lead to the development of new research methods and therapeutic technologies. To date, research on cellular senescence includes approaches such as telomere dynamics, epigenetics, proteomics, genetic determinants, and oxidative stress. However, a comprehensive analysis of this body of research is lacking. Therefore, this article synthesizes research on cellular senescence from an epigenetic perspective. It introduces the basic concepts of cellular senescence and the widely accepted telomere-shortening theory, and discusses various epigenetic mechanisms involved in cellular senescence, including DNA methylation, histone modification, and non-coding RNA. Overall, there is a global loss of heterochromatin with aging.

2. Cellular Senescence and Prevalent Theories of Aging

Aging typically refers to the cumulative effects of a series of physiological and pathological processes that occur over time. As the body's structure and function degrade, its resistance to external factors, perception of the environment, and overall flexibility are significantly reduced. This process is universal and irreversible, and it has remained unchanged throughout history. Even with advanced biomedical technologies, no current theory or scientist can provide a definitive answer as to whether the aging

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process can be reversed. Cellular senescence is a "sub-concept" of aging. It was first reported in 1961 by American biologist Leonard Hayflick, who discovered it while cultivating human fibroblasts in vitro. Hayflick observed that cellular division halts after a certain number of divisions, even under optimal conditions. After this pause, cells enter an irreversible state of growth arrest. Based on this observation, Hayflick proposed the concept of cellular senescence. The limit to which cells can divide is now referred to as the Hayflick limit. Research has shown that the shortening of telomeres, along with the inactivation of telomerase, is responsible for the Hayflick limit. Over time, biologists have discovered that various factors can induce cellular senescence, including the generation of oxygen radicals, activation of oncogenes, inactivation of tumor suppressor genes, ionizing radiation, and different signal transduction pathways [1].

Cellular senescence, driven by different mechanisms, can be categorized into two types: replicative senescence, caused by telomere shortening, and premature senescence, which occurs before the Hayflick limit is reached. Both types lead to significant changes in cells. Senescent cells exhibit similar and specific characteristics that serve as markers for identifying cellular senescence. These include: (1) entry into the G0 phase for an extended period or permanently, (2) flattening of the cell body and enlargement of the nucleus and cytoplasm, (3) formation of senescence-associated heterochromatin foci, (4) telomere shortening, (5) accumulation of senescence-associated β-galactosidase, (6) changes in the senescence-associated secretory phenotype (SASP), including factors such as Insulin-like Growth Factor (IGF), Transforming Growth Factor (TGF)-β, Interleukins (IL), and Plasminogen Activator Inhibitor Type 1 (PAI-1), and (7) expression of tumor suppressor proteins (p16, p21, p53, etc.) [1].

One prevalent theory of cellular senescence is the telomere-shortening theory, which attributes the shortening of telomeres as a leading cause of cellular senescence. Telomeres are composed of repetitive 5'-TTAGGG-3' DNA sequences and associated protein complexes that protect chromosome ends from degradation or fusion. However, due to the inherent limitations of telomerase in replicating telomeres, they cannot be fully replicated during each cell division. As a result, telomeres shorten with every division until their length reaches the Hayflick limit. At this point, the exposure of DNA ends activates the DNA damage response (DDR), which often leads to increased levels of the transcription factor TP53 and subsequent production of p21. Additionally, telomere shortening triggers the production of p16, a cyclin-dependent kinase (CDK) inhibitor. Together, p21 and p16 activate the retinoblastoma protein (RB), leading to cell cycle arrest and cellular senescence [8]. To counteract this process, cells utilize telomerase, which consists of the telomerase RNA component (TERC) and telomerase reverse transcriptase (TERT), to replenish telomeric repeats. However, as telomerase activity is typically only detectable in reproductive and stem cells, most cells are unable to escape cellular senescence.

3. DNA Methylation and Cellular Senescence

DNA methylation refers to the process by which DNA methyltransferases (DNMTs) attach methyl groups to the carbon atoms of CpG (cytosine-phosphate-guanine) islands, using S-adenosylmethionine as the donor. The modified methylated cytosine is called 5-methylcytosine (5mC) [2].

