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Review Article

Recent Advances in Nuclear and Mitochondrial-Related Epigenetic Modifications in Cardiovascular Diseases

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ABSTRACT

Epigenetic modifications are closely associated with cardiovascular diseases. Genome-wide association studies and candidate gene approaches have elucidated the polygenic complexity of cardiovascular diseases. Certain epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, play significant roles in the occurrence and progression of these diseases. Targeting key epigenetic enzymes, particularly DNA methyltransferases, histone methyltransferases, histone acetyltransferases, histone deacetylases, and their regulated target genes, represents a promising new avenue for the diagnosis and treatment of cardiovascular diseases. This review summarizes the latest research on nuclear and mitochondrial-related epigenetic modifications and their critical regulatory mechanisms in cardiovascular diseases.

INTRODUCTION

Cardiovascular diseases, including myocardial infarction, atherosclerosis, heart failure, and cardiac hypertrophy, remain leading causes of morbidity and mortality worldwide [1]. With the rapid development of modern society, the incidence of cardiovascular diseases has been increasing annually, and the age of onset is becoming progressively younger. The etiology of cardiovascular diseases, such as coronary heart disease, heart failure, and hypertension, is closely linked to environmental and genetic factors. Recent research has revealed that epigenetic modifications play a significant role in the occurrence and progression of cardiovascular diseases. Epigenetic modifications are regulatory mechanisms that can alter gene function, expression, and activity without changing the DNA sequence. They are considered primary regulatory mechanisms for cellular responses to environmental changes [2].

These mechanisms include DNA methylation, histone modifications, and non-coding RNAs, which are tissue- and cell-specific and may vary with aging, disease, or environmental stimuli [3]. Epigenetic markers are critical molecular indicators in cardiovascular diseases as they occur early in disease progression and involve key cardiovascular pathological pathways. Importantly, they can serve as biomarkers for detecting the onset and development of cardiovascular diseases, aiding in diagnosis and treatment. Additionally, increasing research [4] suggests that epigenetic mechanisms may also occur in mitochondria, primarily involving the regulation of mitochondrial DNA (mtDNA) replication and transcription, leading to the term "mitochondrial epigenetic modifications". However, compared to the epigenetic regulation of nuclear DNA, the regulatory mechanisms of mtDNA are less studied. Due

to the lack of histones, mtDNA's structure differs from that of nuclear chromatin, making mtDNA methylation one of the most researched epigenetic modifications in mitochondria.

Mitochondria are double-membrane organelles that play a crucial role in various essential biological functions, including the production of Adenosine Triphosphate (ATP) through oxidative phosphorylation (OXPHOS), apoptosis via caspase-dependent and -independent mechanisms, calcium homeostasis, and the generation of reactive oxygen species (ROS) [5]. Mitochondria contain their own DNA, a 16,569 bp molecule, which is maternally inherited in a non-Mendelian manner. Each mitochondrion contains multiple copies of mtDNA, which differs from nuclear DNA in several significant ways. This can be partially explained by the endosymbiotic theory, which posits that mitochondria evolved from α-proteobacteria that invaded early eukaryotic cells [6]. In fact, similar to the DNA of prokaryotic cells such as bacteria, mtDNA is a circular, double-stranded DNA molecule consisting of a heavy strand (H) and a light strand (L). It lacks histones and is organized into tightly packed nucleoprotein complexes known as nucleoids [7]. This review summarizes the regulatory roles of nuclear and mitochondrial-related epigenetic modifications in the development and progression of cardiovascular diseases.

