

Epigenetic Mechanisms in Acute Myocardial Infarction: Functional Implications of DNA and Histone Methylation

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Abstract

Epigenetic mechanisms have emerged as key regulators of acute myocardial infarction (AMI) pathophysiology, fine tuning gene expression without altering the underlying DNA sequence. Among these mechanisms, DNA methylation and histone modifications play pivotal roles in inflammation, apoptosis, angiogenesis, and tissue remodeling. During AMI and atherosclerosis, dysregulated expression of genes such as CREG, FOXP3, VEGF, BCL2, and NOS3 has been documented, driven by enzymes including DNMT3B and TET proteins. Likewise, histone methylation at residues H3K4, H3K9, and H3K27 modulates transcriptional activity in vascular cells under the control of enzymatic complexes such as EZH2 and G9a. This mini review analyses how these epigenetic mechanisms contribute to ischemic injury and highlight their relevance to the molecular understanding of AMI.

Keywords: Acute myocardial infarction; epigenetics; DNA methylation; histones

Abbreviations: AMI: Acute Myocardial Infarction; DNMTs: DNA Methyltransferases; 5mC-5-Methylcytosine; CREG: Cellular Repressor of E1A-Stimulated Genes; VEGF: Vascular Endothelial Growth Factor; NOS3: Nitric Oxide Synthase 3; KMT: Lysine Methyltransferase; KDM: Lysine Demethylase

Introduction

Acute myocardial infarction (AMI) remains one of the leading causes of cardiovascular morbidity and mortality worldwide. Traditionally, its pathophysiology has been attributed to atherosclerosis, inflammation, and ischemic injury. In recent years, however, epigenetic regulation has emerged as a critical modulator of these processes. Mechanisms such as DNA methylation and histone modifications enable dynamic, environment responsive control of gene expression without altering the DNA sequence. These modifications influence genes involved in inflammation,

apoptosis, tissue repair, and cardiac remodeling. Understanding their role in AMI not only deepens our molecular insight into the disease but also opens the door to novel diagnostic and therapeutic strategies based on epigenetic modulation [1,2].

Historical Background

The term epigenetics was introduced in 1942 by the Scottish geneticist and embryologist Conrad H. Waddington to describe regulation of gene expression without changes in nucleotide

sequence; he argued that cellular differentiation depends on the activity or inactivity of specific genes [3]. Later, David Nanney proposed that epigenetic mechanisms, shaped by environmental influences, govern gene expression and persist through cell divisions, coining the phrase “epigenetic control of gene expression.” DNA methylation was the first epigenetic mechanism to be identified. Although its presence was recognized in the 1940s, its regulatory role was not established until three decades later [4]. Subsequent discoveries revealed additional mechanisms, notably histone modifications, which modulate chromatin accessibility [5].

DNA Methylation

DNA methylation involves the covalent addition of a methyl group to the C 5 position of cytosine, predominantly at CpG dinucleotides in mammals [6]. CpG islands - regions rich in CpG sites, often located in gene promoters - usually remain unmethylated to permit transcription. The reaction is catalyzed by DNA methyltransferases (DNMTs): DNMT1 preserves existing patterns, whereas DNMT3A and DNMT3B establish *de novo* marks during embryogenesis. Removal of these marks is mediated by TET enzymes, which oxidise 5 methylcytosine (5mC) to restore unmethylated cytosine [7,8]. Extensive evidence indicates that CpG rich methylation patterns undergo profound alterations in cardiovascular disease, activating or silencing key genes and modulating essential cellular processes. DNA methylation is critically involved in both atherosclerotic progression and the tissue response to AMI [9].

During atherosclerosis, heightened DNMT3B activity promotes hypermethylation of genes regulating inflammation and endothelial function. For instance, hypermethylation of the CREG promoter reduces its expression, contributing to endothelial dysfunction and plaque formation [10]. Likewise, methylation of immune related genes such as FOXP3 modulates regulatory T cell activity, influencing plaque stability [11]. In AMI, differential methylation affects genes such as VEGF (angiogenesis), BCL2 (cell survival), and NOS3 (vascular function). The interplay between methylation and demethylation, orchestrated by DNMTs and TET enzymes, shapes the cardiac response to ischemic injury and governs subsequent remodeling and scar formation [12,13].

Histone Modifications

Histones (H2A, H2B, H3, H4) assemble into octamers around which DNA is wrapped to form nucleosomes. This structure compacts the genome and provides a dynamic platform for regulating DNA accessibility and gene expression [14]. Histone methylation is a post-translational modification whereby lysine methyltransferases (KMTs) add one, two, or three methyl groups to specific lysine or arginine residues on histone tails. Depending on the residue (e.g., H3K4, H3K9, H3K27, H3K36, H3K79, or H4K20) and the degree of methylation, the mark can activate or repress transcription [15]. These marks are reversible through lysine demethylases (KDMs); their combined pattern constitutes the “histone code.” Histone methylation patterns are cell-type, developmental stage, and environment-dependent. In atherosclerotic vascular smooth-muscle cells, reduced H3K9 and H3K27 methylation, together with increased activating marks such as H3K4me2, have been reported

[16,17]. Enzymes such as EZH2 (catalyzing H3K27me3) and G9a (catalyzing H3K9me2/3) regulate genes implicated in plaque formation and endothelial dysfunction; the balance between activation and repression is crucial for vascular homeostasis and disease progression [18,19].

