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REVIEW

Roles of different methylation modifications in cardiovascular disease

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Abstract **Cardiovascular disease remains the foremost contributor to mortality and disability globally, even with significant advancements in prevention, diagnosis, and early intervention. A comprehensive insight into cardiovascular diseases and the intrinsic molecular mechanisms is critical to innovating more effective therapeutic interventions for prevention and therapy. Latest advancements within the realm of epigenetic modulation, especially methylation modification, of gene expression have corroborated the impacts of epigenetic modifications in governing the pathogenesis and progression of cardiovascular diseases and suggested the viability of epigenetic mechanisms as emerging targets for the development of new diagnostic and therapeutic strategies. In this review, we first provide a brief overview of the biological processes of methylation modifications, including DNA methylation, protein methylation, and RNA N^6-methyladenosine (m^{6}A) modification. We then summarize their roles in cardiac hypertrophy, heart failure, ischemic heart disease, and atherosclerosis.**

Keywords DNA methylation; protein methylation; m^{6}A; cardiovascular disease

Introduction

Cardiovascular disease poses a prominent risk to human health, given its high incidence and mortality rates [1,2]. Effective prevention and management of cardiovascular disease depend on the elucidation of the related pathological process and the development of early diagnosis and intervention. Life science researchers have reached a consensus that the inheritance of growth, development, and evolutionary traits by offspring is not solely reliant on gene sequences, but also on alterations in gene expression processes [3]. In recent years, epigenetics, the heritable genetic information changes in gene function that occur without alterations to the DNA sequence, has garnered great attention from researchers worldwide [4]. These epigenetic changes are capable of stable transmission during growth and development, yet they retain the potential for reversibility [5]. Genetics provides the framework for synthesizing various proteins, encompassing those engaged in epigenetic regulation, while epigenetics directs the utilization of this genetic information throughout life [6].

Epigenetics encompasses two primary pathways: regulating gene transcription itself (transcriptional regulation) and modulating processes following transcription (post-transcriptional regulation). The former primarily investigates how environmental factors affecting parents trigger alterations in gene expression in their offspring, which include DNA methylation, histone modification, chromatin remodeling, gene silencing and RNA editing [7,8]. In contrast, the latter mainly pertains to the mechanisms regulating RNA, including non-coding RNAs, antisense RNAs, riboswitches, and RNA methylation, all of which have gained considerable

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attention in recent years [9,10]. Among the various epigenetic mechanisms, methylation modifications are particularly critical in gene expression regulation [11], which manage both gene expression and suppression and are intertwined with cancer [12], growth and development [13], and aging [14].

In this review, we provide an overview of the different types of methylation modifications and their roles in the pathogenesis of several major cardiovascular diseases. While our goal is to offer a comprehensive perspective on methylation modifications in cardiovascular diseases, we acknowledge the complexity of these processes and recognize that it may not be possible to explore the exhaustive details of each specific modification. Additionally, we discuss the potential crosstalk between various types of methylation modifications and how these interactions may contribute to the pathogenesis of cardiovascular diseases. Finally, we share our insights into future research directions and the potential clinical applications of methylation-based strategies for the prevention and treatment of cardiovascular diseases.

Basics of methylation modifications

Methylation describes the catalytic transfer of methyl groups from reactive methyl compounds, such as S-adenosylmethionine (SAM), onto other molecules [15]. This process leads to the formation of various methylated molecules, or the chemical alteration of proteins and nucleic acids to yield methylated products, with enzymes catalyzing this process in biological systems. Methylation is often categorized into DNA [16], RNA [17], and protein methylation [18], respectively aligning with transcriptional, post-transcriptional, and post-translational regulatory mechanisms [19] (Fig. 1).