3.1. DNA Methylation Function

DNA methylation is the process of adding a methyl group to the C5 site of a cytosine residue, a reaction catalyzed by DNA methyltransferases (DNMTs) with S-adenosylmethionine (SAM) as the methyl donor. DNMTs are enzymes with highly conserved catalytic sequences, playing a crucial role in DNA methylation. They are classified into four types: DNMT1, DNMT3a, DNMT3b, and DNMT3L. DNMT1 is involved in maintaining methylation patterns, while DNMT3a, DNMT3b, and DNMT3L are involved in de novo methylation, where they methylate previously unmethylated sites. The most common form of DNA methylation is the addition of a methyl group to the 5' cytosine of CpG nucleotides. Additionally, various modifications and derivatives of methylation on CpG dinucleotides have been reported, including hydroxymethyl, formyl, and carboxyl groups. Methylation at non-CpG sites has also been observed, with 5-hydroxymethylcytosine being the most prominent, functioning as an oxidized form of the classic 5-methylcytosine involved in DNA methylation. CpG dinucleotide pairs are relatively sparse

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in the genome, while CpG islands (CGIs) are regions with a high density of CpG sites, characterized by a CG content greater than 50% and a length exceeding 200 base pairs. CGIs are often associated with gene promoters, with approximately 60% to 70% of human genes containing promoter-associated CGIs. Promoters can be classified into three categories based on CpG density: high CpG promoters (HCPs), low CpG promoters (LCPs), and intermediate CpG promoters (ICPs). While early studies indicated that DNA methylation levels in promoter-associated CGIs were typically negatively correlated with gene expression, recent research has shown a positive correlation with the expression of certain specific genes. DNA methylation also plays a role in repressing repetitive elements such as Alu and LINE-1, which are typically highly methylated in the human genome. If these repeat elements undergo demethylation, their activity as reverse transcription sequences increases, which can alter gene expression and raise the incidence of diseases, including cancer.

Although DNA methylation was initially thought to exclusively regulate transcription, recent evidence suggests that it also influences the alternative splicing of mRNA precursors. Exons, particularly splice sites, exhibit higher levels of DNA methylation compared to adjacent introns, with approximately 22% of selective exon splicing regulated by DNA methylation. By regulating RNA polymerase II elongation via CCCTC-binding factor and methyl-CpG-binding protein 2 or by forming protein bridges through heterochromatin protein 1, splicing factors can be recruited to alternative exons during transcription, ultimately transmitting DNA methylation signals to regulate alternative splicing.

Changes in DNA methylation, alongside genetic-level alterations, reflect the organism's adaptive mechanisms to external environments. However, the mechanisms of DNA methylation changes are more flexible and reversible. Low-nutrient diets can also influence methylation patterns. During the transformation of primordial germ cells into gametes, the parental epigenetic imprints are erased, and sex-specific DNA methylation imprints are re-established during the development of male and female gametophytes [3].

DNA methylation represses transcription both directly, by inhibiting the binding of specific transcription factors, and indirectly, by recruiting methyl-CpG-binding proteins and their associated repressive chromatin remodeling complexes [4].

3.2. DNMT Classification and Introduction

In mammals, the establishment of methylation sites is regulated by DNA methyltransferase 3 (DNMT3) (Chen & Li, 2004), typically occurring in promoter regions with weaker transcriptional activity and gene regions with stronger transcriptional activity. These regions often contain a high amount of H3K4me3 (Piunti & Shilati Fard, 2016). Methyltransferase 1 (DNMT1) maintains the symmetry of CpG sites during DNA replication, preventing the loss of methylation sites caused by replication. DNMT2, previously thought to be a DNA methyltransferase, has been confirmed as a tRNA methyltransferase and has been renamed tRNA aspartate methyltransferase 1 (Goll et al., 2006). DNA methylation is a dynamic modification process, not only because it can be regulated through methylation and demethylation by enzymes, but also because methylated cytosine can spontaneously undergo deamination, increasing the frequency of gene site mutations. 5-methylcytosine can be converted to thymine by spontaneous deamination, transforming CpG dinucleotides into TpG dinucleotides. Unmethylated cytosine is quickly recognized and repaired by cells as uracil, which is produced by spontaneous deamination. Throughout evolution, many methylated CpG sites have undergone deamination and been stably preserved, explaining why the methylation frequency in the human genome is lower than expected [4].

