



Short Communication

Epigenetics: Unraveling the molecular threads of aging and dermal cancer

Sonali Kohli¹, Sanpreet Singh Sachdev^{2*}

¹Dept. of Dermatology, Sir HN Reliance Foundation Hospital, Mumbai, Maharashtra, India

²Dept. of Oral Pathology and Microbiology, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Navi Mumbai, Maharashtra, India



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ABSTRACT

Epigenetics, the study of heritable alterations in gene expression without changes to the DNA sequence, plays a pivotal role in understanding the complex processes of aging and cancer. This manuscript delves into the intricate world of epigenetics, exploring how it influences the pathophysiology of aging and aging-related diseases, with a particular focus on cancer. We discuss the mechanisms of epigenetic regulation, the interplay between genetic and epigenetic alterations, and the potential implications for diagnosis and drug discovery.

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1. Introduction

Aging is a complex process characterized by a gradual decline in physiological organ function, ultimately culminating in mortality. At the heart of this intricate journey lies the interplay between genetic and epigenetic changes within the genome, representing a dynamic narrative of life and its challenges. Telomere attrition and the accumulation of DNA damage stand as primary culprits behind the genomic instability that accompanies aging.¹ However, it is epigenetics, the study of heritable changes in gene expression that do not involve alterations to the DNA sequence itself, that provides the nuanced understanding needed to fathom the molecular intricacies of aging, particularly its connection to diseases like cancer.

The epigenome, comprised of DNA methylation, histone modifications, and various noncoding RNA species, acts as the conductor orchestrating the functional utilization and stability of our genetic information.² The triad of DNA methylation, histone modifications, and noncoding

RNAs collaboratively regulates gene transcription, DNA replication and repair, cell cycle progression, and a multitude of other vital processes (Figure 1). The present manuscript embarks on a journey to unravel the profound impact of epigenetic alterations in shaping the course of aging and the associated diseases, with a particular emphasis on cancer.

In the grand tapestry of aging and age-related diseases, genetic and epigenetic changes harmonize in a complex symphony. Genetic mutations, ranging from deletions and translocations to telomere loss, have been established as the architects of genomic instability during aging and carcinogenesis.³ Yet, the understated partner in this symphony is epigenetic alterations, a category that encompasses changes in DNA methylation, histone modifications, and the dysregulation of noncoding RNAs. These epigenetic shifts, far from being passive spectators, can serve as the catalysts initiating aging and cancer phenotypes or paving the way for subsequent genetic and epigenetic alterations.

* Corresponding author.

E-mail address: sunpreetss@yahoo.in (S. S. Sachdev).

2. Etiology of Epigenetic Alterations

2.1. Ultraviolet (UV) radiation

Prolonged exposure to UV radiation emerges as a formidable adversary in the realm of dermal cancer.⁴ UV radiation not only inflicts direct DNA damage but also beckons DNA methyltransferases and histone-modifying enzymes to the repair sites.⁵ Paradoxically, this restorative process often begets unintended epigenetic consequences that foster tumorigenesis.

2.2. Inflammation

The inflammatory milieu within the skin's microenvironment serves as a potent trigger for epigenetic changes. Inflammatory cytokines and signaling pathways, typified by NF- κ B, wield the power to mold DNA methylation patterns and histone modifications, propelling the expression of genes conducive to cancer development.⁶

2.3. Oncogenic signaling

The Ras-Raf-MEK-ERK and PI3K-AKT pathways, recognized as pivotal players in cancer initiation and progression, can exert their influence on the epigenetic landscape of dermal cancer.⁷ These oncogenic pathways cross paths with epigenetic modifiers, thereby shaping gene expression profiles pivotal to tumorigenesis. (Figure 3)

To summarize, the crux of epigenetic regulation revolves around the nucleosome, the fundamental unit of chromatin that houses DNA wrapped around histones. Histones, with their posttranslational modifications such as phosphorylation, acetylation, methylation, and ubiquitination, craft the platforms that beckon chromatin-associated activities.⁸ Noncoding RNAs, notably microRNAs (miRNAs), govern processes like cell cycle control, differentiation, apoptosis, and tumor suppression by orchestrating the expression of numerous genes within the genome.⁹

3. Epigenetic Alterations in Cancer

The narrative of epigenetic modifications continues in the sphere of carcinogenesis, converging with genetic mutations to compose the complex tale of cancer's genesis. Environmental influences, cellular senescence, chronic inflammation, and autoimmune disorders converge to set the stage for epigenetic transformations that nudge cells toward malignancy.^{10,11} DNA hypermethylation and hypomethylation, particularly within gene promoters, serve as the architects of tumor suppressor gene silencing or act as architects of mutations and deletions, fueling the relentless progression of cancer.¹² Histone modifications and noncoding RNAs also wield their influence, casting shadows of aggressiveness and resistance to treatment upon various cancers.

