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- Review -

The Roles of Epigenetic Reprogramming in Age-related Diseases

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Aging is a complex biological process characterized by a gradual decline in cellular and physiological functions. This natural process is associated with age-related diseases, including Alzheimer's disease, atherosclerosis, and hypogonadism, which are significant health concerns among older individuals and can significantly impact their quality of life. Researchers have found that epigenetic markers play a crucial role in regulating aging and age-related diseases. Epigenetic markers are heritable gene expression alterations that do not change in the DNA sequence. This review focuses on the involvement of various epigenetic marks, such as RNA methylation, DNA methylation, and microRNAs (miRNAs), in regulating gene expression patterns associated with age-related diseases, such as Alzheimer's disease, atherosclerosis, and hypogonadism. These epigenetic alterations can lead to the dysregulation of specific genes and signaling pathways, contributing to the development and progression of Alzheimer's disease, atherosclerosis, and hypogonadism. Understanding the molecular mechanisms behind these epigenetic modifications is essential for both the aging population and individuals seeking ways to promote overall well-being. By gaining deeper insights into how epigenetic marker alteration occurs during aging and age-related diseases, researchers can potentially develop targeted therapeutic strategies to alleviate the impact of these conditions and improve the quality of life for older individuals.

Key words : Aging, alzheimer's disease, atherosclerosis, epigenetics, hypogonadism

Introduction

Epigenetics refer to modulating heritable phenotypes without any alterations in DNA sequences. These alterations are mediated by epigenetic marks, such as RNA methylation, DNA methylation, and non-coding RNA, and play a pivotal role in gene regulation and cellular function [1, 12]. It involves resetting epigenetic patterns to a more undifferentiated or pluripotent state, allowing cells to undergo developmental processes or acquire new cell fates.

RNA methylation refers to adding a methyl group to the nucleotide bases of RNA molecules. It is a post-transcriptional modification that plays crucial roles in gene expression regulation, RNA processing, and various cellular processes. The most abundant RNA methylation in eukaryotes is N6-methyladenosine (m6A). The dynamic interplay between m6A methyltransferases (writers), demethylases (erasers), and recognize genes (readers) allows for precise regulation of RNA methylation levels, affecting RNA stability, localization, translation, and other aspects of RNA metabolism (Fig. 1A) [7, 13, 40, 77]. This process contributes to various biological processes, including embryonic development, cellular differentiation, response to stress, and disease development. The "writers" are a group of enzymes responsible for adding methyl groups to RNA molecules. The key enzyme for m6A methylation is called the methyltransferase-like 3 (METTL3) and METTL14, which binds to RNA and catalyzes the transfer of a methyl group from S-adenosyl methionine (SAM) to the N6 position of adenosine [45, 52, 77]. The "erasers," the fat-mass and obesity-associated protein (FTO), and the AlkB homolog 5 (ALKBH5) are enzymes responsible for removing the methyl groups from RNA molecules [39, 77]. The "readers" are a diverse group of proteins that recognize and bind to methylated RNA, leading to downstream effects on RNA metabolism and function. These reader proteins contain specific RNA-binding domains, such as YTH domain-containing proteins (YTHDC1, YTHDC2) and the YTH fam-

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ily proteins (YTHDF1, YTHDF2, YTHDF3) [62, 63, 79]. The binding of readers to methylated RNA can influence messenger RNA (mRNA) stability, translation efficiency, and splicing.

DNA methylation is an epigenetic modification that involves adding a methyl group to the cytosine in DNA, typically occurring at the carbon 5 position of the pyrimidine ring [54]. DNA methylation is critical in gene expression regulation, genomic imprinting, chromatin structure, and genome stability [17]. The mechanism of DNA methylation involves three main components: DNA methyltransferases (DNMTs) and DNA demethylases (Fig. 1B) [67, 71]. The interplay between DNMTs and DNA demethylases determines the DNA methylation patterns in different genome regions, allowing for establishing and maintaining cell type-specific and developmentally regulated DNA methylation landscapes. DNA methylation patterns can be heritable and change in response to environmental factors or during development, contributing to cellular diversity and phenotypic plasticity.