DNA METHYLATION

Nuclear DNA methylation

DNA methylation is a crucial epigenetic modification, typically referring to the addition of a methyl group at the 5' position of the cytosine ring in CpG dinucleotides within DNA molecules. This process is catalyzed by DNA methyltransferases (DNMTs), which transfer a methyl group from S-adenosylmethionine (SAM) to cytosine [8]. DNA methylation typically occurs in promoter regions and is associated with transcriptional repression. When methyl groups are added to CpG islands in gene promoters, they can prevent the binding of transcription factors and other regulatory proteins, leading to reduced gene expression. This inhibition can be direct, by blocking transcription factor binding, or indirect, by recruiting proteins that recognize methylated DNA and subsequently recruit histone deacetylases and other repressive complexes to the site [9]. DNA methylation plays a critical role in various biological processes, including the suppression of transposable elements, X-chromosome inactivation, and genomic imprinting. Aberrant DNA methylation patterns are often associated with diseases, where hypermethylation of tumor suppressor gene promoters and global hypomethylation are common features observed in tumors [10].

mtDNA Methylation

The mitochondrial network in mammalian cells typically contains hundreds to thousands of copies of circular double-stranded DNA genomes [11]. Each mitochondrion contains multiple copies of mtDNA, which differ significantly from nuclear DNA in many ways. mtDNA is a circular, double-stranded DNA molecule composed of two strands, lacking histones, and organized into tightly packed nucleoprotein complexes known as nucleoids. The two circular strands, distinguished by different buoyant densities, are labeled as the heavy strand (H) and the light strand (L). Together, they encode 37 intron-less genes, responsible for translating 13 unique and essential protein components required for oxidative phosphorylation [12,13].

Unlike nuclear DNA, where each gene typically has its own promoter, mitochondrial DNA (mtDNA) contains only three promoter regions. The Light-Strand Promoter (LSP) is used for genes encoded by the L strand, while HSP1 and HSP2 (heavy-strand promoters, HSP) are used for genes encoded by the H strand. These promoters can transcribe multiple genes simultaneously, producing polycistronic transcripts. These promoters are located within or near a 1124 bp region known as the displacement loop (D-loop). Several nuclear-encoded proteins regulate mtDNA transcription and replication, including mitochondrial RNA polymerase (POLRMT), transcription and mtDNA maintenance factor (TFAM), transcription-specific factors (TFB1M and TFB2M), and the transcription termination factor (mTERF) [15].

The involvement and extent of mtDNA methylation remain controversial. Some studies report that methylation is a specific feature of genomic DNA and is absent in mtDNA [15,16], while other studies suggest that methylation is also present at the mtDNA level [17,18]. Additionally, research has shown that methylation of gene promoters in mtDNA can occur at non-CpG sites. Although DNA methyltransferases (DNMTs) DNMT1, DNMT3a, and DNMT3b exhibit activity in mitochondria, their inhibition does not affect mtDNA methylation [17]. Relevant studies indicate that in mitochondrial DNA, the primary methylation observed is at the adenine (6mA) level in adenine-

thymine dinucleotides (ApT) [19]. Additionally, the accumulation of Methyltransferase-like 4 (METTL4) has been observed in the mitochondrial matrix [20], and knockout of METTL4 leads to a reduction in 6mA levels in mtDNA. Similar to nuclear DNA, in mitochondria, 6mA weakens the binding of TFAM to transcription factors, suggesting that the role of methylation in gene expression is conserved [20]. In the nucleus, the demethylation of 6mA is driven by DNA 6mA demethylases, AlkB homolog 1 (ALKBH1) and ALKBH4 [21]. However, there are currently no studies on the mechanisms of 6mA demethylation in mtDNA.

mtDNA Methylation in Cardiovascular Diseases

Recent studies have suggested that mitochondrial damage characterized by obesity, insulin resistance, diabetes, and cardiovascular diseases may be attributed to altered mtDNA methylation. A study conducted on the platelet mitochondria of 10 CVD patients and 17 healthy individuals provided the first evidence that mtDNA methylation damage might be involved in the etiology of CVD. The study found higher methylation levels in the mitochondrially encoded cytochrome C oxidase I (MT-CO1), MT-CO2, MT-CO3, and mitochondrially encoded TRNA-Leu (UUA/G) 1 (MT-TL1) genes in CVD patients [22]. Studies conducted on human samples, cell cultures, and mouse models of arterial stenosis/occlusive disease have observed that in vascular smooth muscle cells, the DNMT1 enzyme translocates to mitochondria in response to proliferative stimuli and induced D-loop hypermethylation [23]. The hypermethylation of the D-loop leads to the suppression of mtDNA transcription, inducing mitochondrial dysfunction and reduced ATP production. This, in turn, weakens the contractility of vascular smooth muscle cells in cases of vascular restenosis or occlusion [23].