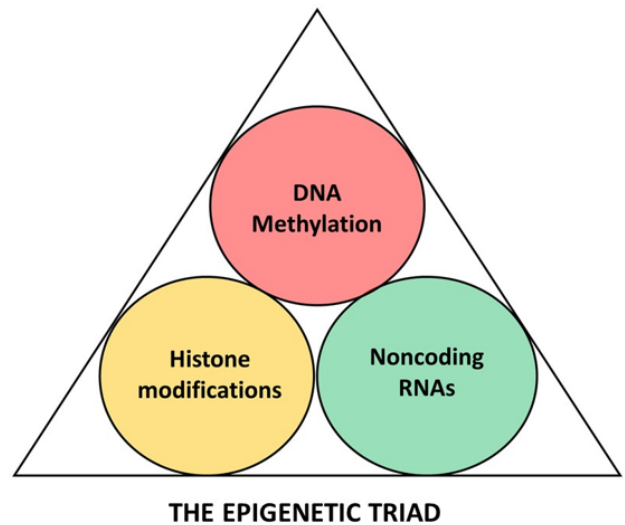


Figure 1: Epigenetic triad that causes DNA alterations during carcinogenesis

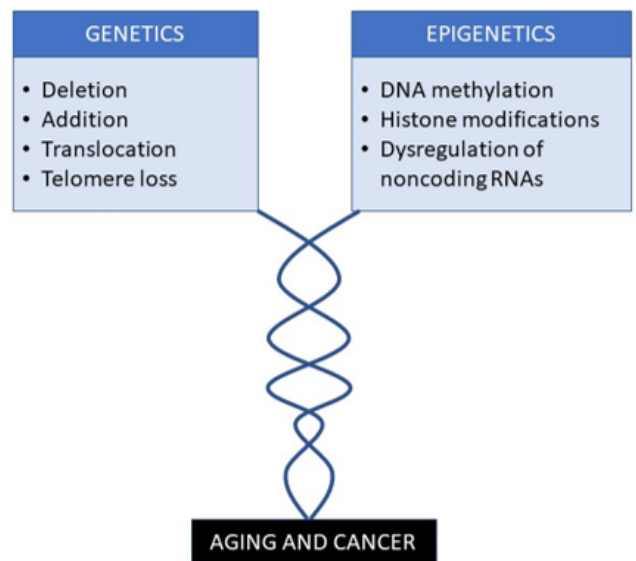


Figure 2: Interplay of Genetics and Epigenetics leading to cell senescence and cancer

4. Epigenetic Modifications in Dermal Cancer

Dermal cancer, spanning entities such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, takes center stage in the realm of global health challenges.^{13,14} Unraveling the molecular nuances underpinning dermal cancer is paramount to crafting diagnostic and therapeutic solutions. Epigenetic alterations, the heritable changes in gene expression without a shift in the DNA sequence itself, have emerged as protagonists.

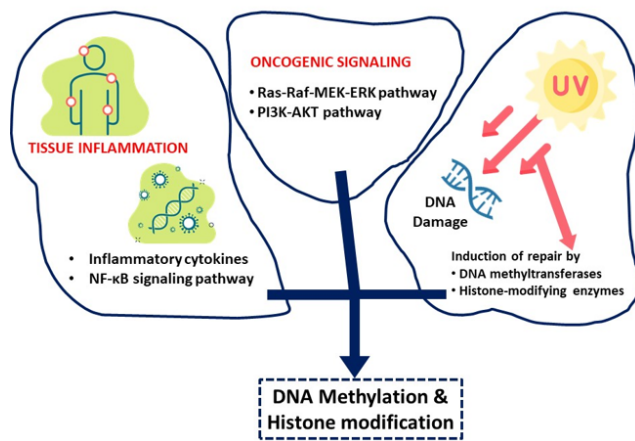


Figure 3: Etiology of epigenetic alterations

4.1. DNA methylation

The age-old epigenetic mechanism of DNA methylation, involving the addition of methyl groups to cytosine residues in CpG dinucleotides, emerges as a prominent player in dermal cancer.¹⁵ Aberrant DNA methylation patterns are frequently observed, with hypermethylation of CpG islands in the promoter regions of tumor suppressor genes leading to their silence. Conversely, global hypomethylation may engender genomic instability. Genes such as p16, E-cadherin, and RASSF1A find themselves in the grip of DNA methylation's influence in dermal cancer.^{16,17}

