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Sarah Salih Hasan *et al*, Cognizance Journal of Multidisciplinary Studies, Vol.5, Issue.9, September 2025, pg. 99-102
(An Open Accessible, Multidisciplinary, Fully Refereed and Peer Reviewed Journal)
ISSN: 0976-7797
Impact Factor: 5.183
Index Copernicus Value (ICV) = 92.57

Epigenetic Modifications and Cellular Senescence: A Critical Review

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DOI: 10.47760/cognizance.2025.v05i09.007

Abstract: Cellular senescence is a central hallmark of aging, functioning as a double-edged process that prevents malignant transformation while contributing to tissue dysfunction and chronic inflammation. Recent advances emphasize the critical role of epigenetic modifications—including DNA methylation, histone changes, chromatin remodeling, and regulation by non-coding RNAs—in both initiating and maintaining the senescent state. These mechanisms drive the senescence-associated secretory phenotype (SASP), promote inflammatory signaling, and shape the aging phenotype. The development of epigenetic clocks has provided powerful tools to estimate biological age and evaluate therapeutic interventions. Emerging strategies such as epigenetic drugs, partial reprogramming with Yamanaka factors, and the integration of senolytics with epigenetic modulators show promise in restoring youthful cellular function and delaying age-related decline. Future directions highlight the integration of multi-omics data, CRISPR-based epigenome editing, and next-generation clocks to refine biomarkers and therapeutic approaches. Collectively, targeting epigenetic regulation of senescence represents a promising pathway toward healthier aging and longevity.

Keywords: Cellular senescence, aging, tissue dysfunction, chronic inflammation

INTRODUCTION

Cellular senescence is a main aging process, involving the irreversible loss of cell divisions. Cellular senescence carries a double purpose: proliferation of damaging or potentially tumor cells is repressed, however, accumulation of senescent cells destroys tissue repair and induces chronic inflammation, hence assisting age-related pathology such as atherosclerosis, fibrosis, and late-life cancers (López-Otín et al., 2023). The exploration of the balance among protective and pathogenic outcomes has been a chief problem among aging studies. Epigenetic changes consist of the regulation of genes without the change of the fundamental DNA sequence of the parent DNA. Epigenetic transformations consist of chemical modifications of the DNA or histone protein, and gene regulation by non-coding RNA.

These changes can either turn on/off some of the said genes, thus modifying some of the cellular activities, such as entry into senescence and environmental stressing reactions. Although traditional mechanisms such as shortening of the telomeres and damage of DNA were implicated in senescence for decades, recent studies highlight the fact that the epigenetic mechanisms play the main function both of initiating and maintaining that state. Main mechanisms consist of changes in DNA methylation, three-dimensional chromatin reorganization, histone modifications, including the impact of non-coding RNAs.

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These changes not only induce senescence but also determine its functional characteristics, such as the secretory profile that is characteristic of cellular senescence (SASP) and adaptive stressing reactions, thus stabilizing the senescent phenotype over the course of life (Tong, Xu, & Chen, 2024). In addition, the epigenetic clocks that were developed based on DNA methylation were also validated as accurate tools of cellular biological aging assessment and aging risk surveillance. (Tomusiak, Watson, & Horvath, 2024; Warner, Johnson, & Singh, 2024). Experimental techniques that have been researched include partial reprogramming by Yamanaka factors (OSKM) or chemicals that can epigenetically restore the cell without the loss of cell identity. Cellular and animal experimental data validate that these interventions can partially compensate for some epigenetic markers of aging, allow normal cellular metabolism, and postpone the development of diseases of old age. (Yang, Kim, & Zhang, 2023).

DNA Methylation

DNA methylation, the deposition of methyl groups on CpG sites, is one of the most researched epigenetic modifications. It usually downregulates gene activity or changes the activity of the genes controlling the cell cycle. It has been observed that aging comes along with global hypomethylation and site-specific hypermethylation at promoter regions, which can cause interference with normal growth and inflammatory mechanisms (Field et al., 2018; Tomusiak, Watson, & Horvath, 2024).

Histone Modifications

Histone proteins form chromatin architecture, and their modifications—acetylation, methylation, phosphorylation, ubiquitination—directly affect gene function. In the aging process, cells decrease H3K9me3 and increase H4K16ac, favoring senescence- and inflammated-related genes, and SASP secretion (Lopes-Paciencia et al., 2025; Pal & Tyler, 2016).

Chromatin Rem

Three-dimensional chromatin structure is critical for nuclear architecture and gene regulatory activities. Age-modified changes of hetero- and euchromatin interaction and of lamina-associated domains (LADs) perturb gene regulatory activities and establish senescence-fixed states. These structural changes accompany Epigenetic changes such as DNA methylation and histone modifications also function to impose SASP activity and enhance pro-inflammatory signaling (Dasgupta et al., 2024).

Non-protien- Coding RNAs

The lncRNAs and microRNAs play central roles in the senescence control. MiR-34a induces p53 activation and p21 induction, for instance, and HOTAIR and MALAT1 lncRNAs have been implicated in chromatin remodeling, driving cellular senescence forward (Kane et al., 2019; Yang, Kim, & Zhang, 2023(.

Senescence-Associated Secretory (SASP)

SASP consists of the secretion of cytokines, proteases, and growth factors by senescent cells. Transient SASP promotes tissue repair, and chronic secretion promotes inflammation, breakdown of tissue, and age-associated pathologies. Epigenetic control of SASP connects cellular senescence with bodywide mechanisms of aging (Coppé et al., 2010).

Epigenetic Clock

Epigenetic clocks are software programs that estimate biological age according to the level of methylation of some CpG sites of the DNA. Epigenetic clocks also provide us with information on cellular senescence rate and the possibility of the assessment of the efficacy of novel therapy interventions (Horvath, 2013; Levine et al., 2018).

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Treatment Technique

Epigenomic drugs

HDAC and DNMT inhibitors can overturn epigenetic changes that accumulate due to aging, restore SASP, cellular parameters, and retard age-associated pathologies (Dai, 2024).

Partial Reprogramming

Transient Yamanaka factor induction (OSKM) can epigenetically reprogram the epigenetic profile towards the youthful state without losing cell identity, lowering the markers of aging, and enhancing tissue function (Antón-Fernández, 2024; Yücel, 2024.

Combining Epigenetic Modulators with Senoly

Senolytics kill senescent cells, and epigenetic modifiers also recover the remaining cells by limiting inflammation, together with the enhancement of the health of the tissue (Lelarge, 2024).

Future Directions

- Multi-Omics Integration: Integration of transcriptomic, proteomic, and epigenomic studies at single-cell resolution to assign novel biomarkers and drug targets (Shen, 2024).
- CRISPR-dCas9 Epigenome Editing: Targeted epigenetic modifications to enhance cellular resilience against stress and inflammation (Liesenfelder, 2025).
- Next-Generation Epigenetic Clocks: Next-generation models allowing more accurate assessment of anti-aging therapy (Fuentealba, 2025).

Conclusion:

Cellular senescence is shaped by a network of epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and regulation by non-coding RNAs. Together, these processes influence the senescence-associated secretory phenotype (SASP), cellular stress responses, and tissue function, ultimately defining how aging manifests. By targeting these pathways—through epigenetic drugs, partial cellular reprogramming, or senolytic combinations—researchers are uncovering promising strategies to slow or even reverse aspects of age-related decline. Looking ahead, the next generation of approaches will focus on precise epigenetic editing, development of robust biomarkers, and advanced single-cell analyses to open new avenues for promoting healthy aging and extending longevity.

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