There are currently five confirmed DNMTs: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. With age, DNMT1 levels gradually decrease. The expression of DNMT3A2 in the aging mouse brain is significantly reduced compared to that of normal mice, indicating a correlation between DNMT expression and cellular aging. Researchers have found that inhibiting DNMT1 in umbilical cord blood pluripotent stem cells promotes the onset of the cellular aging phenotype [3]. Among these, DNMT1, DNMT3A, and DNMT3B are the most important. DNMT3A and DNMT3B are responsible for de novo DNA methylation in unmethylated regions. Studies have shown that mRNA levels of

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DNMT3A and DNMT3B in early ectodermal cells correspond to genome-wide methylation levels, with DNMT3B expressed at relatively higher levels than DNMT3A. Additionally, the inactivation of DNMT3B leads to a greater reduction in methylation than DNMT3A, indicating that DNMT3B plays a more crucial role in DNA methylation during embryonic development. DNMT1 is essential for maintaining DNA methylation patterns, replicating methylation marks from the parent DNA strand to the daughter strand [2].

Embryonic stem cells deficient in DNMTs are viable but die when induced to differentiate. Mouse knockout studies have shown that DNMT1 and DNMT3B are essential for embryonic development, and mice lacking DNMT3A die within a few weeks of birth [4].

3.3. CpG Islands

Approximately 70% to 80% of CpGs in mammalian DNA are methylated, primarily in CpG-scarce regions and repetitive sequences. A CpG island is a region rich in CpG dinucleotides, mainly located in promoter and exon regions. Unlike the global CpG methylation seen in the genome, CpG islands are usually unmethylated. Since unmethylated cytosine is prone to deamination and conversion to uracil, the body's uracil DNA glycosylase repairs this mutation, restoring it to cytosine. However, methylated cytosine deaminates into thymine, which cannot be repaired as thymine is already present in DNA. This leads to a significant conversion of cytosine to thymine, contributing to the low CpG dinucleotide frequency in mammals, including humans. CpG islands, due to their low methylation levels, remain stable throughout evolution. Although methylation in mammals mainly occurs at CpG dinucleotide sequences, recent studies have shown that methylation at non-CpG sites (including CpA, CpT, and CpC) also plays a role in regulating gene expression [4].

Most methylated CpGs have been converted to T, and in regions where CpGs are not dense, methylated CpGs remain without being converted. The retention of unmethylated CpGs helps preserve C and G nucleotides, preventing their loss. A new question arises: Are all ATs in genes derived from metabolic processes related to these nucleotides? This could potentially provide a new perspective on evolution

3.4. DNA Methylation as a Biomarker of Aging

With the continuous in-depth research on the relationship between DNA methylation and aging, the potential of using DNA methylation to predict human lifespan has attracted widespread attention from researchers. The development of disciplines such as molecular biology, genomics, and epigenetics has opened up possibilities for studying aging-related biomarkers. Using an elastic network regression algorithm, Horvath analyzed the methylation levels of CpG sites in different tissues and identified 353 aging-related CpGs as epigenetic clocks, which can accurately predict age. Using the same algorithm, Hannum et al. analyzed 656 blood samples across a wide age range (19–101 years) and identified 71 CpG markers. Another blood-based study identified 99 methylation sites that can accurately predict age, with a mean absolute deviation (MAD) of only 4.12 years between the predicted biological age and actual age. After adjusting for gender and age factors, a deviation exceeding 5 years in predicted age was associated with a 21% increase in the risk of death.

The exact role of epigenetics in aging and death is currently unclear, and further research is needed to answer these questions. The above studies suggest that DNA methylation can accelerate aging and affect life expectancy. Through deduction and validation studies on two populations, Zhang et al. confirmed these findings, showing that specific CpG sites are significantly correlated with expected lifespan, though these sites exhibited low methylation during aging. More advanced methylation site analysis methods, such as pyrosequencing and mass spectrometry, may provide more accurate results.

Although DNA methylation patterns evolve significantly with age, only a portion of genes are associated with age-related diseases. Currently, cancer is the most extensively studied disease in this context, as low levels of DNA methylation can reduce genomic stability and increase the rate of chromosomal aberrations. However, hypermethylation of specific genes may also increase susceptibility to cancer.

