JKAU: Sci., **Vol. 34**, No. 2, pp: 1 - 15 (2024)
DOI:10.4197/Sci.34-2.1

Epigenetic Modifications in Cellular Senescence: Mechanisms, Implications, and Therapeutic Potential

Ahmed Mohammed Adam[1], Mohammad Imran Khan[2] and **Faisal A. Alzahrani[1*]**

[1]Department of Biochemistry, Faculty of Science, King Abdulaziz University, and [2]Research Center, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia.

faahalzahrani@kau.edu.sa

Abstract. Stressors, has attracted attention in the biological and medical sciences. Epigenetic modifications, which impact gene expression patterns and ultimately dictate the fate of cells, play a crucial role in managing cellular senescence. DNA methylation is a crucial epigenetic process implicated in cellular senescence. Research has demonstrated that changes in gene expression profiles result from global hypomethylation and localized hypermethylation of genes during senescence. Cellular senescence is also significantly influenced by histone alterations. Histone acetylation or methylation can change the chromatin structure, which can impact transcription factors' ability to bind to gene promoters. Consequently, this may have an impact on the expression of genes linked to senescence processes. Furthermore, due to their capacity to post-transcriptionally control gene expression, non-coding RNAs like microRNAs have become significant regulators of cellular senescence. Dysregulation of microRNAs has been linked to the induction or inhibition of senescence in different cell types. In this comprehensive review, we discuss the epigenetic modifications that occur during cellular senescence and explore their potential as therapeutic targets to regulate the senescent phenotype, a crucial step in addressing age-related diseases.

Keywords: Epigenetic modifications, Cellular senescence, Senescence-associated secretory phenotypes.

1. Introduction

Senescence is a cellular mechanism which causes a long-term growth halt along with certain phenotypic changes, such as enhanced autophagy, chromatin remodeling, metabolic reprogramming, and the release of a wide range of proinflammatory secretomes [1]. Hayflick and his colleague initially reported this phenomenon after observing the proliferation of cells in culture medium, in which human diploid fibroblasts undergo repeated passage *in vitro* and then permanently leave the cell cycle [2].

Two forms of senescence processes exist: one is replicative senescence, which usually occurs after multiple divisions of the cell due to the loss of proliferation capability as part of the normal aging process. The other type is stress-induced senescence, which results from the response of the cell to different triggers such as damage of the DNA, reactive oxygen species, in addition to oncogenic activation [3].

The biological processes of cellular senescence have several advantages in the control of embryonic growth, wound recovery, and tumor suppression. Prolonged senescence, on the other hand, might have negative consequences such as tumor formation, ongoing inflammation, immunological deficiency, and stem cell fatigue [4, 5].

Developing the arrest of the cell cycle in mammalian cells is primarily dependent on p53 and the retinoblastoma (RB) family proteins (Fig. 1). Certain cyclin-dependent kinases such as (CDK4, CDK6, CDK2) phosphorylate RB1 and its family members, which promote p16

(CDKN2A) and p21 to accumulate in the senescent cells. When this buildup occurs, RB family proteins become persistently activated, E2F transactivation is inhibited, and senescence develops [6].

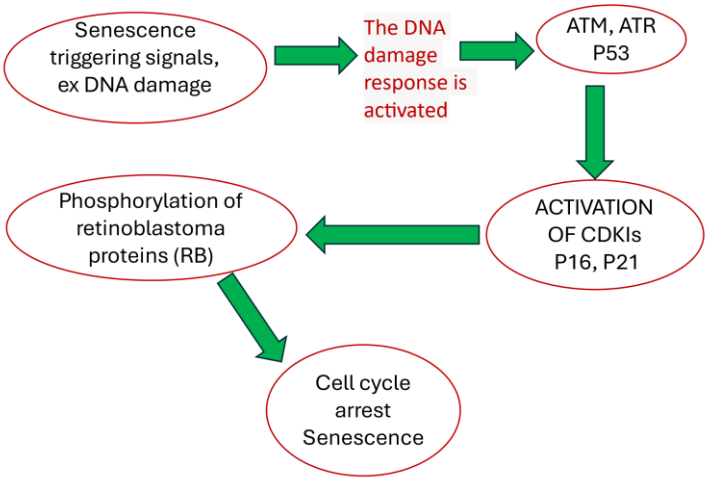

Fig. 1. Senescence is activated by stressors such DNA damaging, reactive oxygen species (ROS), and telomere shortening, resulting in activation of the DNA damage response (DDR) pathway and subsequent cell cycle arrest via (CDKIs) and retinoblastoma protein (RB) hyperphosphorylation.

Variety of factors can participate in the induction of the cellular senescence (Fig. 2), including reactive oxygen species, damaging of the telomere, damaging of the DNA, inflammatory secretions, malfunctioning of the mitochondria and disturbance in epigenetic markers [7].

Senescent cells exhibit specific characteristics such as big nucleus, double nucleus which created when cell division is halted, and varying degrees of cellular invagination [8], in addition to chromatin remodeling including chromosomal condensation, redistribution, and the creation of heterochromatic foci. These changes may be brought on by the missing of LMNB1 from the nuclear membrane inner surface [9]. Others recognized biomarkers of cellular senescence include p16, p21, and SA-βgal [10]. Senescent cells also exhibit dysregulation of autophagy, nuclear lamina, as well as disturbances in the homeostasis of organelles, such as lysosomal and mitochondrial malfunction. Moreover, these disturbances may cause an arrest in cell cycle and production of components of SASP [11].

The term "epigenetic modifications" refers to heritable changes that impact gene transcriptional activity through DNA methylation, histone modification, chromosomal remodeling, and non-coding RNA and alter gene expression independently of changes in DNA sequence [12, 13]. Epigenetic alterations, such as methylation of the DNA, modification of histones, and chromatin modifications, have been identified as an additional marker of aging and are essential for the induction and Preservation of cellular senescence [14]. Importantly, these alterations are reversible following cessation of stimulation and might be either reasonably stable and persistent over time or reversible upon pharmaceutical intervention. This presents the intriguing prospect of pharmacologically eradicating detrimental epigenetic modifications to prevent diseases, an area that is receiving a lot of attention [15]. Epigenetic markers (Table 1) contribute to aging and aging-related disorders by controlling the aging process. Consequently, comprehending the epigenetic processes involved in aging will open novel opportunities for creating anti-aging treatments. In fact, aging therapies based on modifying epigenetic pathways have prevented or prolonged aging in animal models [16].

A popular indicator to estimate life expectancy and age-related disorders is DNA methylation. Specifically, since 2013, numerous aging biomarkers also referred to as clocks have been developed. Among these, the first-generation clocks, including the Horvath and Hannum clocks, estimate a person's biological age by using CpG sites, which are strongly correlated with chronological age [17, 18]. DNA methylation causal analysis identifies important regulators of aging and senescence finds that 4.1% of methylated sites are associated with aging outcomes, suggesting that DNA methylation has a major impact in aging. Important genes, including ETFB, MARS2, and CISD2, were identified as mediating these effects. The induction of cellular senescence is caused by silencing of these genes through methylation [19].

