

Epigenetics of Cardiac Aging, Decline, and Repair

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Abstract

Epigenetic modifications, including DNA methylation, histone alterations (acetylation, methylation), and non-coding RNAs, are critical drivers of cardiac aging and disease progression. These mechanisms meticulously regulate gene expression, promote cellular senescence, and profoundly impair myocyte proliferation and regenerative capacity. Furthermore, they significantly contribute to cardiac dysfunction, adverse remodeling, and fibrosis in the aging heart. Understanding these intricate epigenomic changes provides critical insights into the pathogenesis of age-related cardiovascular decline. Targeting these specific epigenetic pathways offers promising therapeutic strategies for mitigating cardiac aging and improving heart health.

Keywords

Cardiac Aging; Epigenetics; DNA Methylation; Histone Modifications; Non-coding RNAs; Myocyte Senescence; Cardiac Fibrosis; Regenerative Capacity; Cardiovascular Disease; Therapeutic Targets

Introduction

Epigenetic modifications, such as DNA methylation, histone acetylation, histone methylation, and non-coding RNAs, are critical contributors to cardiac aging and its associated pathologies. These mechanisms play significant roles in regulating gene expression, driving cellular senescence, and diminishing the regenerative capacity of myocytes, thereby offering valuable insights into potential therapeutic targets for age-related cardiovascular diseases [1].

Furthermore, research highlights how epigenetic mechanisms, including DNA methylation and histone modifications, specifically control myocyte senescence within the context of cardiovascular disease and aging. The impact of these epigenetic changes extends

to cellular function and proliferation arrest, directly contributing to cardiac dysfunction and suggesting them as potential targets for interventions [2].

A closer look at histone modifications reveals the intricate roles of acetylation, methylation, and phosphorylation in shaping chromatin structure and influencing gene expression during cardiac aging. Dysregulation of these epigenetic marks leads to an age-related decline in myocyte function and proliferative capacity, underscoring their potential as therapeutic targets to mitigate cardiac aging [3].

The emerging roles of circular RNAs (circRNAs) as key epigenetic regulators in cardiac aging are also gaining attention. These circRNAs modulate myocyte proliferation, senescence, and fibrosis by sponging microRNAs or interacting with proteins, contributing to age-related cardiac dysfunction and offering new perspectives for diagnostic and therapeutic strategies [4].

In a broader sense, a comprehensive understanding recognizes the pivotal roles of DNA methylation, histone modifications, and non-coding RNAs in driving cardiac aging and related pathologies.

These epigenetic alterations significantly impact myocyte proliferation and function, prompting discussions on promising therapeutic strategies that target these pathways to ameliorate age-related cardiovascular decline [5].

The dynamic involvement of DNA methylation in cardiac aging and disease is particularly noteworthy. Age-related shifts in methylation patterns influence gene expression, cellular processes, and myocyte proliferation, leading to a functional decline; this positions DNA methylation as a potential biomarker and therapeutic target for cardiovascular aging [6].

Specific epigenetic modulators, such as sirtuins and histone deacetylases (HDACs), are also key players in cardiac senescence. Their activity changes with aging, affecting chromatin structure, gene expression, and myocyte function, including vital processes like proliferation and survival, suggesting that targeting these enzymes could provide therapeutic avenues for age-related cardiac decline [7].

Epigenetic contributions are additionally observed in cardiac fibrosis, a common feature of cardiovascular aging. DNA methylation, histone modifications, and non-coding RNAs in both myocytes and fibroblasts contribute to adverse remodeling, which in turn impacts the proliferative capacity of cardiac cells and overall heart function with advancing age [8].

Beyond cellular function, epigenetic mechanisms profoundly influence the regenerative capacity of cardiac stem cells (CSCs) during aging. Age-related epigenetic changes can impair CSC proliferation and differentiation, directly contributing to the heart's diminished regenerative potential and heightened vulnerability to disease in older individuals [9].

An overarching view of the epigenomic landscape reveals significant changes in cardiac aging, with a focus on DNA methylation and various histone modifications. These alterations cause transcriptional dysregulation, affect myocyte proliferation and differentiation, and ultimately contribute to the functional decline seen in the aging heart, pointing to crucial targets for anti-aging interventions [10].

Description

Epigenetic mechanisms are profoundly important in understanding cardiac aging and its associated pathologies. These complex and dynamic modifications, which encompass DNA methylation, a diverse range of histone modifications (including acetylation, methylation, and phosphorylation), and various non-coding RNAs, col-

lectively orchestrate gene expression and cellular function within the aging heart [1, 5, 10]. Specifically, they are instrumental in processes such as the onset of cellular senescence and the progressive decline of regenerative capacity in cardiac myocytes, which are hallmark features of an aging cardiovascular system [1, 2, 5]. Ultimately, dysregulation of these epigenetic marks directly contributes to age-related cardiac dysfunction and adverse remodeling, positioning them as prime candidates for targeted therapeutic interventions [3, 8, 10].