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In addition, DNA methylation is closely related to age-related diseases, particularly Alzheimer's disease (AD), which is the most common neurodegenerative disorder, characterized by senile plaques and neurofibrillary tangles. DiFrancesco et al. found that the methylation level of peripheral blood mononuclear cells in AD patients is negatively correlated with cognitive function. DNA hypermethylation in AD patients is associated with higher expression levels of the DNA methyltransferase I (DNMT1) gene and protein, and methylation levels are linked to the presence of the APOEε4 allele. However, the relationship between DNA methylation levels and AD pathology is complex. For example, in AD patients, genomic DNA methylation levels are reduced in the entorhinal cortex, temporal lobe cortex, and hippocampus, regions important for learning, memory, and emotion, leading to cognitive dysfunction. Conversely, other studies have reported opposite DNA methylation results in the same brain areas of AD patients, which may be due to insufficient sample sizes, different tissue processing methods, and varying detection procedures [3].

4. Histone Modification and Aging

Histone modification refers to the dynamic, covalent changes made to histones by adding or removing functional groups at specific sites. Histone modification can regulate gene activity and, consequently, influence the aging process in organisms. There are various types of histone modifications, the most common being histone methylation, histone acetylation, histone phosphorylation, and histone ubiquitination. This section will discuss the changes in histone modification observed during aging.

4.1. Histone Methylation

The methylation of histone lysine residues can have either activating or repressive effects on chromatin transcription, depending on the location of the lysine residues. For example, the methylation of H3K4, H3K36, and H3K79 has activating effects on chromatin transcription, whereas the methylation of H3K9, H3K27, and H4K20 exerts repressive effects on transcription.

Lysine residues can undergo mono-, di-, or trimethylation, each conferring a specific level of chromatin compaction and providing a different binding platform. The methylation of histone lysine residues creates binding sites for chromodomain-containing proteins. For example, H3K9 methylation creates binding sites for HP1 (heterochromatin protein 1), while H3K27 methylation creates binding sites for polycomb group proteins, both of which repress transcription [3].

Changes in histone methylation patterns have been observed during aging. Early studies in rats showed a gradual decline in the methylation of histones H3 and H4 with increasing age. Seven methylation sites were detected in histones H3 and H4 of aged mice. Among these, H4K20me (H4 monomethylated on lysine 20) and H3K36me3 (H3 trimethylated on lysine 36) significantly decreased in the brains of 12-month-old SAMP8 mice compared to 3-month-old mice. In contrast, the abundance of H3K27me3, H3K79me, and H3K79me2 increased in the brains of older mice. Another study in the kidneys and livers of aged rats showed a marked increase in H4K20me3 levels during aging in these tissues. This histone mark is stabilized by the coordinated actions of histone methyltransferases (HMTs) Suv4-20h1 and Suv4-20h2 and the retinoblastoma protein family (pRb, p107, and p130). Therefore, changes in the expression or activity of these proteins during aging may contribute to alterations in H4K20me3 levels.

Polycomb proteins and associated repressive epigenetic marks regulate replication timing and the silencing of the ink4a/ARF locus. In young cells, members of the polycomb repressive complex (PRC2), including EZH2 (enhancer of zeste homolog 2), and PRC1 complex members Bmi1 (B-cell-specific Moloney murine leukemia virus integration site 1) and M33 are highly expressed and targeted to the ink4a/ARF locus. This leads to the silencing of the locus and its replication during the late S phase. Upon entry into senescence, PRC1 and PRC2 complexes are lost from the locus, resulting in decreased H3K27me3 levels. Simultaneously, the upregulation of the histone demethylase Jumonji domain-containing 3 and the recruitment of mixed lineage leukemia gene 1 protein to the locus lead to the expression of the ink4a/ARF genes and replication of the locus during the early S phase.

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4.2. Histone Acetylation

Acetylation of histone lysine residues can have either activating or repressive effects on chromatin transcription. Research has demonstrated different patterns of acetylation changes at various histone loci during aging. These loci include H3K9, H3K56, H4K12, and H4K16. Below, we discuss the key changes at each locus and the associated phenomena [5].

4.2.1. H3K9. SIRT1 deacetylates histone H3 at lysine 9 (H3K9). It has been observed that the level of SIRT1 protein decreases with reduced mitotic activity during aging in both mouse and human cells. Consequently, there may be an overall increase in H3K9 acetylation during aging [5].