MicroRNAs (miRNAs) are small non-coding RNA molecules, typically around 21-23 nucleotides in length, that play important roles in post-transcriptional gene regulation [4, 6, 23]. They are involved in various biological processes, including development, cellular differentiation, immune response, and disease development. After miRNA genes are transcribed, the processing of primary miRNA (pri-miRNA) into precursor miRNA (pre-miRNA) hairpin structures by Drosha and the subsequent export of pre-miRNAs from the nucleus to the cytoplasm by Exportin 5 (Fig. 1C) [72]. Once in the cytoplasm, pre-miRNAs are further processed by the Dicer, resulting in the generation of small double-stranded RNA duplexes [25]. Finally, the RISC-loaded mature miRNA recognizes and interacts with target mRNAs, leading to post-transcriptional gene regulation. The specific binding of miRNAs to target mRNAs is mediated by base pairing between the miRNA and the mRNA, primarily through the recognition of complementary sequences known as miRNA response elements. The degree of complementarity between the miRNA and its target mRNA can vary, resulting in different levels of translational repression or mRNA degradation.

In conclusion, this review emphasizes the significant role of epigenetic reprogramming in age-related diseases, mainly focusing on Alzheimer's disease, atherosclerosis, and hypogonadism. By exploring the molecular mechanisms through which epigenetic alterations occur, we can gain valuable insights into disease pathogenesis and potentially discover novel therapeutic approaches for these conditions.