DNA methylation

DNA methylation stands out as the most extensively and thoroughly investigated epigenetic process [20,21]. Generally, hypermethylation restricts gene expression, while hypomethylation facilitates gene expression [22,23]. Human chromosome CpG nucleotides are the most important methylation sites, regulated by three

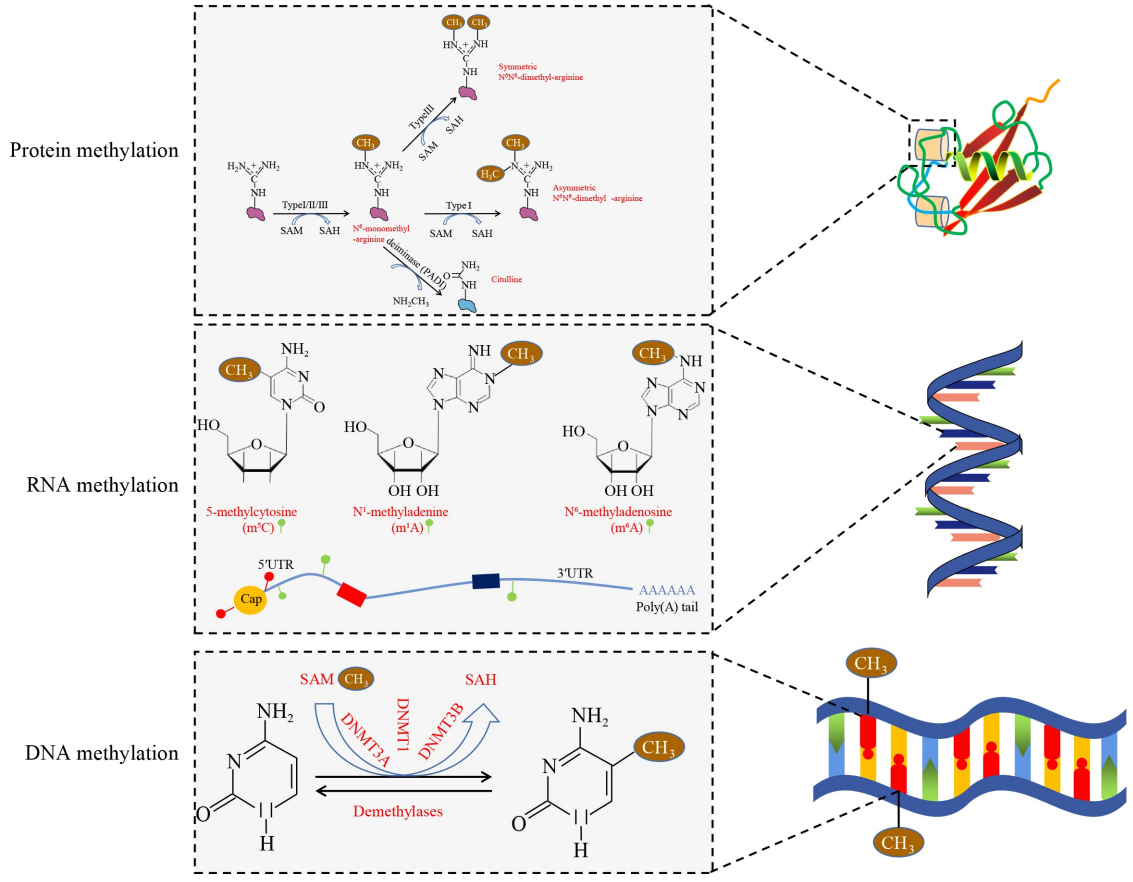

Fig. 1 General schematics of the basics of methylation modification. DNA methylation is mediated by DNA methyltransferases (DNMTs), which transfer the methyl group from SAM to CpG cytosine. RNA methylation mainly includes N^6-methyladenine (m^6A), N^1-methyladenine (m^1A), and C^5-methylcytosine (m^5C). Protein methylation mostly occurs in the post-translational modifications of N-terminal tails of histones.

distinct DNA methyltransferases (DNMTs), including DNMT1 (for the methylation patterns during replication), DNMT3a and DNMT3b (for the *de novo* methylation formation) [24,25]. These enzymes are capable of catalyzing the methyl group transfer from SAM to CpG cytosine to form m5CpG, which in turn alters the chromatin conformation and causes gene silencing [26] (Fig. 2). As a crucial mechanism regulating gene expression in eukaryotes, DNA methylation not only affects the process of gene expression but also inherits from parental cells and continues through cell mitosis and meiosis [27]. Evidence from studies have indicated that DNA methylation serves a prominent role in early stages of embryogenesis, organ formation, genetic imprinting, and the occurrence and development of cancer [28–32].