4.2.2. H3K56. Global levels of H3K56 acetylation (H3K56ac) decline during replicative senescence in yeast [5]. The acetylation of lysine 56 on histone H3 (H3K56ac) promotes de novo nucleosome assembly, genomic stability, transcription, and the formation of heterochromatin/euchromatin boundaries. In yeast, the level of H3K56 acetylation decreases with age, while the level of H4K16 acetylation increases. Feser et al. demonstrated that the deletion of Rtt109, a major acetyltransferase for H3K56, reduces lifespan in yeast. Unexpectedly, they also found that deleting the H3K56-associated deacetylases Hst3 and Hst4 also slightly reduces lifespan. These contradictory findings suggest that a delicate balance of H3K56 acetylation may be required to promote longevity [6].

4.2.3. H4K12. Chameau, a histone lysine acetyltransferase, is associated with the acetylation of histone H4 at lysine 12 (H4K12). A study showed that the level of Chameau decreases during senescence in Drosophila, leading to an increased level of H4K12 acetylation, which is caused by elevated acetyl-CoA levels. Additionally, increased H4K12 acetylation levels have also been observed in aging-related infertile mouse oocytes. Thus, it can be inferred that elevated H4K12 acetylation levels, accompanied by gene activation, are correlated with aging [7].

4.2.4. H4K16. SIRT1 also deacetylates histone H4 at lysine 16 (H4K16). During replicative aging in yeast, global levels of H4K16 acetylation increase, leading to the activation of telomeric repeats. The gradual loss of Sir2 expression in yeast during aging is accompanied by a steady increase in H4K16 acetylation, which is mediated by the histone acetyltransferase Sas2, an antagonist of Sir2.

In mammals, the role of H4K16 acetylation in aging is unique due to its involvement in telomere maintenance. A reduction in global H4K16ac levels during physiological aging and in a Hutchinson-Gilford Progeria Syndrome (HGPS) model (zmpste24-deficient mice) may be linked to the diminished association of histone acetyltransferases (HATs) with the nuclear periphery. SIRT1 deacetylates histone H4 at lysine 16 (H4K16) and histone H3 at lysine 9 (H3K9), as well as p53, reducing p53 activity. A decline in SIRT1 protein levels has been observed alongside decreased mitotic activity in both mouse and human cells, with marked reductions found during aging or in prematurely aging mice [5].

4.2.5. H4 N-Terminal. Nat4 is a type of N-terminal acetyltransferase with high substrate selectivity for histone H4. It has been shown that the deletion of Nat4 and the resulting loss of H4 N-terminal acetylation extends the lifespan of yeast. This effect is attributed to the involvement of Nat4 in a calorie-restriction pathway, which has the ability to modulate lifespan [6].

5. Non-coding RNA and Aging

For a long time, research on the molecular mechanisms of cellular aging has primarily focused on protein-coding genes. However, in higher mammals, over 90% of transcription products are non-coding RNAs (ncRNAs), which mainly include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Non-coding RNAs regulate gene expression at multiple levels, including epigenetic, transcriptional, and post-transcriptional levels, and thus participate in various biological processes. In recent years, the role of non-coding RNAs in cellular aging has gained increasing attention and significant progress has been made [7].

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miRNA is a highly conserved class of non-coding small RNA molecules, approximately 22 nucleotides in length. By binding to the 3' untranslated region (UTR) of target gene mRNA, miRNAs cause mRNA degradation or block translation, thereby achieving negative regulation of the target gene at the post-transcriptional level. Numerous studies have shown that miRNAs play crucial roles in cellular aging, including miR-34a, and the miR-17-92 family. Multiple miRNAs can affect the cellular aging process by negatively regulating target genes in aging-related signaling pathways.

5.1. Micro-RNA

Micro-RNAs are highly conserved RNA molecules typically consisting of about 22 nucleotides. They function by binding to the 3' UTR of target mRNA, leading to mRNA degradation or translation failure [8].

miR-195, miR-34a, miR-570, miR-766, miR-217, miR-138, miR-22, miR-181a, and miR-449: These miRNAs inhibit the activity of sirtuins, a family of NAD-dependent deacetylases [9].