A crucial epigenetic modification that controls gene expression by compressing or decondensing the chromatin is histone acetylation/deacetylation. Global histone hyperacetylation has been linked to cellular senescence, even though these modifications only affect the local regulation of specific genes [20]. Global histone expression has been found to be significantly lower in human retinal pigment epithelium (HRPE) cells under replicative and chronological aging models. Aged RPE showed significantly higher levels of senescence-associated secretory phenotype (SASP) components and senescence-associated β-galactosidase (SA-β-Gal) staining. These results clearly show that histone loss is a distinct characteristic of RPE aging and offer important novel perspectives on the possible pathways that connect aging, cellular senescence, and histone instability [21].

It was formerly believed that non-coding RNAs were restricted to regulating post-transcriptional gene expression. However, recent studies have demonstrated that non-coding RNAs are the most common type of regulatory RNAs; additionally, an increasing body of evidence suggests that regulatory non-coding RNAs play a critical role in epigenetic control. Thus, these non-coding RNAs highlight the important role RNA plays in regulating gene expression [22]. Different sized and types of non-coding RNAs have been found to affect cellular senescence. The primary senescence-regulatory processes, the p53/p21 route, the pRB/p16 pathway, SASP, and protein patterns governing these, and other aspects of senescence are all known to be robustly modulated by an increasing number of microRNAs and lncRNAs [23].

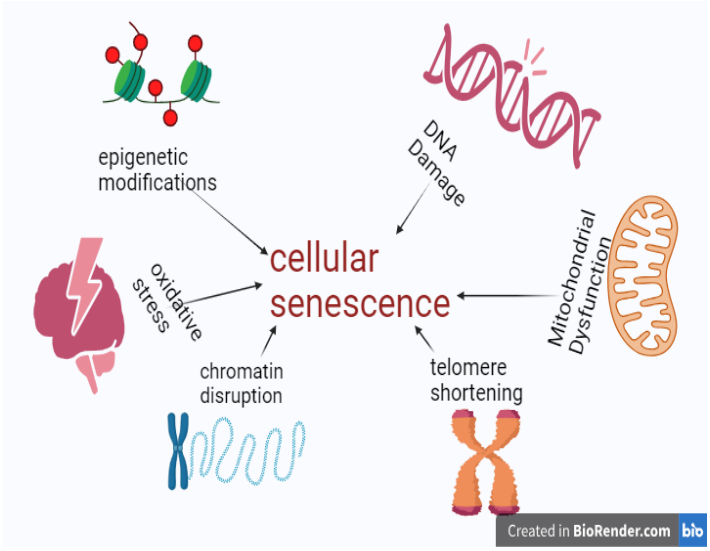

Fig. 2. Illustration of the major causes of cellular senescence which include DNA damage, Mitochondrial dysfunction, Telomere shortening, Chromatin disruption, Oxidative stress and Epigenetic alterations. All these factors initiate a complicated network of signaling pathways that stop cell division and cause alterations in cell shape, gene expression, and secretory profile, which are hallmarks of the senescent phenotype.

This review discusses the epigenetic alterations that implicated in the initiation and preservation of senescence phenomenon in the following points:

2. DNA Methylation in Cellular Senescence

Methylation of the DNA is one of epigenetic markers that is linked with gene silencing when the methylation occurs in CpG islands of promoter sequences. Through chemical alterations of DNA bases, epigenetic mechanisms can control gene expression without directly changing the DNA sequence [24].

Methylation processes of DNA are executed by specific enzymes named DNA methyltransferases (DNMTs). As of right now, three DNMTs, DNA methyltransferases1, DNA methyltransferases 3a, and DNA methyltransferases 3b have been found in mammals. By imitating the parent DNA strand's methylation pattern on the freshly synthesized strand, DNMT1 preserves DNA methylation throughout replication. *De novo* DNA methylation is carried out by DNMT3b and DNMT3a, which also collaborate with DNMT1 to guarantee the spread of methylation arrangements during DNA replication and target unmethylated CpG dinucleotides. If methylated CpGs are unable to proliferate after DNA replication, then comparatively slow "passive" DNA demethylation may take place [25]. Removal of methylation is carried out via the procedure of demethylation, that might happen with 5-hydroxymethylcytosine [26].

When Ramini and his colleagues examined whole genome DNA methylation of young senescent endothelial cells, they discovered substantial hypomethylation of Long-Interspersed Element sequences and elevated quantities of demethylated regions in senescent cells [27]. In the examination of 2 subclasses of HNSC by Lee et al. they found subclass1 exhibited notably lower levels of hypomethylation at many CpG sites compared to those in subclass2, and the methylation of silencing genes in subclass1 were more abundant in transcription factor targets, particularly ZNF528 target genes. According to this research, ZNF528's epigenetic silencing may play a significant role in determining the tumor microenvironment subtype associated with senescence in HNSC [28].

2.1 Role of DNA Methyltransferases in Senescence

A decline in DNMT1 expression causes hypomethylated areas of cellular DNA to accumulate, leading to progressive gene reprogramming, which results in stimulation of some genes that regulate senescence [29]. DNMT1 expression was found to be higher in early-passage MSCs than in mesenchymal stem cells at later passages, but not in DNA methyltransferase 3A or DNA methyltransferase 3B. Moreover, DNMT1 overexpression in mesenchymal stem cells at later passages has the opposite effect from DNMT1 knockdown, which causes senescence [30]. In human dermal fibroblasts (HDFs), ultraviolet A (UVA)-induced senescence is associated with DNA methyltransferase 1. It has been shown that the expression of DNMT1 was dramatically downregulated during the senescence caused by UVA, and that DNMT1 up- or down-regulation might therefore either mitigate or exacerbate this senescence [31].

Reports state that the senescence phenotype was dramatically promoted by DNMT1 knockdown in younger human skin fibroblasts (HSFs), and DNMT1 expression was shown to be much higher in HSFs than in aged HSFs. The upstream miRNA (miR-377) would control DNMT1 expression through acceleration or inhibition of its expression [32].

Transient DNMT3L expression was found to enforce global and regional chromatin monitoring, hence halting senescence in aging and pre-senescent mouse embryonic fibroblasts.

By upregulating histone H3 and the outer nuclear envelope protein, DNMT3L therapy of aged MEFs brought their nuclear structure closer to that of young cells [33].

According to Jung et al., increased activity of DNA methyl transferase 3 (DNMT3A) is brought about by a decrease in certain microRNA, which has a detrimental effect on the production of mitochondrial superoxide dismutase, which in turn causes senescence through an increase in reactive oxygen species [34].