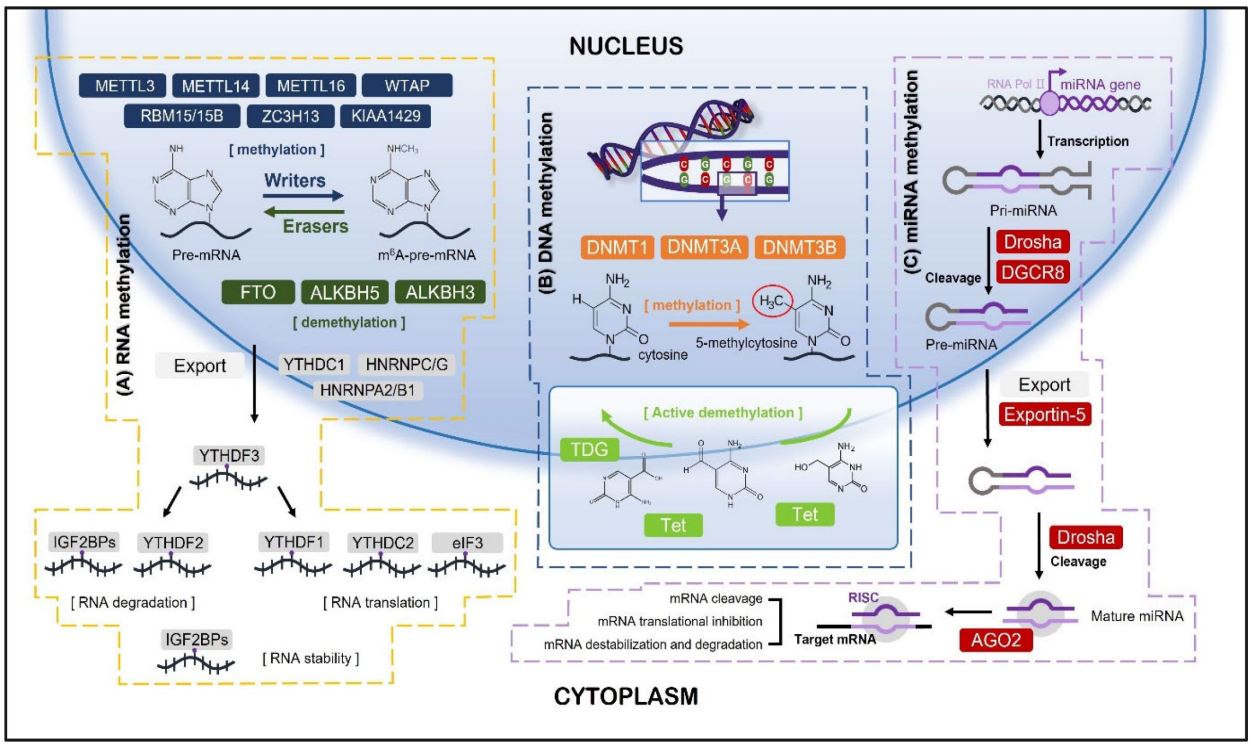

Fig. 1. Epigenetic mechanisms. (A) RNA methylation, (B) DNA methylation, and (C) non-coding RNA.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and declining cognition. The exact cause of AD is not fully understood, but it is believed to result from a combination of genetic, environmental, and lifestyle factors. Aging is considered the most significant risk factor for developing the disease [16, 24, 34, 60, 65]. Although the exact causes of AD are still not fully understood, emerging evidence suggests that epigenetic reprogramming, including DNA methylation, RNA methylation, and miRNAs, may contribute to its development and progression.

RNA methylation and Alzheimer's disease

Several studies have demonstrated dysregulation of m6A modification in AD, affecting the levels and functions of specific mRNAs associated with the disease [21, 75]. For example, one study found that m6A modification levels were significantly decreased in the brains of individuals with AD compared to healthy groups [76]. This attenuation was associated with alterations in the downregulation of METTL3 expression, resulting in neuronal function, synaptic plasticity, and inflammation. Furthermore, specific mRNAs related to AD pathology, including amyloid precursor protein (APP), tau protein, and apolipoprotein E (ApoE), have been identified as targets of m6A dysregulation [11, 37, 51]. Alterations in m6A levels on these mRNAs can influence their stability, translation, and subsequent protein expression, potentially contributing to the disease process. While the precise mechanisms linking RNA methylation to AD remain to be fully elucidated, these emerging findings suggest that dysregulation of m6A modification could contribute to the development and progression of AD. Further research is needed to ensure the functional consequences of RNA methylation alterations in AD and explore its potential as a therapeutic target or diagnostic biomarker.

DNA methylation and Alzheimer's disease

Several studies have investigated DNA methylation patterns in individuals with Alzheimer's and identified specific alterations associated with the disease. Studies have shown alterations in DNMT expression in the brains of individuals with AD versus healthy individuals. Attenuation of DNMT1 was observed in AD patients, which is the loss of DNA methylation and contributes to AD pathology [8, 38]. Gene expression changes by alteration of DNA methylation can occur in genes involved in various biological processes, including oxidative stress, neuronal function [27], synaptic plasticity [5], inflammation [5], and amyloid-beta (Aβ) processing [38]. One of the most well-studied genes in relation to DNA methylation and AD is the amyloid precursor protein (APP) gene [5, 27, 38]. Abnormal DNA methylation in the promoter region of the APP gene has been observed in individuals with AD, potentially affecting APP expression and Aβ production, which are implicated in the formation of plaques in the brain. Other genes involved in AD pathologies, such as β-secretase (BACE), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), have also been found to exhibit altered DNA methylation [19, 44]. These genes play a role in the production of Aβ and tau protein, both of which are central to AD development. Notably, DNA methylation alterations are not static and can be influenced by various environmental factors, including lifestyle, diet, and exposure to toxins. Thus, understanding the role of DNA methylation in AD may have implications for developing novel therapeutic strategies or early detection biomarkers.

miRNAs and Alzheimer's disease

miRNAs are small non-coding RNA molecules that play essential roles in post-transcriptional modification. miRNAs bind to mRNA molecules and regulate their stability and translation into proteins. Recently, dysregulation of specific miRNAs has been observed and implicated in the pathogenesis of AD. Emerging evidence has shown miRNA expression profiles in AD, both in brain tissue and various biological fluids such as cerebrospinal fluid and blood [37]. These studies have identified specific miRNAs that are differentially expressed in individuals with AD compared to healthy controls. For example, miR-125b is downregulated in AD and has been implicated in regulating neuroinflammation [58]. It targets genes involved in the immune response, such as tumor necrosis factor-alpha (TNF-α) and nuclear factor kappa B (NF-κB), and its downregulation may contribute to the inflammatory processes observed in AD. miR-132 and miR-212 are involved in synaptic plasticity and neuronal function [49]. They are downregulated in AD and have been shown to regulate genes associated with synaptic activity and neurotrophin signaling pathways, such as brain-derived neurotrophic factor (BDNF). miR-146a is upregulated in AD and regulates the immune response and inflammation [3]. It targets genes involved in the innate immune pathway, including interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6), and its dysregula-

tion may contribute to neuroinflammation in AD. These dysregulated miRNAs have been associated with various processes involved in AD, including neuroinflammation, synaptic dysfunction, Aβ processing, tau pathology, and neuronal cell death.