miR-34a: SIRT1, SIRT6, and SIRT7 are sirtuins that may localize at chromosome ends to maintain telomere length. Previous studies have shown that the deacetylase activity of sirtuins promotes telomere integrity by maintaining chromatin condensation and facilitating interactions between histones and telomere regulatory factors, including components of the DNA repair machinery. Additionally, sirtuins suppress the DNA damage response (DDR) at the telomere by inactivating TP53. miR-34a is recognized as a major repressor of SIRT1, SIRT6, and SIRT7 levels. In cardiomyocytes, miR-34a modulates telomere maintenance by reducing the abundance of protein phosphatase 1 nuclear targeting subunit (PNUTS, also known as PPP1R10), which directs protein phosphatase 1 (PP1) to the nucleus. PNUTS was previously found to inhibit the DDR and interact with TRF2, further preventing telomere shortening. Furthermore, miR-34a induces senescence in human hepatocellular carcinoma (HCC) cells by modulating telomerase activity. In HCC tumors, miR-34a levels are inversely correlated with telomere length and telomerase activity, while increasing miR-34a ectopically in HCC cells triggers senescence and affects cell viability. The actions of miR-34a on telomere maintenance are attributed to its suppression of the forkhead box M1 and MYC pathways, which are required for hTERT transcription and telomerase activity [9].

miR-195: Compared with young mesenchymal stem cells (MSCs), where telomerase is abundant and miR-195 levels are low, old MSCs express high levels of miR-195. The 3' UTR of TERT mRNA has been identified as a target of miR-195, and depletion of miR-195 rescues hTERT expression and cell proliferation in old MSCs. Notably, injecting old MSCs with depleted miR-195 significantly improves the regeneration of mouse hearts after infarction. Further studies have shown that miR-195 promotes senescence in skeletal muscle cells by reducing the production of SIRT1 [9].

miR-155: Elevated levels of miR-155 have been observed in breast cancer specimens, accompanied by reduced levels of TRF1, a protein component of the shelterin complex. In breast cancer cells, miR-155 interacts with the 3' UTR of TRF1 mRNA and represses TRF1 protein translation. Increased miR-155 levels are associated with telomere and genomic instability, as well as poor clinical outcomes in estrogen-receptor-positive breast cancer. Notably, miR-155 levels are often reduced in senescent cells [10].

miR-126: miR-126 plays a critical role in endothelial remodeling. Research has shown that miR-126 can participate in the inflammatory response of endothelial cells by binding to high mobility group protein 1, an inflammation-related gene. In experiments where HUVECs (human umbilical vein endothelial cells) were transfected with miR-126 mimetics and antagonists, overexpression of miR-126 reduced the expression of downstream components of high mobility group protein 1, including TNF-α, reactive oxygen species clusters, and NADH. Inhibiting miR-126 expression had the opposite effect. Inhibition of miR-126-5p in the injured carotid artery leads to a decrease in endothelial cell proliferation, which is associated with increased expression of cell cycle inhibitors P21 and P15, both of which are involved in endothelial cell replication and aging. Notch 1 signaling is crucial for preventing vascular endothelial senescence. Schober et al. found that miR-126-5p promotes vascular endothelial cell

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proliferation by inhibiting the expression of the Notch 1 inhibitor imprint gene, thereby limiting the progression of atherosclerotic plaques [10].

miR-216a: Numerous studies have confirmed the importance of autophagy in delaying aging. Aging is accompanied by decreased autophagy levels, and activating autophagy can prolong lifespan by reducing oxidative stress and inflammation in endothelial cells and increasing nitric oxide (NO) levels. In oxidized low-density lipoprotein (ox-LDL)-induced aging of HUVECs, miR-216a expression increased while autophagy activity decreased. Further experiments showed that overexpression of miR-216a in HUVECs inhibits autophagy-related genes ATG5 and Beclin 1, leading to ox-LDL accumulation and increased monocyte adhesion. Inhibiting miR-216a expression in senescent cells protects against ox-LDL stimulation and promotes autophagy. Thus, miR-216a can promote endothelial aging by inhibiting autophagy in vascular endothelial cells [10].

5.2. Long Non-coding RNA

Long non-coding RNAs (lncRNAs) are functional non-coding RNAs that are longer than 200 nucleotides [6]. lncRNAs were initially believed to be nonfunctional. However, increasing evidence suggests that lncRNAs regulate gene expression at different levels. In fact, lncRNAs can regulate aging by influencing telomere dynamics, tumor proteins, secretion types, methylation patterns, and other genes [11].