DNA methylation, a fundamental epigenetic modification, assumes a dynamic and critical role in the progression of cardiac aging and disease. Age-related alterations in the intricate patterns of DNA methylation significantly impact gene expression profiles and cellular processes, directly influencing myocyte proliferation and thereby contributing to a broader functional decline of the heart [6]. This process is also central to the control of myocyte senescence within the context of cardiovascular disease, where changes in methylation can instigate proliferation arrest and exacerbate cardiac dysfunction [2]. Beyond cellular senescence, DNA methylation actively contributes to cardiac fibrosis, a prevalent and detrimental feature of cardiovascular aging, affecting both myocytes and fibroblasts and critically influencing the heart's overall structural integrity and contractile function [8].

Histone modifications represent another crucial layer of epigenetic regulation that profoundly influences cardiac health. Acetylation, methylation, and phosphorylation of histones are vital biochemical events that shape chromatin structure and precisely regulate gene expression during the aging process of the heart [3, 10]. When these epigenetic marks become dysregulated, it is a significant factor in the age-related decline of myocyte function and their inherent proliferative capacity [3]. Furthermore, specific epigenetic modulators, such as the sirtuin family of proteins and histone deacetylases (HDACs), play pivotal roles in cardiac senescence. Their enzymatic activities undergo alterations with aging, leading to profound effects on chromatin structure, gene expression, and essential myocyte functions, including proliferation and survival. Consequently, targeting these enzymes offers promising therapeutic avenues for addressing and potentially mitigating age-related cardiac decline [7].

Non-coding RNAs, particularly circular RNAs (circRNAs), are rapidly emerging as significant epigenetic regulators with far-reaching implications in cardiac aging. These fascinating molecules influence key cellular processes such as myocyte proliferation, senescence, and fibrosis through diverse mechanisms, including their ability to sponge microRNAs or interact directly with specific

proteins [4]. Their intricate involvement in these fundamental processes directly contributes to the development and progression of age-related cardiac dysfunction, thereby providing valuable new insights for both diagnostic tools and therapeutic strategies aimed at ameliorating overall cardiovascular decline [1, 4, 5, 8].

The broader impact of these intricate epigenetic mechanisms extends critically to the heart's intrinsic regenerative capacity. Age-related epigenetic changes have been shown to impair the proliferation and differentiation capabilities of cardiac stem cells (CSCs), directly diminishing the heart's natural ability to repair itself and consequently increasing its vulnerability to various diseases in older individuals [9]. Collectively, these pervasive epigenetic alterations profoundly affect myocyte proliferation, function, and the overall cellular dynamics within the cardiac tissue, underscoring their comprehensive and indispensable role in the complex pathogenesis of age-related cardiovascular conditions [2, 5, 10].

The growing understanding that epigenetic modifications are fundamental drivers of cardiac aging has opened up exceptionally promising avenues for novel therapeutic interventions. By strategically targeting these specific epigenetic pathways, such as precisely modulating DNA methylation patterns, altering the activity of histone modification enzymes like sirtuins and HDACs, or intelligently interfering with specific non-coding RNAs, it may become possible to effectively slow down or even reverse the progression of age-related cardiovascular decline [1, 5, 7, 10]. This burgeoning field offers a fertile ground for the development of innovative anti-aging strategies that hold the potential to significantly improve cardiac health and quality of life in the elderly population.

Conclusion

Epigenetic modifications, encompassing DNA methylation, various histone alterations like acetylation, methylation, and phosphorylation, along with non-coding RNAs such as circular RNAs, are pivotal in cardiac aging and associated pathologies. These mechanisms meticulously regulate gene expression, contributing significantly to cellular senescence and the reduction of regenerative capacity in myocytes. Research illustrates how these epigenetic changes actively control myocyte senescence, influencing cellular function, proliferation arrest, and ultimately leading to cardiac dysfunction. Dysregulation of these epigenetic marks critically alters chromatin structure and gene expression during cardiac aging, impairing myocyte function and proliferative capabilities. Moreover, the dynamic role of DNA methylation, alongside the activity of epigenetic modulators like sirtuins and histone deacetylases (HDACs), impacts

fundamental cellular processes and the myocyte proliferation rate, contributing to functional decline. These epigenetic contributions also extend to cardiac fibrosis, a hallmark of aging, affecting both myocytes and fibroblasts and influencing the heart's overall function. Emerging evidence shows how these mechanisms, including changes in the epigenomic landscape, affect the regenerative potential of cardiac stem cells, impairing their proliferation and differentiation. Understanding these intricate epigenomic changes provides crucial insights into the functional decline observed in the aging heart and points toward promising therapeutic strategies to ameliorate age-related cardiovascular conditions.

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