Protein methylation

Post-translational protein modification represents one of the core processes that regulate the biological functions of proteins [33]. As an important form of protein post-translational modification, methylation modification was first discovered in the N-methylated lysine of the flagellin of Salmonella typhimurium in the 1960s [34]. With the development of molecular biology technology, protein methylation has proven to be ubiquitous across a range of cellular processes in eukaryotes and prokaryotes [35]. Studies have shown that approximately 2% of arginine residues are methylated in total protein extracts from rat liver cell nuclei [36]. In eukaryotes, the structure of chromatin is critical to the regulation of gene expression, with the protruding N-terminal tail of histones providing sites for various post-translational modifications that influence protein activity [37–39]. The methylation of histones was first discovered in 1964 [40–42], a post-translational modification that occurs when the protein side chain interacts with SAM [43]. Histone methylation, known for its stability as a post-translational modification [44], targets multiple lysine and arginine residues, mainly those at the N-terminal of H3 and H4 [45]. Methylation at these specific sites often changes chromatin structure [46], which then controls gene transcription and impacts multiple physiological processes [47] (Fig. 3). Nowadays, a wide variety of methyltransferases and demethylases have been discovered, functioning together to preserve the balance of amino acid methylation and demethylation [48]. Alongside histones, numerous other proteins can also undergo methylation [49]. Identified non-histone proteins featuring methylation and demethylation modifications encompass elements in cell signaling transcriptional regulation, such as receptor kinases, effector proteins, activators and repressors, transcription factors, and the tumor suppressor p53 [50–52]. RNA-binding protein TAF10 has additionally been reported to undergo methylation modification [53]. As a critical molecular event of biological processes, protein methylation plays an indispensable part in regulating numerous pathophysiological processes.

RNA methylation

Methylation modification is a primary and essential form of chemical modification of RNA in eukaryotic post-transcriptional regulation [54]. The vast majority of eukaryotic mRNA modifications occur within the 5'cap region and 3'poly(A) tail [55], including N^6-

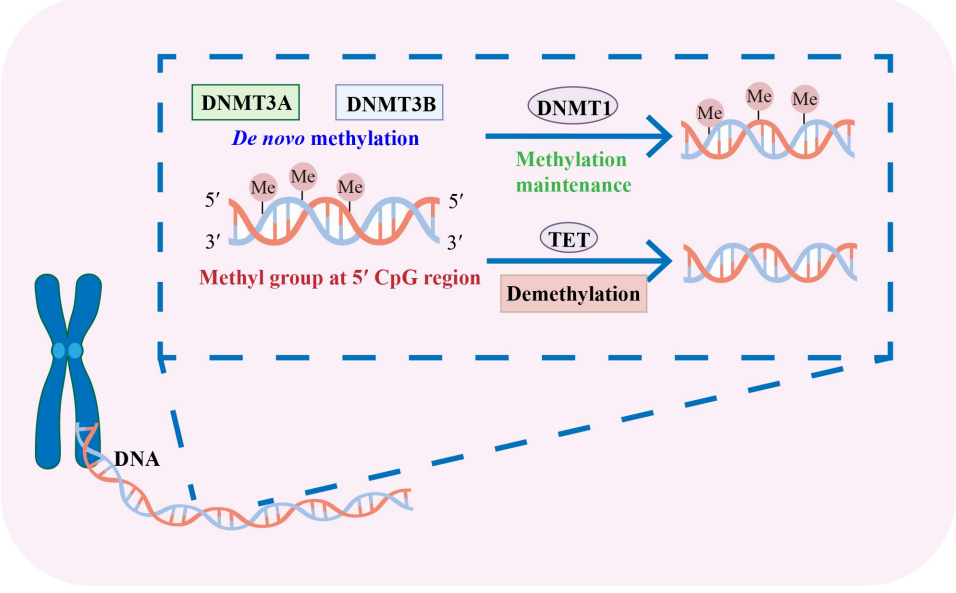

Fig. 2 Mechanistic role of DNA methylation in gene regulation.