3. Histone Modifications in Senescence

Histone proteins assist in the packaging of DNA inside nuclei to create chromatin, a combination of DNA and proteins. The nucleosome, the fundamental building block of chromatin, is made up of DNA and the core histones (Histone 2A, Histone 2B, Histone 3, and Histone 4) [35]. Numerous post-translational modifications (PTM) can affect the overall chromatin conformation, which in turn impacts replication, genomic stability, and gene expression. PTMs on histones can take many different forms. This variety of histone changes works in harmony to control several biological processes, including cellular senescence [36]. Histone modifications are frequently caused by ubiquitination, phosphorylation, acetylation, and methylation. In contrast to methylation, this kind of chemical alteration that occurs in histones can affect how genes are expressed. Histone methyltransferase, histone acetyltransferase, and histone deacetylase are the enzymes that control histone modifications [37].

Histone quantities are altered in harmony with senescence; nevertheless, not much is understood regarding the functions and processes of histone decrease in cellular senescence [38]. In replicative senescence, there are global declines in Histone H4 Lysine 16 Acetylation, Histone H3 Lysine 4 Trimethylation, Histone H3 Lysine 9 Trimethylation, and Histone H3 Lysine 27 Trimethylation. Increasing levels of Histone H3 Lysine 9 Acetylation and Histone H4 Lysine 20 Trimethylation were also reported. Such histone alterations have additionally been discovered in stress-triggered cells that undergo earlier senescence [39].

3.1 Role of Histone Methyltransferases in Senescence

Active promoters and gene transcription are correlated with lysine 4 methylation (H3K4) in histone H3. KMT2 methyltransferases are responsible for catalyzing this change; however, to be active, they must connect with four key subunits: WDR5, RBBP5, ASH2L, and DPY30. Both tissue homeostasis and organismal development require Ash2L. Ash2l deletion causes gene repression in mouse embryo fibroblasts (MEFs), which leads to a senescence phenotype [40].

Histone-lysine N-methyltransferase (SUV39H1) overexpression reduced SASP by H3K9me3 enrichment on gene promoters; downregulation of the protein was linked to the upregulation of genes associated with SASP. According to these findings, SUV39H1 is essential for managing inflammation during the process of cellular senescence. The discovery that SUV39H1 is an SASP controller advances our knowledge of the molecular processes that underlie cellular aging. By clarifying how SUV39H1 affects the expression of SASP [41].

Through H3K4me1, Protein 2 Smyd2 and histone methyltransferase SET both include MYND domains and create a hyper-methylated chromatin state, which activates enhancing components next to important senescence genes like Cdkn1a and Cdkn2a and further induces symptoms associated with senescence. Smyd2 was shown to be substantially increased in angiotensin II-triggered vascular endothelial cells, and Smyd2 depletion reduced senescence-associated phenotypes *in vivo* and *in vitro* [42].

3.2 Role of Histone Acetyltransferases in Senescence

Histones get acetyl groups added to them by important enzymes known as histone acetyltransferases (HATs). Enzymes called histone acetyltransferases (HATs) add acetyl groups to histones, controlling chromosomal architecture and gene expression in the process. Previous research has demonstrated that histone deacetylases, called sirtuins, can be activated to lengthen life. This implies that blocking HATs might provide a comparable advantageous outcome. HAT inhibitors and targeted RNA interference, induced Ngg1 or Gcn5 knockdown and decreased age marker levels, thus stimulating senescent cell growth in human cell lines [43].

Histone acetyltransferase, PCAF, or P300/CBP-Associated Factor, is a N-acetyltransferase linked to GCN5 that facilitates transcriptional activity. It interacts with numerous nonhistone proteins in addition to acetylating core histones (H3 and H4). Evidence has shown that PCAF contributes to the regulation of differentiation, carcinogenesis, gluconeogenesis, and cell cycle progression. Interestingly, multiple investigations show that PCAF is actively engaged in p53-dependent transcription of p21 and p16, cyclin-dependent kinase inhibitors that are strongly linked to the formation of senescence. Thus, endothelial cell PCAF inhibition may mitigate cellular senescence [44].

A histone acetyltransferase called KAT7 was found to be one of the genes whose deficit prevented cellular senescence; this gene was the greatest hit for the two progeroid human mesenchymal precursor cells (hMPC) models. KAT7 inactivation relieved hMPC senescence, suppressed p15INK4b transcription, and reduced histone H3 lysine acetylation [45].

3.3 Role of Histone Deacetylases in Senescence

Enzymes in the class of histone deacetylases (HDACs) alter the structure of chromatin by eliminating acetyl groups from histone tail lysine residues. HDAC1/2 has been found to have a significant role in the response to DNA damage and that they were quickly attracted to DNA-damage sites to encourage hypoacetylation of H3K56 [46]. Ultrastructural analysis of Hdac1 and 2 deletion podocytes revealed that lipofuscin droplet buildup inside the podocyte cell body and foot process effacement, both of which are indicative of cellular senescence, were further conformed by the SA-β-gal level, which is commonly used as an indicator for senescence [47].

HDAC4, or histone deacetylase 4, belongs to the class IIa group of histone deacetylases (HDACs), which is made up of proteins that are crucial for regulating gene expression that regulates a variety of cellular processes. After examining HDAC4's function in controlling cellular senescence, it was found that silencing HDAC4 causes premature senescence in human fibroblasts, whereas overexpressing HDAC4 inhibits cellular senescence [48].

Class IIb of the HDAC family includes histone deacetylase 6 (HDAC6), which is controlled by several protein kinases. Overexpression has an impact on genes relevant to the cell cycle. HDAC6 inhibition, found to cause glioblastoma cells to enter G2/M arrest and senescence [49]. Histone Deacetylase 6 levels in senescent human dermal fibroblasts (HDFs) and tissues of the skin from elderly mice were considerably lower. The migration speed of HDFs was significantly reduced, and proliferation was significantly suppressed upon HDAC6 activity inhibition with highly specific inhibitors or HDAC6 knockdown with siRNA. These findings indicated that HDAC6 is involved in maintaining crucial biological processes in dermal fibroblasts [50].

4. Non-Coding RNAs (ncRNAs) in Cellular Senescence

A diverse collection of transcripts known as non-coding RNAs are incapable of being transformed into proteins. Since their discovery, non-coding RNAs (ncRNAs) have demonstrated their importance as mediators of a wide range of biological activities in a variety of cells and tissues; their abnormal regulation has been linked to illnesses [51]. Improvements in RNA-sequencing techniques have been accompanied by the discovery of multiple non-coding transcripts with unclear roles. There are several different types of non-coding linear RNAs, including microRNAs (miRNA), circular RNAs (circRNAs), and long non-coding RNAs (lncRNA) [52].