Atherosclerosis

Atherosclerosis, a slow and progressive inflammatory disease, is characterized by the development of lipid-rich plaques within the layers of the artery walls [26]. Aging is associated with alterations in lipid metabolism, including increased low-density lipoprotein (LDL) levels and decreased high-density lipoprotein (HDL) levels [29]. These age-related lipid abnormalities contribute to the formation of atherosclerotic plaques derived from genetic and environmental factors. The studies of epigenetic modifications, such as DNA methylation, RNA methylation, and non-coding RNA, provide new molecular insights into the development and progression of atherosclerosis by regulating gene expression without changing the DNA sequence.

RNA methylation and atherosclerosis

Several studies have shown dysregulated m6A RNA modification in genes associated with critical processes in atherosclerosis, such as inflammation, lipid metabolism, cholesterol efflux, and endothelial dysfunction [18, 78]. Dysregulation of METTL3 can lead to enhanced inflammatory responses and impaired endothelial function, which are critical events in atherosclerosis development. For example, METTL3-induced pro-inflammatory transcription factor, signal transducer, and activator of transcription 1 (STAT1) have been implicated in regulating macrophage polarization and foam cell formation, which are central to the progression of atherosclerotic plaques [14]. Indeed, the downregulation of METTL14 in endothelial cells has been shown to regulate the expression of genes involved in endothelial inflammation and dysfunction, including adhesion molecules and cytokines production [28]. In terms of lipid metabolism and cholesterol efflux, the m6A modification of fatty acid synthase (FASN) mRNA affects its stability and translation efficiency, thereby influencing the de novo synthesis of fatty acids [64]. Similarly, m6A modification has been shown to regulate the expression of sterol regulatory element-binding proteins (SREBPs), which are key transcription factors involved in cholesterol biosynthesis [20].

DNA methylation and atherosclerosis

DNA methylation is an important epigenetic modification that can influence gene expression patterns. Alterations of DNA methylation have been observed in various cell types involved in atherosclerosis, including endothelial cells, smooth muscle cells, and immune cells. These DNA methylation changes can affect the expression of genes involved in inflammation, lipid metabolism, oxidative stress, vascular remodeling, and thrombosis, all of which are important processes in the development of atherosclerosis [33, 55, 61]. Several studies have investigated DNA methylation alteration associated with the progression and development of atherosclerosis using both targeted and genome-wide approaches [43, 69, 74]. For example, DNA methylation can stimulate the expression of inflammation-related genes [61]. For example, hypermethylation of the promoter regions of anti-inflammatory genes, such as interleukin-10 (IL-10), can contribute to decreased expression, while hypomethylation of pro-inflammatory genes, such as TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6) can lead to stimulating inflammatory responses and plaque formation [36, 46]. DNA methylation can also impact lipid metabolism. Alteration of DNA methylation can influence the expression of genes involved in cholesterol metabolisms, such as ATP-binding cassette transporter A1 (ABCA1) and low-density lipoprotein receptor (LDLR), affecting lipid uptake, efflux, and transport.

miRNA and atherosclerosis

miRNAs have been extensively studied in atherosclerosis due to their regulatory roles in gene expression and their involvement in various disease processes. miR-155 is one of the most extensively studied miRNAs in atherosclerosis [70]. It is involved in regulating inflammatory responses and immune cell activation within atherosclerotic plaques. miR-146a is another miRNA that has been implicated in promoting inflammation and atherosclerotic plaque formation. It acts as a negative regulator of pro-inflammatory signaling pathways by targeting genes such as IRAK1 and TRAF6 [41, 57]. miR-33 is a miRNA that plays a critical role in lipid metabolism. It targets genes involved in cholesterol efflux genes, such as ABCA1, and fatty acid oxidation genes, such as CPT1A, thereby influencing cellular lipid homeostasis. miR-33 has been shown to modulate cholesterol transport and metabolism in atherosclerosis, and its inhibition has been proposed as a potential therapeutic strategy [48]. miR-21 is upregulated in atherosclerosis and is involved in the regulation of smooth muscle cell proliferation and migration. It targets

genes involved in apoptosis and extracellular matrix remodeling. Conversely, miR-126 is predominantly expressed in endothelial cells and may prevent the initial trigger for atheroma formation [15, 22]. It promotes endothelial cell survival, proliferation, and vascular integrity. Reduced levels of miR-126 have been observed in atherosclerotic plaques, and its recovery has been shown to enhance endothelial repair and reduce plaque formation in animal models.