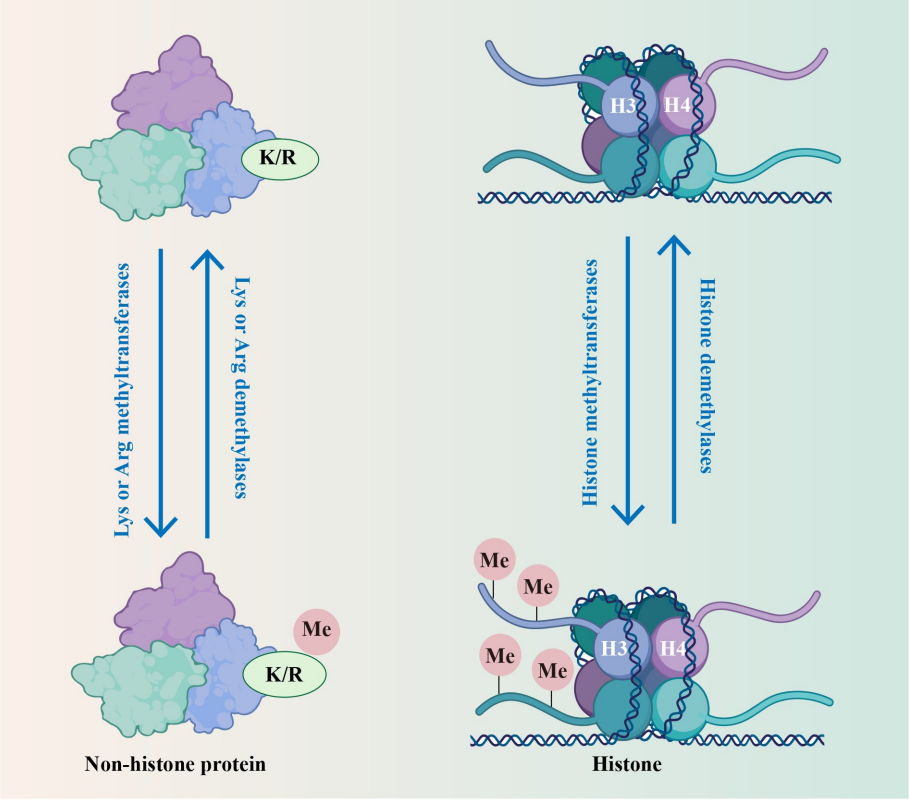

Fig. 3 Mechanistic role of histone methylation.

methyladenine (m^6A), N^1-methyladenine (m^1A), and C^5-methylcytosine (m^5C) [56–58]. When the nitrogen atom located at position six on the adenylate of an RNA molecule undergoes methylation modification, it is termed N^6-methyladenosine modification, namely m^6A methylation modification. This is the predominant methylation modification within the internal regions of eukaryotic mRNAs [59]. Although m^6A modification was discovered in eukaryotic mRNAs as early as the 1970s [60], the research on its function and significance has not become the focus of attention until recent years [61]. Analogous to the methylation of DNA and histones, m^6A RNA methylation is likewise both dynamic and reversible in mammals [62]. Through high-throughput sequencing, the findings reveal that m^6A modifications in mature transcripts are largely clustered in stop codons, 3'UTRs, and long exon regions, rather than being randomly positioned [63–65]. m^6A exhibits a certain degree of sequence conservation, and the highly conserved consensus sequence is RRACH (R = G or A; H = A, C, or U) [66].

m^6A methylation modification has been revealed to be regulated in a dynamic manner by three regulatory factors: methyltransferase (Writers), demethylase (Erasers) and reading proteins (Readers) [67]. The multi-component methyltransferase complexes that play a catalytic role largely encompass methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14) and Wilms tumor 1 associated protein (WTAP) . METTL3 significantly contributes to m^6A methylation by creating a 1:1 dimer complex with METTL14, primarily localized in the nuclear spot area [68–70]. While WTAP does not possess methylation activity on its own, it interacts with the METTL3 dimer to facilitate the gathering of the m^6A methyltransferase complex to mRNA targets [71], which subsequently influences the efficiency of methylation. Additionally, the virus-like m^6A methyltransferase related protein (VIRMA, additionally identified as KIAA1429), which participates in alternative splicing, is another element of the complex of methyltransferase that mainly collaborates with WTAP [72]. The identification of demethylases indicates that the methylation modification of m^6A is reversible. The presently discovered demethylases predominantly encompass fat mass and obesity-associated protein (FTO) [73] and AlkB homolog 5 (ALKBH5) [74], both of which fall within the AlkB family. Importantly, in order to carry out specific biological functions, mRNA modified by m^6A methylation necessitates a certain RNA binding protein, known as methylated reading protein. The reading proteins identified to date include YTH domain proteins (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2), nuclear heterogeneous ribonucleoprotein HNRNP family (RNPA2B1 and HNRNPC) and IGF2BPs

family (IGF2BP1, IGF2BP2, and IGF2BP3) and they participate in the translation [75], degradation [76] and processing of mRNA [77] (Fig. 4).