Conclusion

Current evidence underscores the central role of epigenetic mechanisms in regulating key processes during acute myocardial infarction, including inflammation, apoptosis, and tissue repair. DNA methylation and histone modifications enable precise, dynamic gene regulation orchestrated by enzymes such as DNMT3B, TET, EZH2, and G9a. These epigenetic marks not only reflect cellular responses to ischaemic damage but also represent promising targets for more specific therapeutic interventions. Elucidating how these processes shape cardiovascular pathophysiology offers new opportunities for epigenetics based diagnostic and therapeutic strategies.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the preparation or publication of this manuscript. No external funding or institutional support was received that could have influenced the content of this work.

References

1. Fernández-Sanlés A, Sayols-Baixeras S, Subirana I, Sentí M, Pérez-Fernández S, et al. (2021) DNA methylation biomarkers of myocardial infarction and cardiovascular disease. *Clin Epigenetics* 13(1): 86.
2. Rask-Andersen M, Martinsson D, Ahsan M, Enroth S, Ek WE, et al. (2016) Epigenome-wide association study reveals differential DNA methylation in individuals with a history of myocardial infarction. *Human Molecular Genetics* 25(21): 4739-4748.
3. Peixoto P, Cartron PF, Serandour AA, Hervouet E (2020) From 1957 to Nowadays: A Brief History of Epigenetics. *Int J Mol Sci* 21(20): 7571.
4. Ospelt C (2022) A brief history of epigenetics. *Immunology Letters* 249: 1-4.
5. Jarrell DK, Lennon ML, Jacot JG (2019) Epigenetics and Mechanobiology in Heart Development and Congenital Heart Disease. *Diseases* 7(3): 52.
6. Kelsey G (2020) Imprints in the history of epigenetics. *Nat Rev Mol Cell Biol* 21(10): 566-567.
7. Wang G, Wang B, Yang P (2022) Epigenetics in Congenital Heart Disease. *J Am Heart Assoc* 11(7): e025163.
8. Yan L, Geng Q, Cao Z, Liu B, Li L, et al. (2023) Insights into DNMT1 and programmed cell death in diseases. *Biomedicine & Pharmacotherapy* 168: 115753.
9. Zhang L, Xia C, Yang Y, Sun F, Zhang Y, et al. (2023) DNA methylation and histone post-translational modifications in atherosclerosis and a novel perspective for epigenetic therapy. *Cell Commun Signal* 21(1): 344.
10. Zhu L, Jia L, Liu N, Wu R, Guan G, et al. (2022) DNA Methyltransferase 3b Accelerates the Process of Atherosclerosis. *Oxid Med Cell Longev* 2022: 5249367.
11. Liu Y, Tian X, Liu S, Liu D, Li Y, et al. (2020) DNA hypermethylation: A novel mechanism of CREG gene suppression and atherosclerogenic endothelial dysfunction. *Redox Biol* 32: 101444.
12. Han W, Wang W, Wang Q, Maduray K, Hao L, et al. (2024) A review on regulation of DNA methylation during post-myocardial infarction. *Front Pharmacol* 15: 1267585.

13. Boovarahan SR, AlAsmari AF, Ali N, Khan R, Kurian GA (2022) Targeting DNA methylation can reduce cardiac injury associated with ischemia reperfusion: One step closer to clinical translation with blood-borne assessment. *Front Cardiovasc Med* 9: 10231909.
14. He K, Cao X, Deng X (2021) Histone methylation in epigenetic regulation and temperature responses. *Curr Opin Plant Biol* 61: 102001.
15. Zhang Y, Sun Z, Jia J, Du T, Zhang N, et al. (2021) Overview of Histone Modification. *Adv Exp Med Biol* 1283: 1-16.
16. Wang Y, Yuan Q, Xie L (2018) Histone Modifications in Aging: The Underlying Mechanisms and Implications. *Curr Stem Cell Res Ther* 13(2):125-135.
17. Wei X, Yi X, Zhu XH, Jiang DS (2020) Histone methylation and vascular biology. *Clin Epigenetics* 12(1): 30.
18. Neele AE, Chen HJ, Gijbels MJJ, van der Velden S, Hoeksema MA, et al. (2021) Myeloid Ezh2 Deficiency Limits Atherosclerosis Development. *Front Immunol* 11: 594603.
19. Gao R, Liu M, Yang H, Shen Y, Xia N (2025) Epigenetic regulation in coronary artery disease: from mechanisms to emerging therapies. *Front Mol Biosci* 12: 1548355.