To elucidate the differences in mitochondrial activity between Stable Coronary Artery Disease (SCAD) and Acute Coronary Syndrome (ACS), the mtDNA copy number and methylation levels of the nuclear Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PPARGC1A) and the D-loop region were evaluated in peripheral blood leukocytes from 50 SCAD patients and an equal number of ACS patients [24]. The results indicated that SCAD patients had higher mtDNA content and lower D-loop methylation levels compared to ACS patients. This suggests that changes in mtDNA copy number and methylation may influence the clinical phenotype of coronary artery diseases [24]. To better understand why some obese individuals develop cardiovascular diseases while others remain disease-free, the methylation levels of several mtDNA genes, including MT-CO1, MT-CO2, MT-CO3, MT-TL1, and MT-TF, as well as the D-loop and light-strand replication origin (MT-OLR) regions, were evaluated in the platelet mtDNA of 200 overweight and obese adults, 84 of whom developed cardiovascular diseases [25]. The authors found that the methylation levels of MT-CO1, MT-CO3, and MT-TL1 were higher in subjects who developed cardiovascular diseases, suggesting that the methylation levels of these genes may be strong predictors of future CVD incidence in overweight and obese adults.

HISTONE MODIFICATIONS

Histones and their modification mechanisms

Histones are basic proteins found in the chromatin of eukaryotic cells, forming nucleosome structures together with DNA. They play a critical role in epigenetic modifications, serving as the primary protein components that confer dynamic and fluid structures to chromatin. Histones regulate gene expression by determining which regions of DNA are utilized for gene regulation and transcription mechanisms within the cell [26]. Histones typically consist of five components: H1, H2A, H2B, H3, and H4. Except for H1, the other four histones form dimers (which combine to make an octamer) to create the nucleosome core. DNA wraps around this nucleosome core. H1, on the other hand, binds to the DNA between nucleosomes. Therefore, histones are generally considered to play a more significant role as structural supports rather than in gene regulation [27].

Epigenetic modifications of histones primarily involve Post-Translational Modifications (PTMs) of the core histone structures. These modifications generally occur through methylation, acetylation, phosphorylation, succinylation, ubiquitination, SUMOylation, ADP-ribosylation, and glycosylation of specific residues [28,29]. These modifications play crucial roles in DNA replication, DNA repair, transcriptional regulation, alternative splicing, and chromosome condensation. They regulate gene expression without altering the underlying DNA sequence [30,31]. Histone methylation is a common modification that involves the addition of one, two, or three methyl groups to amino acids. This modification directly influences processes such as heterochromatin formation, genomic imprinting, X-

chromosome inactivation, and the regulation of gene transcription [32]. Histone methylation occurs specifically at certain lysine and arginine residues on histones H3 and H4 [33]. In histone H3, lysines 4, 9, 26, 27, 36, 56, and 79, as well as arginines 2, 8, and 17, can be methylated. In contrast, histone H4 has fewer methylation sites, with only lysines 5, 12, and 20, and arginine 3 being methylated [34,35]. Histone Methyltransferases (HMTs), particularly histone lysine methyltransferases (KMTs), are involved in transferring methyl groups from S-adenosylmethionine to the N-terminal tails of lysine residues on histones [36]. Histone demethylases, such as lysine-specific demethylase 1 (LSD1), regulate the demethylation of histones [37].

Histone modifications and cardiovascular diseases

Histones are characterized by a large number of modifying residues [36,38], and at least eight modifications have been identified in histones that are catalyzed by different enzymes [39,40], and histone modifications influence the progression of various forms of CVDs [41]. A Genome-Wide analysis shows that 596 of 1109 differentially regulated genes contain at least one histone modifier in the promoter region in adult mouse cardiomyocytes from a hypertrophic cardiomyopathy model, suggesting that epigenetic modifications have a critical function in the reprogramming of the transcriptome in hypertrophic cardiomyocytes [42].