Methylation modification and cardiovascular diseases

Although the mortality rate of cardiovascular diseases in developed countries has decreased significantly, cardiovascular diseases continue to rank as the top cause of death worldwide [78]. Investigations have revealed that epigenetic modifications are vital for vascular biology and cardiovascular diseases [79]. Methylation modification, in particular, has been implicated in the onset and advancement of cardiovascular disease, including cardiac hypertrophy, heart failure (HF), ischemic heart disease (IHD), atherosclerosis, and pulmonary hypertension [80–83].

Ischemic heart disease

IHD, which is caused by stenosis or occlusion of the myocardial coronary arteries and encompasses myocardial infarction (MI) and HF [84], ranks as a prominent contributor to morbidity and mortality across the globe [85]. IHD directly affects the oxygenation capacity of cardiomyocytes, and thus induces a series of pathophysiological processes [86]. The current therapeutic strategies offer limited effectiveness in managing IHD and the associated adverse remodeling, partly due to an incomplete understanding of the pathophysiological process and the lack of more precise therapeutic targets. Recent findings indicate that many molecules critical to the pathological process of IHD are subject to methylation modifications [87], which opens up new avenues to innovate superior approaches for treating the condition.

DNA methylation and ischemic heart disease

DNA methylation and IHD exhibit a bidirectional regulatory relationship. Specifically, myocardial ischemia alters the level of DNA methylation [21], while conversely, abnormal DNA methylation can aggravate myocardial ischemia [88].

Chen *et al*. [89] reported that the mother with gestational diabetes mellitus (GDM) elicited oxidative stress and hypermethylation of DNA in myocardium of the offspring. The DNA hypermethylation caused an epigenetic downregulation of the *Sirt1* gene alongside atypical development of a phenotype sensitive to ischemia, suggesting Sirt1 a candidate for therapeutic intervention in IHD in the offspring. Another study demonstrated that perinatal nicotine exposure (PNE) can induce rearrangement of expression of cardiac miR-181a and DNA methylation profile, thereby impacts epigenetic