5.2.1. lncRNAs in Telomere Regulation. Telomere damage is a key manifestation of cellular aging, with the loss of telomerase and shortened telomere repeat sequences being the main causes. lncRNA TERC serves as a template for the synthesis of telomere repeat sequences and acts as a scaffold for the binding of telomerase protein subunits to accessory proteins, thereby extending telomere DNA and balancing telomere shortening during cell division. The effect of lncRNA TERRA on telomeres is bidirectional: increased expression of TERRA can inhibit telomere DNA replication and lead to aging, while TERRA can also delay aging by stabilizing telomere function. Elevated TERRA expression can induce cellular aging. The binding of TERRA to histone methyltransferase Dot1 promotes cellular aging, while inhibiting TERRA expression can prevent this interaction and delay aging. In addition to inducing aging, TERRA can form a DNA-RNA R-loop heteroduplex at telomeres, regulating telomere stability. The absence of TERRA increases telomerase activity and induces pathological changes in telomeres [12].

5.2.2. lncRNAs in the p53/p21 Pathway and p16/pRB Pathway. The p53/p21 and p16/pRB pathways are key regulators of cellular aging. p53 activation is a stress response that can trigger multiple events. p21, a downstream effector of p53, works in synergy with p53 to regulate the expression of pro-aging genes. Cyclin-dependent kinase inhibitors and tumor suppressor p16, which promotes growth arrest, are widely used as aging markers. p16 inhibits pRB phosphorylation and inactivation. Therefore, the p53/p21 and p16/pRB pathways, along with their upstream and downstream regulatory factors, can serve as non-specific biomarkers of aging.

lncRNA 7SL inhibits p53 translation, promoting cell cycle progression and preventing cell aging and autophagy. Silencing 7SL promotes p53 translation and accumulation, leading to cell cycle arrest and aging in cervical cancer cells. lincRNA-p21 inhibits transcription complexes in the p53 pathway and acts as a co-activator of p53-dependent p21 transcription in synergy with hnRNPK. lncRNA PURPL inhibits p53 expression by preventing the formation of the p53-MYBBP1A complex in the nucleolus. lncRNA DINO binds to p53 protein, promoting its stability and regulating the p53 auto-amplification loop, which is essential for p53-dependent gene expression and cell cycle arrest.

5.2.3. The Association Between lncRNAs and Age-related Diseases. Aging is a major risk factor for many chronic and degenerative diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders. These age-related diseases involve multiple mechanisms, and lncRNAs regulate gene expression and signaling pathways at different stages [13].

lncRNAs are associated with systemic changes in age-related cardiovascular diseases and the regulation of gene expression and signaling pathways at various stages. For instance, elevated expression of KCNO10T1 is linked to atherosclerosis and heart disease. MALAT1 activates the mTOR signaling pathway by regulating miR-5b-5p and MAPK1, inhibiting cellular autophagy and apoptosis, and promoting coronary heart disease progression. In adult endothelial cells, lncRNA H19 levels decrease with age, and H19 depletion leads to premature aging and inflammatory activation. However, high expression of H19 improves the function of aged aortic endothelial cells. In endothelial progenitor cells, GAS5 inhibits NAMPT, promotes cell proliferation, and prevents aging by downregulating miR-223. ANRIL enhances cell viability by negatively regulating miR-181a and inhibiting the p53-p21 signaling pathway, thereby preventing cellular aging and cell cycle arrest in vascular smooth muscle cells.

6. Conclusion

Epigenetic mechanisms are involved in the regulation of normal cellular aging processes and age-related diseases through similar or distinct pathways. However, no specific epigenetic modifications have been identified for a particular type of senescent cell or age-related disease, and not all senescent cells exhibit these markers. Further research is needed to explore the relationship between different epigenetic modifications and aging. As studies on the role of epigenetic modifications in aging and age-related diseases progress, they will provide a deeper understanding of evolution, growth, development, and aging. This research may also offer new directions for diagnosing and treating age-related diseases, developing new drugs, and exploring anti-aging strategies. However, many questions remain regarding the association between epigenetic modifications, aging, and age-related diseases, such as their specific mechanisms of action, the extent of their influence on cellular aging, and whether they can serve as precise therapeutic targets. Future research must address the expression patterns of epigenetic changes, their interactions, and how expression changes affect cellular function. Additionally, appropriate animal models are needed to study the biological functions and mechanisms of different epigenetic modifications, their roles in tissues, organs, and systems, and how they impact aging and age-related diseases. This knowledge will be crucial for developing effective preventive interventions, delaying aging, and preventing the onset and progression of age-related diseases.

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