Histone methylation regulates relevant genes targeting the heart given the close interaction between histone methyltransferases, demethylases (Histone Demethylase, HDM), and major regulators of myocardial phenotype [36,43]. WDR5 is an important component of the SET/MLL family of methyltransferases and regulates the expression of SMC-specific genes (including SMα -actin, SM22α, SM-MHC, and cardiac muscle) through methylation of H3K4 at the corresponding promoters [44]. The interaction of a commonly transcribed tetrapeptide repeat sequence on the X chromosome (UTX, an H3K27-specific histone demethylase), Serum Response Factor (SRF), and other core cardiac transcription factors can synergistically regulate the expression of downstream genes, such as the transcription and translation of cardiac natriuretic factor-related genes.

Histone methylases such as G9a, EZH2, MLL2, DOT1L, SMYD1, SMYD3, and SUV39H1 as well as demethylases such as LSD1LSD2, JMJD2A, UTX, and JMJD3 regulate the transcription of a wide range of cardiovascular genes and play an important role in cardiovascular development and cardiovascular disease. G9a mediates H3K9 dimethylation and further represses the expression of cardiomyocyte-associated genes [45]; histone demethylase, JMJD2A, promotes cardiac hypertrophy [46]; when exposed to stimuli, Myocardin-Related Transcription Factors (MRTFS) regulate the expression of downstream genes through their interaction with methyl methyltransferases and demethylases to regulate downstream gene expression; in endothelial cells, MRTF-A interacts with Ash2 and WDR5 of the H3K4 methyltransferase complex and is recruited to the promoter of endothelin-1, which plays a key role in vasoconstriction and vascular endothelial dysfunction [47]; SMYD1, a regulator of cardiac transcription factors in heart formation that is essential for cardiomyocyte differentiation and cardiac morphogenesis, and its mediated histone methylation regulates the expression of the cardiac transcription factors Hand2 and Irx4, which are essential for heart formation [48,49].

Overexpression of Rae28, Which Is Involved in the Composition of the Protein Regulator of Cytokinesis 1 (PRC1) Complex in Cardiomyocytes, Leads to Cardiomyocyte Apoptosis, Myofiber Irregularity, and Dilated Cardiomyopathy [50]. In contrast, H3K79me3 is added by the histone-lysine N-methyltransferase DOT1L, which is inhibited in dilated cardiomyopathy [51]. Specific depletion of DOT1L in cardiomyocytes triggers complete depletion of H3K79me2/3, ultimately leading to a reduction in the dystrophin (DMD) gene [52]. Similarly, a decrease in H3K9me2/3 and an increase in H3K4me2 were associated with dilated cardiomyopathy with increased levels of myeloid/lymphoid or mixed-spectrum leukemia protein 3 in the left ventricle [44].

NON-CODING RNA

Non-Coding RNA

The discovery that many genomic sequences in complex organisms are transcribed in a developmentally and organizationally regulated manner has triggered a series of explorations of all the different types of non-coding RNAs (non-coding RNAs, ncRNAs) that are transcribed [53,54]. They mainly include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), heterogeneous nuclear

RNAs (hnRNAs), PIWI-interacting RNAs (piRNAs), ribosomal RNAs (rRNAs), small nucleolar RNAs (snRNAs), small nucleolus RNAs (snoRNAs) and transfer RNAs (tRNAs). More studied in human diseases are miRNAs, lncRNAs, and circRNAs, all of which are recognized as important regulators of various biological processes [55-58].

miRNAs

miRNAs are small ncRNAs of approximately 22 nucleotides and are the most widely studied class of ncRNAs, which can mediate post-transcriptional gene silencing by controlling the translation of mRNAs into proteins, and which can regulate the translation of approximately 60% of protein-coding genes [59]. The complexity of this regulation is demonstrated by the fact that a single miRNA can target hundreds of different mRNAs, while multiple miRNAs can target the same mRNA [60]. In conclusion, miRNAs function in fundamental biological processes including cell proliferation, differentiation, and embryonic development, and their tissue-specific functions have all been demonstrated [61-63].