Recent research has demonstrated the role that many kinds of non-coding RNAs play in cellular senescence. Three groups of these transcripts (lncRNAs), (miRNAs), and (circRNAs) have had their roles in this process well studied. Through various means, these three groups of transcripts can control the expression of genes. While lncRNAs can influence gene expression at several levels, miRNAs mostly function at the post-transcriptional level by interacting with mRNAs and causing mRNA degradation or slowing translation [53].

4.1 Long Non-Coding RNA in Cellular Senescence

It has been suggested to describe lncRNAs as non-coding transcripts with over 200 nucleotides that do not have the ability to code for open reading frames. They play several roles in different biologic processes, including transcription, post-transcriptional control of gene expression, and epigenetics [54]. Though many lncRNAs that are transcribed by Pol II are inefficiently processed and remain in the nucleus, their precise roles are dependent on their location and association with DNA, proteins, and RNA, despite their significant involvement in the control of gene expression at several levels. Among their various abilities are the ability to modify the composition and functionality of chromatin, alter the transcription of genes both close and far away, and interfere with signaling pathways [55].

Through its binding to miR-296-5p and activating the PI3K/mTOR pathway, H19 lncRNA may upregulate IGF2, boost AQP3 expression, and prevent human dermal fibroblast senescence [56]. Downregulation of the long noncoding RNA MAGI2-AS3 prevented the proteasome from breaking down the HSPA8 protein, which in turn reduced the amount of hydrogen peroxide and postponed cell senescence. Additional data demonstrated that MAGI2-AS3 is associated with HSPA8's C-terminal domain [57].

LncRNAs additionally participate in age-related disorders, such as osteoporosis. For example, lncRNA ob-1 increases the production of osteoblasts by upregulating the osteogenic transcription factor osterix, which in turn mediates its action by blocking H3K27me3 methylation [58].

4.2 MicroRNAs in Cellular Senescence

MiRNAs are shorter non-coding sequences of nucleotides that attach to mRNA sequences in the 3′-untranslated areas. When miRNA binds, it either prevents translation or encourages the target mRNA's destruction, which has the negative effect of controlling post-transcriptional gene expression and its contribution to the development of senescence [59].

An increase in osteoblast senescence and bone loss was caused by the miR-29a deletion. By attacking Dnmt3b-mediated FoxO3 methylation and upregulating antioxidant proteins, miR-29a improved the senescence program by reversing FoxO3 loss [60].

MiR-216a was shown to block the Smad3/IκBα pathway, which led to the promotion of endothelial senescence and inflammation. Notably, elderly people with coronary artery disease had higher plasma miR-216a concentrations, suggesting that miR-216a might be a possible target for therapy [61].

By targeting Sirt1, miR-199a-5p enhanced Ang II-induced Vascular Smooth Muscle Cell (VSMC) senescence, while miR-199a-5p suppression reduced the senescence of these cells. MiR-199a-5p/Sirt1 signaling has been demonstrated to be essential for Ang II-induced VSMC senescence [62].

5. Epigenetic Alterations in Senescence-Associated Secretory Phenotype

The capacity of senescent cells for expressing and producing a range of extracellular modulators, such as growth factors, proteases, chemokines, cytokines, and bioactive lipids, is known as the senescence-associated secretory phenotype, or SASP [63]. SASP participates in the pathogenesis of many diseases, including cancer, as well as physiological reactions like wound healing. The SASP commonly encourages treatment resistance and recurrence in cancer [64]. epigenetic modification Processes are engaged in SASP control; MMPs and chemokines are examples of SASP genes that physically cluster together, indicating that alterations in chromatin architecture may play a role in regulating their expression. It is true that a variety of histone variations can affect how SASP genes express themselves [65]. It has been shown that the crucial element of the feedback loop that sustains SASP gene expression and initiates the induction of paracrine senescence is the tumor suppressive histone variation H2A1, which is a critical player in controlling the expression of the SASP gene during senescence [66]. Histone H2A.J, a little-studied variation of H2A that is unique to mammals, builds up in human fibroblasts during senescence and causes ongoing DNA damage. In addition, H2A.J. accumulates in human skin and in aged rats. Overexpression of H2A.J promotes the expression of certain of these genes in proliferating cells, while knockdown of H2A.J decreases the activation of inflammatory genes that are linked to the SASP [67].

Studies conducted *in vitro* as well as *in vivo* showed that SUV39H1 declined with age and inhibited SASP, specifically IL-6, MCP-1, and Vcam-1, by changing the H3K9me3 abundance in their promoter region. These findings offer fresh perspectives on the epigenetic control of SASP [68]. Additionally, there was a notable concentration of SASP in the methyltransferase polycomb repressive complex 2 (PRC2), which was linked to transcriptional regulation by the tri-methylation of histone H3 on the lysine 27 residue. PRC2 inhibition reduces inflammation linked to senescence by de-repressing SASP genes, which is seen in several sensitive animals [69].

It has been discovered that the methyltransferase disruptor of telomeric silencing 1-like (DOT1L) serves as an epigenetic controller of the SASP, and its expression is not influenced by the senescence-associated cell cycle arrest. Increased H3K79me2/3 occupancy at the IL1A gene locus was both required and sufficient for DOT1L but not for other SASP genes [70]. Significantly, glutamate dehydrogenase inhibition by pharmaceuticals suppresses the abnormally activated transcription of IL-6 and IL-8, two important SASP players. This action is linked, mechanistically, to the removal of the repressive H3K9me3 marks at the promoters of IL-6 and IL-8 because histone demethylation requires α-ketoglutaric acid, which is obtained from a GDH-mediated reaction as a cofactor [71]. Following the overexpression of AROS, SIRT1 is triggered, which results in the deacetylation of histone H3K9ac and p53, respectively, and the deactivation of p53 and reduced expression of SASP genes [72].

Table 1. Shows key epigenetic modulators that play a crucial role in controlling genes associated with induction and preservation of cellular senescence and its secretory phenotypes.

Epigenetic modulator	Function in senescence	Reference
DNA methyltransferases (DNMTs)	Alter gene expression and contribute to the senescent phenotype via modifying DNA methylation patterns.	[73]
Histone methyltransferases	either increase or decrease the expression of a gene associated with senescence by adding methyl groups to certain arginine or lysine residues which can change the structure of histones.	[74]
Histone acetyltransferases	Histone acetyltransferases contribute to the dynamic chromatin structural alterations required for the initiation and maintenance of the senescent state by acetylating histones.	[75]
Histone deacetylases (HDACs)	HDACs aid in the stable arrest of the cell cycle, which is a hallmark of senescence. By deacetylating histones close to gene promoters, HDACs help maintain the repression of genes important to the cell cycle by preventing cells from reentering the cell cycle.	[76]
MicroRNAs	MicroRNAs have been linked to senescence and are known to regulate gene expression through translational repression or mRNA degradation.	[77]
Long non-coding RNAs	Long non-coding RNAs are key regulators of cellular senescence and can affect gene expression through interactions with chromatin, transcription factors, and other RNA molecules. This regulation is crucial for controlling the expression of genes associated with senescence	[78]

6. Discussion

The term senescence refers to the phenomenon of an irreversible state of growth in which cells cease proliferation due to cell cycle arrest. Those cells are usually marked by the production of a wide range of inflammatory materials known as SASP, which Permits senescent cells to alter pathways in adjacent and distant cells and tissues. This phenomenon has been identified as one of the key players in aging and age-related diseases [79]. Cellular senescence is caused by telomere erosion, oxidative stress, oncogene activation, chromatin changes, and DNA damage. Telomere shortening and DNA damage combine to cause growth halt. While oxidative stress damages biological components, oncogene activation and chromatin changes hinder normal cell activity. Cell division ceases completely when these components come together [80]. Additionally, epigenetic modifications, which have been demonstrated as one of the drivers of cellular senescence through their ability to control the expression of multiple genes involved in the senescence process [81].