Hypogonadism

Hypogonadism is known to be associated with aging [56]. As individuals age, especially in males, there is a natural decline in the production of sex hormones, testosterone. The symptoms and potential health complications of hypogonadism are decreased libido, sarcopenia, depressed mood, and reduced vitality [31, 53, 56]. Although hypogonadism is attributable to several mechanisms, like dysfunction of Leydig cells and lower testicular response to luteinizing hormone (LH), understanding of epigenetic reprogramming in hypogonadism during aging remains unknown, and more research is needed to elucidate the mechanisms involved fully. Nevertheless, studying epigenetic modifications in relation to aging hypogonadism may provide insights into the underlying molecular processes and potentially identify targets for therapeutic interventions.

RNA methylation and hypogonadism

RNA methylation is involved in gonadal development, hormone synthesis, and reproductive processes. And also, RNA methylation can influence the expression and function of sex hormone receptors, such as the androgen receptor (AR). Dysregulation of m6A modification of the receptor genes may affect their stability, localization, or translation efficiency, potentially impacting hormone signaling and leading to hypogonadism [9]. METTL3 and METTL14 can regulate the expression of CYP11A1, a critical enzyme in testosterone biosynthesis. The m6A modification on CYP11A1 mRNA promotes its stability and increases CYP11A1 protein levels, thereby enhancing testosterone production. Chen et al. [10] showed that alteration of METTL14 and ALKBH5 decreased testosterone synthesis by modulation of autophagy in *in vivo* and *in vitro* studies.

DNA methylation and hypogonadism

Several studies have investigated the association between DNA methylation patterns and hypogonadism. DNA methylation modification in the promoter region of the AR gene has been related to hypogonadism [73]. Hypermethylation of the AR gene can result in decreased AR expression or function, leading to androgen insensitivity and the development of hypogonadism [73]. Indeed, DNA methylation alterations in the promoter region of the GnRH have been observed in certain forms of hypogonadism. Changes in GnRH gene methylation may impact the production and release of gonadotropin-releasing hormone, which is essential for the regulation of reproductive hormone secretion [32]. Several studies have shown that DNA methylation changes in genes involved in sex steroid synthesis and metabolism have also been implicated in hypogonadism [2, 59]. For example, altered DNA methylation patterns in genes encoding enzymes involved in steroidogenesis, such as aromatase and 17β-hydroxysteroid dehydrogenase, can affect the production and metabolism of sex hormones [42, 47].

miRNAs and hypogonadism

miRNAs are small non-coding RNA molecules that play a crucial role in post-transcriptional gene regulation. While research on the specific involvement of miRNAs in hypogonadism is limited, some studies have explored the potential links between miRNAs and this condition. miR-122 is highly expressed in the liver and regulates genes involved in cholesterol and lipid metabolism. Dysregulated expression of miR-122 has been associated with several liver disorders, including non-alcoholic fatty liver disease (NAFLD), which can impact gonadal function and contribute to hypogonadism [35]. The let-7 miRNA family is involved in the regulation of cellular proliferation and differentiation [30]. Some studies have suggested that miR-let-7a may contribute to regulating Leydig cell differentiation and steroidogenesis, which are essential for proper gonadal function [50]. miR-34a, a member of the has been implicated in the regulation of cell cycle progression, apoptosis, and senescence [68]. Reduced levels of miR-34a have been observed in testicular tissues of patients with testicular germ cell tumors, which can lead to abnormal testicular function and potential hypogonadism. The miR-17-92 cluster, which includes several miRNAs, has been shown to regulate cell proliferation and differentiation [66]. Studies have suggested that dysregulated expression of miR-17-92 cluster members may be associated with impaired spermatogenesis and male infertility, which can be accompanied by hypogonadism [66].