lncRNAs

lncRNAs are a large class of highly diverse ncRNAs, more than 200 nucleotides in length, that constitute the largest portion of the mammalian noncoding transcriptome [64]. The first lncRNAs found in eukaryotes, i.e., H19 and Xist, were discovered long before the genomic era [65,66]; however, it took quite some time before their broad biological functions were recognized. Although many lncRNAs have been identified to date, only very few have been functionally characterized. Among them, lncRNAs are known to mediate epigenetic modification of DNA by recruiting chromatin remodeling complexes to specific loci [67,68]. Hundreds of lncRNAs are expressed continuously in time and space at the human HOX locus, and these lncRNAs regulate chromatin accessibility in processes involving histone modifying enzymes and RNA polymerases [69].

circRNAs

CircRNAs are produced by reverse splicing of linear transcripts and can originate from exons, introns, exon-intron junctions or intergenic regions of the genome [70-72]. Compared to linear RNAs, cyclic RNAs are highly stable due to their ring structure, which makes them unsuitable for further processing and reduces their sensitivity to exonuclease activity [73]. The expression of circRNAs is usually independent of host gene expression [74], and due to their stability, they may be more abundantly expressed than related linear mRNAs [75]. In terms of localization, circRNAs usually accumulate in the cytoplasm [75]; however, they are also present in the nucleus and, similar to lncRNAs, circRNAs can bind to DNA and form circR-loops [76]. Although the updating of circRNAs is largely unknown [74], it is likely secreted via exosomes [77].

ncRNAs in cardiovascular diseases

ncRNAs are associated with cardiac physiological activities and participate in the CVD process by regulating apoptosis, proliferation, migration, cardiac remodeling, fibrotic responses, and cardiac hypertrophy [78,79]. Studies have shown that miRNAs are involved in the pathogenesis of cardiovascular disease. A notable example is miR-21, which is upregulated in humans and mice with heart transplant vasculopathy, a complication of heart transplantation that limits long-term survival [80]. In addition, miR-21 was also overexpressed in a mouse model of myocardial fibrosis induced by myocardial infarction and was associated with reduced levels of TGF β RIII [81]. Silencing miR-21 by antagomir-21 disrupts cardiac allograft vasculopathy, prolongs cardiac allograft survival [80], reduces hypertrophy and fibrosis, and restores impaired cardiac function [82]. In a porcine model of ischemia-reperfusion injury, anti-miR-21 treatment successfully inhibits miR-21 and improves cardiac function, reducing cardiac fibrosis and hypertrophy [83]. Showing miR-122 upregulation in patients with systolic dysfunction, cardiovascular fibrosis and cardiovascular remodeling [84]. Mechanistically, miR-122 showed direct inhibition of the anti-apoptotic protein Xiap and promoted endothelial cell apoptosis in a CVD mouse model [85]. In addition, circulating miR-122 levels are negatively correlated with cardiac function and have been shown to be an important indicator of predictive and prognostic value for cardiac recovery(84). miR-122 was also found to inhibit the expression of anti-apoptotic BCL-2, thereby reducing cardiomyocyte viability [84].

Cardiac Mesoderm Enhancer-associated Non-coding RNAs (CARMNs) are among the most thoroughly annotated lncRNAs. These lncRNAs are predominantly expressed in smooth muscle cells and are significantly upregulated after myocardial infarction [86,87]. Analysis of publicly available transcriptomic datasets reveals reduced expression of CARMNs in cerebral