DNA methylation is one significant epigenetic process that significantly affects cellular senescence. According to earlier research, specific genomic regions undergo hypermethylation as a person ages, which suppresses genes necessary for cell cycle control and DNA repair. Our study follows the same path as earlier studies. For instance, studies by Xie W. et al. (2018) have shown a connection between the hypermethylation of gene promoters and the onset of senescence [82]. Another important epigenetic regulator that has a major effect on cellular senescence is histone modification. Our study agrees with previous studies. For example, Li X. et al. (2024) have demonstrated the connection between senescence and particular histone changes [83]. Moreover, non-coding RNAs are essential regulators of cellular senescence because they influence gene expression and cellular processes. Like our work, several studies have shown the vital roles that specific ncRNAs play in senescence. As an illustration, Cheng Y et al.'s study from 2024 revealed that the short nucleolar RNA SNORA regulates ribosome assembly and cellular stress responses, which is a major regulator of senescence [84].

The above findings demonstrate the complexities of epigenetic alterations in cellular senescence and highlight the possibility of utilizing these pathways as targets for therapeutic interventions in age-related illnesses. To completely comprehend how various epigenetic alterations interact and affect cellular senescence, more research is required.

On the other hand, these findings are challenged by numerous factors that can be considered as major limitation for this study. For instance, the possibility of off-target effects with epigenetic therapy is one of the main considerations. Because early epigenomic treatments frequently lacked specificity, it was possible for non-target genes or pathways to be affected [85]. Other major issues are the stability and long-term sustainability of epigenetic modifications. Environmental influences can influence epigenetic alterations, such as histone modifications and DNA methylation, and they can be reversible. Because of its reversibility, the therapeutic effects could not continue for very long [86].

7. Conclusion

To sum up, the study of epigenetic alterations in cellular senescence sheds light on the intricate mechanisms governing the aging process. Cellular senescence, defined as a chronic state of cell cycle arrest, is mostly influenced by epigenetic modifications, such as DNA methylation, histone modification, and chromatin remodeling. The senescence-associated secretory phenotype (SASP), which is distinguished by both the cessation of cellular growth and the production of pro-inflammatory molecules, is the result of these alterations taken together. Understanding these changes in the aging process is critical because it points to potential targets for treatment that could mitigate the negative effects of senescence. The review's conclusions show how promising it is to target epigenetic changes in cellular senescence for therapeutic effects. Nonetheless, the difficulties and limitations mentioned highlight the necessity for more investigation and advancement. To successfully apply those drugs, it is imperative to address off-target effects, ensure the stability of epigenetic modifications, overcome therapeutic resistance, and identify appropriate patient populations.

References

[1] Hamazaki J, Murata S. Relationships between protein degradation, cellular senescence, and organismal aging. *The Journal of Biochemistry*. 2024;175(5):473-480. doi:10.1093/jb/mvae016

[2] HAYFLICK L, MOORHEAD PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961;25:585-621. doi:10.1016/0014-4827(61)90192-6

[3] Wan R, Srikaram P, Guntupalli V, Hu C, Chen Q, Gao P. Cellular senescence in asthma: from pathogenesis to therapeutic challenges. *EBioMedicine*. 2023;94:104717. doi:10.1016/j.ebiom.2023.104717

[4] Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. *Nat Rev Nephrol*. 2022;18(10):611-627. doi:10.1038/s41581-022-00601-z

[5] de Magalhães JP. Cellular senescence in normal physiology. *Science (1979)*. 2024;384(6702):1300-1301. doi:10.1126/science.adj7050

[6] Kumari R, Jat P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. *Front Cell Dev Biol*. 2021;9. doi:10.3389/fcell.2021.645593

[7] Kumari R, Jat P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. *Front Cell Dev Biol*. 2021;9. doi:10.3389/fcell.2021.645593

[8] Ge T, Shao Y, Bao X, Xu W, Lu C. Cellular senescence in liver diseases: From mechanisms to therapies. *Int Immunopharmacol*. 2023;121:110522. doi:10.1016/j.intimp.2023.110522

[9] Freund A, Laberge RM, Demaria M, Campisi J. Lamin B1 loss is a senescence-associated biomarker. *Mol Biol Cell*. 2012;23(11):2066-2075. doi:10.1091/mbc.e11-10-0884

[10] Suda M, Paul KH, Minamino T, et al. Senescent Cells: A Therapeutic Target in Cardiovascular Diseases. *Cells*. 2023;12(9):1296. doi:10.3390/cells12091296

[11] Kuehnemann C, Wiley CD. Senescent cells at the crossroads of aging, disease, and tissue homeostasis. *Aging Cell*. 2024;23(1). doi:10.1111/acel.13988

[12] Huo S, Tang X, Chen W, et al. Epigenetic regulations of cellular senescence in osteoporosis. *Ageing Res Rev*. 2024;99:102235. doi:10.1016/j.arr.2024.102235

[13] Dhar P, Moodithaya SS, Patil P. Epigenetic alterations—The silent indicator for early aging and age-associated health-risks. *AGING MEDICINE*. 2022;5(4):287-293. doi:10.1002/agm2.12236

[14] Kwiatkowska KM, Mavrogonatou E, Papadopoulou A, et al. Heterogeneity of Cellular Senescence: Cell Type-Specific and Senescence Stimulus-Dependent Epigenetic Alterations. *Cells*. 2023;12(6):927. doi:10.3390/cells12060927

[15] Bontempo P, Capasso L, De Masi L, Nebbioso A, Rigano D. Therapeutic Potential of Natural Compounds Acting through Epigenetic Mechanisms in Cardiovascular Diseases: Current Findings and Future Directions. *Nutrients*. 2024;16(15):2399. doi:10.3390/nu16152399

[16] Wang K, Liu H, Hu Q, et al. Epigenetic regulation of aging: implications for interventions of aging and diseases. *Signal Transduct Target Ther*. 2022;7(1):374. doi:10.1038/s41392-022-01211-8