4.2. Histone modifications

Histone modifications, encompassing a spectrum of changes like acetylation, methylation, phosphorylation, and ubiquitination, serve as the conductors orchestrating chromatin remodeling and the regulation of gene expression. Within the realm of dermal cancer, alterations in histone modifications surface as pivotal players in the orchestration of oncogenesis.¹⁸ The downregulation of histone deacetylases (HDACs), for instance, liberates acetylation, fostering cell cycle progression and tumor expansion. Conversely, histone methyltransferases like EZH2 take the stage, playing a leading role in the epigenetic silencing of tumor suppressor genes.¹⁹

4.3. Noncoding RNAs

Noncoding RNAs, a diverse category that includes microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), stand as formidable regulators of gene expression.²⁰ Their altered expression levels have been intricately linked to the pathogenesis of dermal cancer. miRNAs, for example, wield their power by targeting genes essential for cell proliferation, apoptosis, and metastasis. Dysregulation of specific miRNAs, such as

miR-21 and miR-155, finds resonance in the progression of dermal cancer.

5. Clinical Implications

Epigenetic changes in cancer involve global DNA hypomethylation, site-specific promoter hypermethylation, alterations in histone modifications, and dysregulation of miRNAs.¹⁸ These changes can activate oncogenes, silence tumor suppressor genes, induce cell cycle defects, and enhance genomic instability, contributing to tumorigenesis. Identifying genetic and epigenetic markers for cancer is crucial for targeted gene therapy strategies. As aging increases cancer susceptibility through the accumulation of mutations and epigenetic alterations, understanding these processes can aid in early diagnosis and treatment.

5.1. Diagnostics

Epigenetic alterations hold promise as diagnostic biomarkers for dermal cancer. DNA methylation patterns and miRNA signatures can distinguish between different types and stages of skin cancer.^{21–23} These biomarkers may improve early detection and risk stratification.

5.2. Prognostics

Epigenetic alterations can also serve as prognostic indicators in dermal cancer. Specific epigenetic signatures have been associated with disease progression, metastasis, and overall survival.^{22,24} Identifying patients at higher risk of aggressive disease can guide treatment decisions.

5.3. Therapeutic strategies

Targeting epigenetic alterations has emerged as a promising therapeutic approach. Epigenetic drugs, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors, are being investigated in clinical trials for dermal cancer treatment.²⁵ Additionally, miRNA-based therapies are being explored to restore normal gene expression patterns.

6. Conclusion

The interplay between genetic and epigenetic alterations in aging and cancer is a multifaceted phenomenon. Epigenetic changes, encompassing DNA methylation, histone modifications, and noncoding RNA regulation, are central to the pathophysiology of aging and aging-related diseases, with a profound impact on cancer. The challenge ahead is to unravel the molecular mechanisms that govern this complex interplay, potentially identifying master epigenetic regulators. Such discoveries hold the promise of advancing cancer screening and accelerating drug discovery, ultimately improving human health in the context of aging and cancer.

Epigenetic alterations play a pivotal role in the complex landscape of dermal cancer. Understanding the mechanisms by which DNA methylation, histone modifications, and noncoding RNAs influence tumorigenesis and progression is crucial for advancing diagnostic and therapeutic strategies. Epigenetic biomarkers offer potential for early detection and risk assessment, while epigenetic-targeted therapies hold promise for improving patient outcomes. Continued research in this field is essential for unraveling the molecular complexity of dermal cancer and translating discoveries into clinical practice.

7. Source of Funding

None.


8. Conflict of Interest


None.

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Author biography

Sonali Kohli, Consultant Dermatologist  <https://orcid.org/0009-0003-3185-3663>

Sanpreet Singh Sachdev, Assistant Professor  <https://orcid.org/0000-0001-7655-8180>

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