arteries with aneurysms and in human atherosclerotic arteries [86]. Downregulation of CARMNs in Human Coronary SMCs Leads to Enhanced Cell Proliferation and Migration in Vitro and Significantly Reduces the Expression Levels of SMC-Specific Marker Genes, Including MYH11, ACTA2, CNN1, and TAGLN [86]. Furthermore, RNA immunoprecipitation assays confirmed that CARMN can interact with cardiac myocardin (Myocardin, MYOCD), an activator of SMC-specific genes with transcriptional activity in cardiomyocytes and SMCs [86]. The inability of the adult mammalian heart to regenerate after ischemic injury is largely due to a decline in cardiomyocyte mitosis. However, the specific molecular mechanisms explaining the nondividing nature of adult cardiomyocytes remain largely unknown [88]. Cardiac regeneration-associated lncRNA (CAREL) expression is increased in the postnatal heart and is associated with regeneration during cardiac injury. Indeed, in transgenic mice overexpressing CAREL, the proliferative capacity of cardiomyocytes was diminished. In contrast, knockdown of CAREL in cardiomyocytes by adenoviral short hairpin RNA (shRNA) increased cardiomyocyte proliferation and enhanced cardiac regeneration after injury. Further experiments in Human Embryonic Kidney Cells (HEK293) and neonatal cardiomyocytes using biotin-avidin traction and luciferase assays demonstrated that CAREL is a competitive endogenous RNA for miR-296, a positive regulator of cardiac replication and regeneration [88]. Other lncRNAs, such as ZFAS1 [89], SNHG3 [90], ExACT1 [91], MIAT, CPhar, Mhrt779 [92], H19 [93], and CPR [94], have been associated with myocardial ischemia-reperfusion injury, aortic valve calcification, pathologic hypertrophy and heart failure, carotid artery atherosclerosis, physiologic cardiac hypertrophy, respectively , pulmonary hypertension and cardiomyocyte proliferation.

Certain circRNAs have also been reported to have important roles in heart failure and myocardial infarction. Global circRNA mapping showed that the ultraconserved circ-INSR, derived from the gene encoding the Insulin Receptor (INSR), regulates mitochondrial function in cardiomyocytes in response to doxorubicin stress [95]. Decreased expression of circ-INSR induces cardiomyocyte apoptosis and impairs metabolic activity in human and mouse failing heart tissue [95]. Consistent with this observation, overexpression of circ-INSR successfully reduced doxorubicin-induced DNA damage and apoptosis in primary rat cardiomyocytes.

In a recent study, researchers characterized and investigated the function of circHIPK3, which is derived from an exon of the HIPK3 gene in the mouse heart. circHIPK3 negatively regulates RBP Hur at the post-transcriptional level, leading to p21 mRNA destabilization in a rat cardiomyocyte cell line (H9C2) and primary mouse cardiomyocytes [96]. Another study [97] showed that circMAP3K5 is associated with SMC differentiation due to its ability to adsorb miR-22-3p, which induces TET2 expression. A recent study demonstrated the protective role of circSlc8a1, a circular antisense RNA, in cardiac injury, emphasizing the important role of circSlc8a1 in the protection of physiological cardiac functions [98]. Experimental induction of cardiac-specific expression of cA-circSlc8a1 in mice resulted in profound phenotypic alterations characterized by significant weight gain, hepatic steatosis and impaired cardiac function. Another study showed that circNlgn and its translation product Nlgn173 are mediators of adriamycin-induced myocardial fibrosis [99]. Silencing of endogenous circNlgn has been found to reduce adriamycin-induced cardiomyocyte apoptosis and enhance cardiomyocyte viability. Furthermore, silencing of circNlgn effectively inhibited collagen deposition and enhanced the expression of fibrosis markers. These findings suggest that targeting circNlgn may attenuate the side effects associated with adriamycin, particularly its effect on fibrosis progression.

CONCLUSION

This article reviews the mechanisms involved in epigenetic modifications, such as DNA methylation, histone modifications, and the role of noncoding RNAs in various cardiovascular diseases. In conclusion, epigenetic modification is a promising area for cardiovascular disease diagnosis and intervention. The rapid development of epigenetic modifications and genomics may provide new directions for precise treatment of cardiovascular diseases. In the future, we hope to further explore the molecular mechanisms by which epigenetic modifications regulate cardiovascular diseases and find more strategies for the prevention and treatment of cardiovascular diseases in order to better guide clinical treatment.

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