[17] Lee E, Carreras-Gallo N, Lopez L, et al. Exploring the effects of Dasatinib, Quercetin, and Fisetin on DNA methylation clocks: a longitudinal study on senolytic interventions. *Aging*. 2024;16(4):3088-3106. doi:10.18632/aging.205581

[18] Bergsma T, Rogaeva E. DNA Methylation Clocks and Their Predictive Capacity for Aging Phenotypes and Healthspan. *Neurosci Insights*. 2020;15:263310552094222. doi:10.1177/2633105520942221

[19] Cui T. Causal analysis on DNA methylation reveals key regulators in aging and senescence. *Transactions on Materials, Biotechnology and Life Sciences*. 2024;3:16-27. doi:10.62051/mf8ssf93

[20] Joshi R, Suryawanshi T, Mukherjee S, Shukla S, Majumder A. Chromatin Condensation Delays Senescence in Human Mesenchymal Stem Cells by Safeguarding Nuclear Damages during *In Vitro* Expansion. *J Tissue Eng Regen Med*. 2024;2024:1-13. doi:10.1155/2024/1543849

[21] Dubey SK, Dubey R, Prajapati SC, et al. Histone deficiency and hypoacetylation in the aging retinal pigment epithelium. *Aging Cell*. 2024;23(5). doi:10.1111/acel.14108

[22] Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics. *Oncol Rep*. 2017;37(1):3-9. doi:10.3892/or.2016.5236

[23] Abdelmohsen K, Gorospe M. Noncoding <scp>RNA</scp> control of cellular senescence. *WIREs RNA*. 2015;6(6):615-629. doi:10.1002/wrna.1297

[24] Al Aboud NM, Tupper C, Jialal I. *Genetics, Epigenetic Mechanism*.; 2024.

[25] Moore LD, Le T, Fan G. DNA Methylation and Its Basic Function. *Neuropsychopharmacology*. 2013;38(1):23-38. doi:10.1038/npp.2012.112

[26] du Preez PH, Breeds K, Burger NF V., Swiegers HW, Truter JC, Botha AM. DNA Methylation and Demethylation Are Regulated by Functional DNA Methyltransferases and DnTET Enzymes in Diuraphis noxia. *Front Genet*. 2020;11. doi:10.3389/fgene.2020.00452

[27] Ramini D, Latini S, Giuliani A, et al. Replicative Senescence-Associated LINE1 Methylation and LINE1-Alu Expression Levels in Human Endothelial Cells. *Cells*. 2022;11(23):3799. doi:10.3390/cells11233799

[28] Lee YC, Nam Y, Kim M, et al. Prognostic significance of senescence-related tumor microenvironment genes in head and neck squamous cell carcinoma. *Aging*. 2024;16(2):985-1001. doi:10.18632/aging.205346

[29] Jung HJ, Byun HO, Jee BA, et al. The Ubiquitin-like with PHD and Ring Finger Domains 1 (UHRF1)/DNA Methyltransferase 1 (DNMT1) Axis Is a Primary Regulator of Cell Senescence. *Journal of Biological Chemistry*. 2017;292(9):3729-3739. doi:10.1074/jbc.M116.750539

[30] Lin SP, Chiu FY, Wang Y, Yen ML, Kao SY, Hung SC. RB Maintains Quiescence and Prevents Premature Senescence through Upregulation of DNMT1 in Mesenchymal Stromal Cells. *Stem Cell Reports*. 2014;3(6):975-986. doi:10.1016/j.stemcr.2014.10.002

[31] Yi Y, Xie H, Xiao X, et al. Ultraviolet A irradiation induces senescence in human dermal fibroblasts by down-regulating DNMT1 via ZEB1. *Aging*. 2018;10(2):212-228. doi:10.18632/aging.101383

[32] Xie H fu, Liu Y zi, Du R, et al. Correction: miR-377 induces senescence in human skin fibroblasts by targeting DNA methyltransferase 1. *Cell Death Dis*. 2019;10(11):859. doi:10.1038/s41419-019-2097-9

[33] Yu YCY, Hui TZ, Kao TH, et al. Transient DNMT3L Expression Reinforces Chromatin Surveillance to Halt Senescence Progression in Mouse Embryonic Fibroblast. *Front Cell Dev Biol*. 2020;8. doi:10.3389/fcell.2020.00103

[34] Jung Y deun, Park SK, Kang D, et al. Epigenetic regulation of miR-29a/miR-30c/DNMT3A axis controls SOD2 and mitochondrial oxidative stress in human mesenchymal stem cells. *Redox Biol*. 2020;37:101716. doi:10.1016/j.redox.2020.101716

[35] Sokolova V, Sarkar S, Tan D. Histone variants and chromatin structure, update of advances. *Comput Struct Biotechnol J*. 2023;21:299-311. doi:10.1016/j.csbj.2022.12.002

[36] Yang D, Wei G, Long F, et al. Histone methyltransferase Smyd3 is a new regulator for vascular senescence. *Aging Cell*. 2020;19(9). doi:10.1111/acel.13212

[37] Ding Q, Shao C, Rose P, Zhu YZ. Epigenetics and Vascular Senescence–Potential New Therapeutic Targets? *Front Pharmacol*. 2020;11. doi:10.3389/fphar.2020.535395

[38] Lin C, Li H, Liu J, et al. Arginine hypomethylation-mediated proteasomal degradation of histone H4—an early biomarker of cellular senescence. *Cell Death Differ*. 2020;27(9):2697-2709. doi:10.1038/s41418-020-0562-8

[39] Zhu X, Chen Z, Shen W, et al. Inflammation, epigenetics, and metabolism converge to cell senescence and ageing: the regulation and intervention. *Signal Transduct Target Ther*. 2021;6(1):245. doi:10.1038/s41392-021-00646-9

[40] Barsoum M, Stenzel AT, Bochyńska A, et al. Loss of the Ash2l subunit of histone H3K4 methyltransferase complexes reduces chromatin accessibility at promoters. *Sci Rep*. 2022;12(1):21506. doi:10.1038/s41598-022-25881-0

[41] Li R, Teng Y, Guo Y, et al. Aging-related decrease of histone methyltransferase SUV39H1 in adipose-derived stem cells enhanced SASP. *Mech Ageing Dev*. 2023;215:111868. doi:10.1016/j.mad.2023.111868

[42] Su Z, Su H, Xu J, et al. Histone methyltransferase Smyd2 drives vascular aging by its enhancer-dependent activity. *Aging*. 2023;15(1):70-91. doi:10.18632/aging.204449

[43] Huang B, Zhong D, Zhu J, et al. Inhibition of histone acetyltransferase GCN5 extends lifespan in both yeast and human cell lines. *Aging Cell*. 2020;19(4). doi:10.1111/acel.13129