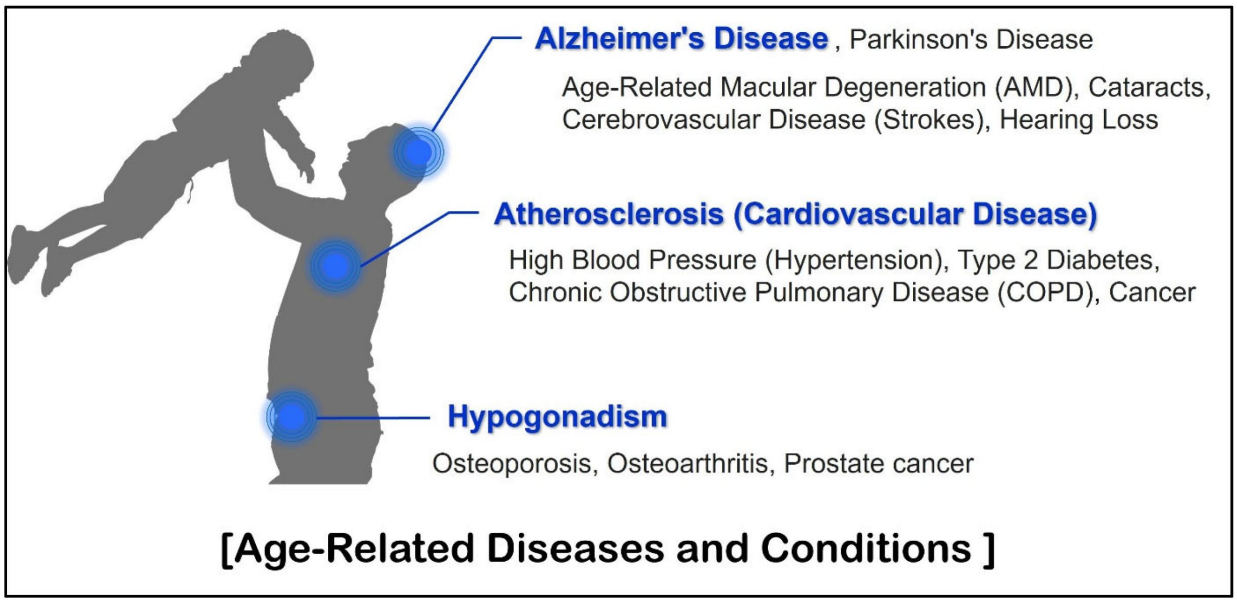

Fig. 2. Age-related diseases such as Alzheimer's disease, atherosclerosis, and hypogonadism.

Conclusion

Aging is a pivotal risk factor for age-related diseases such as AD, atherosclerosis, and hypogonadism, influenced by a combination of genetic and environmental factors (Fig. 2). Although epigenetic alterations represent an exciting and rapidly evolving field for understanding the underlying mechanisms of age-related diseases, numerous questions remain unanswered. In conclusion, a greater understanding of the epigenetic basis of age-associated disorders is needed to inform the development of new therapeutic intervention agents and prevention strategies targeting these diseases.

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The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 노화관련 질환에 대한 후성유전의 역할

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노화란 세포 및 생리 기능이 점진적으로 손상되는 복잡한 과정이다. 알츠하이머, 동맥경화 및 갱년기와 같은 노화와 관련된 질병은 노화가 진행이 되면서 발생된다. 노화와 관련된 질환은 다양한 원인에 의해 발생된다. 그 중 유전적인 변화 없이 유전자 발현을 조절하는 후성유전의 변화는 노화, 그리고 노화와 관련된 질환의 발생에 중요한 조절자로 알려져있다. 이 리뷰에서는 후성유전의 변화가 노화 및 노화와 관련된 질병의 발전과 진행에 어떠한 역할을 하는지에 대해 서술하였다. 노화 중에 일어나는 유전적 변화의 분자적 기전과 이러한 변화가 노화와 관련된 질병에 미치는 영향, 특히 노화와 관련된 질환과 관련된 유전자 발현 양식을 조절하는 RNA 메틸화, DNA 메틸화 및 miRNA에 대해 중점적으로 초점을 맞추었다.