[44] Kong C, Wang D, Wang F, et al. PCAF Accelerates Vascular Senescence via the Hippo Signaling Pathway. *Oxid Med Cell Longev*. 2022;2022:1-17. doi:10.1155/2022/1200602

[45] Wang W, Zheng Y, Sun S, et al. A genome-wide CRISPR-based screen identifies *KAT7* as a driver of cellular senescence. *Sci Transl Med*. 2021;13(575). doi:10.1126/scitranslmed.abd2655

[46] Miller KM, Tjeertes J V, Coates J, et al. Human HDAC1 and HDAC2 function in the DNA-damage response to promote DNA nonhomologous end-joining. *Nat Struct Mol Biol*. 2010;17(9):1144-1151. doi:10.1038/nsmb.1899

[47] Medina Rangel PX, Cross E, Liu C, et al. Cell Cycle and Senescence Regulation by Podocyte Histone Deacetylase 1 and 2. *Journal of the American Society of Nephrology*. 2023;34(3):433-450. doi:10.1681/ASN.2022050598

[48] Han X, Niu J, Zhao Y, Kong Q, Tong T, Han L. <scp>HDAC</scp> 4 stabilizes <scp>SIRT</scp> 1 via sumoylation <scp>SIRT</scp> 1 to delay cellular senescence. *Clin Exp Pharmacol Physiol*. 2016;43(1):41-46. doi:10.1111/1440-1681.12496

[49] Yang WB, Wu AC, Hsu TI, et al. Histone deacetylase 6 acts upstream of DNA damage response activation to support the survival of glioblastoma cells. *Cell Death Dis*. 2021;12(10):884. doi:10.1038/s41419-021-04182-w

[50] Qin YM, Li P, Mu XP, et al. Histone deacetylase 6 promotes skin wound healing by regulating fibroblast migration and differentiation in aged mice. *Sheng Li Xue Bao*. 2022;74(6):979-992.

[51] Nemeth K, Bayraktar R, Ferracin M, Calin GA. Non-coding RNAs in disease: from mechanisms to therapeutics. *Nat Rev Genet*. 2024;25(3):211-232. doi:10.1038/s41576-023-00662-1

[52] Loganathan T, Doss C GP. Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets. *Funct Integr Genomics*. 2023;23(1):33. doi:10.1007/s10142-022-00947-4

[53] Ghafouri-Fard S, Khoshbakht T, Hussen BM, et al. Emerging Role of Non-Coding RNAs in Senescence. *Front Cell Dev Biol*. 2022;10. doi:10.3389/fcell.2022.869011

[54] Mattick JS, Amaral PP, Carninci P, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. *Nat Rev Mol Cell Biol*. 2023;24(6):430-447. doi:10.1038/s41580-022-00566-8

[55] Tavares e Silva J, Pessoa J, Nóbrega-Pereira S, Bernardes de Jesus B. The Impact of Long Noncoding RNAs in Tissue Regeneration and Senescence. *Cells*. 2024;13(2):119. doi:10.3390/cells13020119

[56] Tang H, Yao F, Yin M, et al. Anti-senescent effects of long non-coding RNA H19 on human dermal fibroblast cells through impairing microRNA-296-5p-dependent inhibition of IGF2. *Cell Signal*. 2022;94:110327. doi:10.1016/j.cellsig.2022.110327

[57] Zhang Y, Qiao X, Liu L, et al. Long noncoding RNA MAGI2-AS3 regulates the H2O2 level and cell senescence via HSPA8. *Redox Biol*. 2022;54:102383. doi:10.1016/j.redox.2022.102383

[58] Sarkar S, Chowdhury SG, Karmakar P. Drugging non-coding <scp>RNAs</scp> —A new light of hope in senescence-related cancer therapy. *Chem Biol Drug Des*. 2023;101(5):1216-1228. doi:10.1111/cbdd.14200

[59] Potter ML, Hill WD, Isales CM, Hamrick MW, Fulzele S. MicroRNAs are critical regulators of senescence and aging in mesenchymal stem cells. *Bone*. 2021;142:115679. doi:10.1016/j.bone.2020.115679

[60] Lian WS, Wu RW, Chen YS, et al. MicroRNA-29a Mitigates Osteoblast Senescence and Counteracts Bone Loss through Oxidation Resistance-1 Control of FoxO3 Methylation. *Antioxidants*. 2021;10(8):1248. doi:10.3390/antiox10081248

[61] Chen Y, Wang S, Yang S, et al. Inhibitory role of ginsenoside Rb2 in endothelial senescence and inflammation mediated by microRNA-216a. *Mol Med Rep*. 2021;23(6):415. doi:10.3892/mmr.2021.12054

[62] Tao W, Hong Y, He H, et al. MicroRNA-199a-5p aggravates angiotensin II–induced vascular smooth muscle cell senescence by targeting Sirtuin-1 in abdominal aortic aneurysm. *J Cell Mol Med*. 2021;25(13):6056-6069. doi:10.1111/jcmm.16485

[63] Lopes-Paciencia S, Saint-Germain E, Rowell MC, Ruiz AF, Kalegari P, Ferbeyre G. The senescence-associated secretory phenotype and its regulation. *Cytokine*. 2019;117:15-22. doi:10.1016/j.cyto.2019.01.013

[64] Takasugi M, Yoshida Y, Hara E, Ohtani N. The role of cellular senescence and SASP in tumour microenvironment. *FEBS J*. 2023;290(5):1348-1361. doi:10.1111/febs.16381

[65] Giroud J, Bouriez I, Paulus H, Pourtier A, Debacq-Chainiaux F, Pluquet O. Exploring the Communication of the SASP: Dynamic, Interactive, and Adaptive Effects on the Microenvironment. *Int J Mol Sci*. 2023;24(13):10788. doi:10.3390/ijms241310788

[66] Chen H, Ruiz PD, McKimpson WM, Novikov L, Kitsis RN, Gamble MJ. MacroH2A1 and ATM Play Opposing Roles in Paracrine Senescence and the Senescence-Associated Secretory Phenotype. *Mol Cell*. 2015;59(5):719-731. doi:10.1016/j.molcel.2015.07.011

[67] Contrepois K, Coudereau C, Benayoun BA, et al. Histone variant H2A.J accumulates in senescent cells and promotes inflammatory gene expression. *Nat Commun*. 2017;8(1):14995. doi:10.1038/ncomms14995

[68] Li R, Teng Y, Guo Y, et al. Aging-related decrease of histone methyltransferase SUV39H1 in adipose-derived stem cells enhanced SASP. *Mech Ageing Dev*. 2023;215:111868. doi:10.1016/j.mad.2023.111868

[69] Chu L, Qu Y, An Y, et al. Induction of senescence-associated secretory phenotype underlies the therapeutic efficacy of PRC2 inhibition in cancer. *Cell Death Dis*. 2022;13(2):155. doi:10.1038/s41419-022-04601-6

[70] Leon KE, Buj R, Lesko E, et al. DOT1L modulates the senescence-associated secretory phenotype through epigenetic regulation of IL1A. *Journal of Cell Biology*. 2021;220(8). doi:10.1083/jcb.202008101

[71] Sun X, Li Q, Tang Y, et al. Epigenetic activation of secretory phenotypes in senescence by the FOXQ1-SIRT4-GDH signaling. *Cell Death Dis*. 2023;14(7):481. doi:10.1038/s41419-023-06002-9

[72] Lee SH, Yang JH, Park UH, et al. SIRT1 ubiquitination is regulated by opposing activities of APC/C-Cdh1 and AROS during stress-induced premature senescence. *Exp Mol Med*. 2023;55(6):1232-1246. doi:10.1038/s12276-023-01012-1

[73] Roger L, Tomas F, Gire V. Mechanisms and Regulation of Cellular Senescence. *Int J Mol Sci*. 2021;22(23):13173. doi:10.3390/ijms222313173

[74] Huang C, Zhu B. Roles of H3K36-specific histone methyltransferases in transcription: antagonizing silencing and safeguarding transcription fidelity. *Biophys Rep*. 2018;4(4):170-177. doi:10.1007/s41048-018-0063-1

[75] Wang J, Feng S, Zhang Q, et al. Roles of Histone Acetyltransferases and Deacetylases in the Retinal Development and Diseases. *Mol Neurobiol*. 2023;60(4):2330-2354. doi:10.1007/s12035-023-03213-1

[76] Dubey SK, Dubey R, Prajapati SC, et al. Histone deficiency and hypoacetylation in the aging retinal pigment epithelium. *Aging Cell*. 2024;23(5). doi:10.1111/acel.14108

[77] Dhahbi JM, Atamna H, Boffelli D, Magis W, Spindler SR, Martin DIK. Deep Sequencing Reveals Novel MicroRNAs and Regulation of MicroRNA Expression during Cell Senescence. *PLoS One*. 2011;6(5):e20509. doi:10.1371/journal.pone.0020509

[78] Zhao P, Chang J, Chen Y, et al. Cellular Senescence-Related Long Non-coding RNA Signatures Predict Prognosis in Juvenile Osteosarcoma. *Phenomics*. Published online July 8, 2024. doi:10.1007/s43657-023-00132-y

[79] Hense JD, Isola JV V., Garcia DN, et al. The role of cellular senescence in ovarian aging. *npj Aging*. 2024;10(1):35. doi:10.1038/s41514-024-00157-1

[80] Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A. Cellular Senescence: Aging, Cancer, and Injury. *Physiol Rev*. 2019;99(2):1047-1078. doi:10.1152/physrev.00020.2018

[81] Cheng LQ, Zhang ZQ, Chen HZ, Liu DP. Epigenetic regulation in cell senescence. *J Mol Med*. 2017;95(12):1257-1268. doi:10.1007/s00109-017-1581-x

[82] Xie W, Kagiampakis I, Pan L, et al. DNA Methylation Patterns Separate Senescence from Transformation Potential and Indicate Cancer Risk. *Cancer Cell*. 2018;33(2):309-321.e5. doi:10.1016/j.ccell.2018.01.008

[83] Li X, Chen M, Chen X, et al. TRAP1 drives smooth muscle cell senescence and promotes atherosclerosis via HDAC3-primed histone H4 lysine 12 lactylation. *Eur Heart J*. Published online August 1, 2024. doi:10.1093/eurheartj/ehae379

[84] Cheng Y, Wang S, Zhang H, et al. A non-canonical role for a small nucleolar RNA in ribosome biogenesis and senescence. *Cell*. Published online July 2024. doi:10.1016/j.cell.2024.06.019

[85] Feehley T, O'Donnell CW, Mendlein J, Karande M, McCauley T. Drugging the epigenome in the age of precision medicine. *Clin Epigenetics*. 2023;15(1):6. doi:10.1186/s13148-022-01419-z

[86] Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. *Mol Cancer*. 2020;19(1):79. doi:10.1186/s12943-020-01197-3

التعديلات فوق الجينية في شيخوخة الخلايا: الآليات والتأثيرات والإمكانات العلاجية

أحمد محمد آدم[١]، و **محمد عمران خان**[٢]، و **فيصل أ. الزهراني**[١]

[١]قسم الكيمياء الحيوية، كلية العلوم، جامعة الملك عبد العزيز، جدة، المملكة العربية السعودية و[٢]مركز الأبحاث، مستشفى الملك فيصل التخصصي ومركز الأبحاث، جدة، المملكة العربية السعودية

faahalzahrani@kau.edu.sa

المستخلص. شيخوخة الخلايا، وهي الحالة غير القابلة للتراجع لوقف النمو استجابةً لمجموعة متنوعة من العوامل المسببة للتوتر، جذبت اهتمامًا كبيرًا في العلوم البيولوجية والطبية. تلعب التعديلات الجينية فوق الجينية، التي تؤثر على أنماط التعبير الجيني وتحدد في النهاية مصير الخلايا، دورًا حاسمًا في تنظيم شيخوخة الخلايا. تُعتبر مثيلة الحمض النووي (DNA methylation) عملية جينية فوق جينية أساسية مرتبطة بشيخوخة الخلايا. وقد أظهرت الأبحاث أن التغيرات في أنماط التعبير الجيني تنتج عن نقص المثيلة العام وزيادة المثيلة الموضعية للجينات أثناء عملية الشيخوخة. تتأثر شيخوخة الخلايا أيضًا بشكل كبير بتعديلات الهستونات. يمكن أن تؤدي أستلة (acetylation) أو مثيلة (methylation) الهستونات إلى تغيير بنية الكروماتين، مما يؤثر على قدرة عوامل النسخ على الارتباط بمحفزات الجينات. وبالتالي، قد يؤثر ذلك على التعبير عن الجينات المرتبطة بعمليات الشيخوخة. علاوة على ذلك، أصبح الحمض النووي الريبي غير المشفر، مثل الميكرو RNA (microRNAs)، عوامل تنظيمية مهمة لشيخوخة الخلايا نظرًا لقدرتها على التحكم في التعبير الجيني بعد النسخ. وقد تم ربط اضطراب تنظيم الميكرو RNA بتحفيز أو تثبيط الشيخوخة في أنواع خلايا مختلفة. في هذه المراجعة الشاملة، نناقش التعديلات فوق الجينية التي تحدث أثناء شيخوخة الخلايا ونستكشف إمكاناتها كأهداف علاجية للتحكم في النمط الظاهري للشيخوخة، وهي خطوة حاسمة في معالجة الأمراض المرتبطة بالتقدم في العمر.

الكلمات المفتاحية: التعديلات فوق الجينية، شيخوخة الخلايا، الأنماط الظاهرية الإفرازية المرتبطة بالشيخوخة.