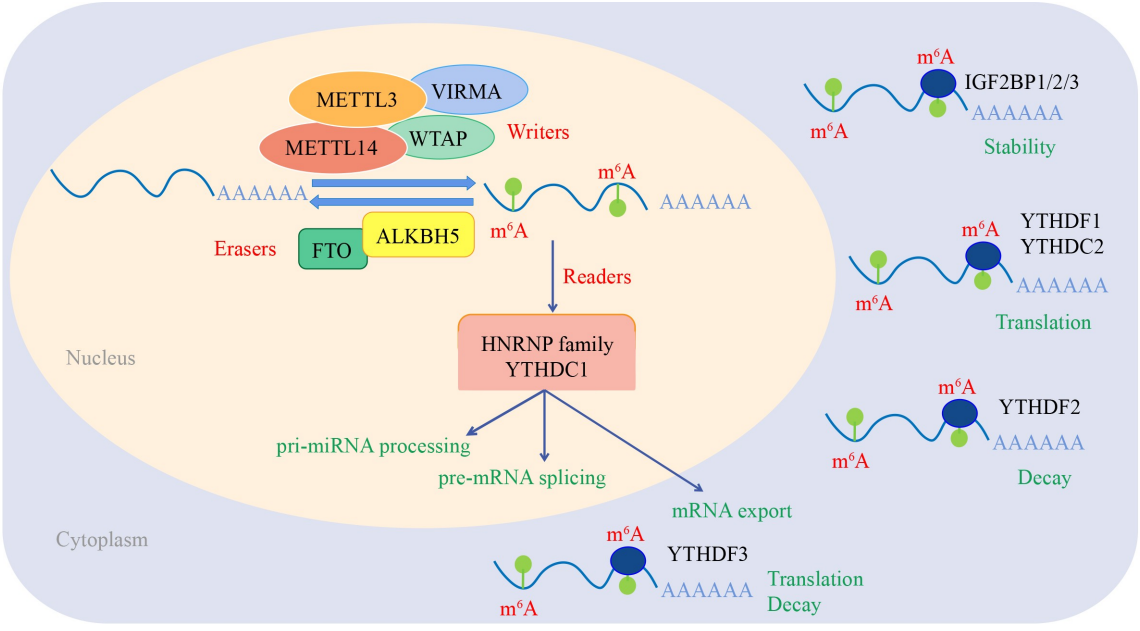

Fig. 4 Regulation of m^{6}A modification and its functions in RNA metabolism. Methyltransferase (METTL3, METTL14, and WTAP) and demethylase (FTO and ALKBH5) regulate the dynamic and reversible process of m^{6}A. Recognition of m^{6}A by HNRNPs in the nucleus mediates splicing of pre-mRNA and promotes pri-miRNA processing to pre-miRNA. In the cytoplasm, IGF2BP1/2/3 mainly regulates the stability of m^{6}A-modified mRNAs, YTHDF1/YTHDC2 binds m^{6}A-modified mRNAs to increase translation, whereas m^{6}A identification by YTHDF2 triggers mRNA decay.

regulation of the angiotensin receptor (ATR)/TGF-β/autophagy signaling pathway, resulting in gender-specific manifestation of an ischemia-susceptible phenotype during postnatal stages. Additionally, miR-181a antisense serves as a candidate for therapeutic intervention for restoring this phenotype [90]. In addition, recent studies suggest that the whole genome methylation level can be used as a marker of cardiovascular disease [91]. Ma *et al*. [92] detected the whole-genome methylation level in peripheral blood lymphocytes of individuals suffering from coronary heart disease (CHD) and noted that, relative to healthy control individuals, the whole-genome methylation level of patients with CHD increased. The same results were also found in rat and rabbit models of myocardial ischemia. Beyond the overall genome methylation, specific gene methylation also is instrumental in IHD. Notably, the methylation levels of *TIMP1*, *ABCA1*, and *ACAT1* in the blood samples of patients with CHD are over 50% higher than those of the control subjects. Corbin *et al*. [93] further pointed out that DNA methylation at F2RL3 mediates the impact of smoking on the increased threat of MI, and DNA hypomethylation of F2RL3 increases PAR4 expression, which has downstream effects on platelet reactivity. Li *et al*. [94] found that lncRNA-ZFAS1 is capable of directly engaging with the promoter region of Notch1, bringing DNMT3b to facilitate DNA methylation at that site, thereby inducing cardiomyocyte apoptosis along with reactive oxygen species (ROS) production subsequent to myocardial ischemia-reperfusion injury (MIRI).

Thus far, more than 170 genes related to myocardial ischemia injury and CHD have been found and DNA methylation of these genes changes significantly in IHD [91]. Given the significant impact of DNA methylation on IHD, these epigenetic modifications hold promise as novel therapeutic targets. The development of DNA methyltransferase inhibitors or methylation-regulated gene-targeted drugs could offer a new approach to diagnosing and treating IHD. As our understanding of DNA methylation in IHD continues to evolve, it is likely that these epigenetic changes will provide critical insights into disease mechanisms and therapeutic interventions.

Protein methylation and ischemic heart disease

Arginine methylation, facilitated by the family of arginine methyltransferases (PRMTs), constitutes a post-translational modification that occurs widely in eukaryotes [95]. SAM acts as a methyl donor and conveys the methyl group to the nitrogen atom of arginine side chain of the protein to generate the S-adenosine isotype Cysteine and methylarginine [96]. Arginine methylation is a very typical type of modification in organisms, resulting in a high abundance of proteins containing methylarginine, such as histones and RNA-binding proteins [97]. Therefore, PRMTs are implicated in multiple pathophysiological processes, including rheumatoid arthritis, Alzheimer's disease, systemic lupus erythematosus, asthma, atherosclerosis, cancer, and IHD [98–102]. The study by Wang *et al*. [103] revealed a substantial increase in PRMT4 expression in the ischemic heart and hypoxic cardiomyocytes. Overexpression of PRMT4 specifically in cardiac tissue showed reduced survival, impaired left ventricular function, and exacerbated cardiac remodeling after MI. Mechanistically, overexpression of PRMT4 triggers apoptosis caused by hypoxia in cardiomyocytes, whereas its suppression eliminates this effect. Similarly, PRMT5, an additional member of the PRMT family, functions in regulating the inflammatory response [98]. Tan *et al*. [104] reported that the expression of PRMT5 in the peripheral blood of individuals suffering from acute myocardial infarction (AMI) was lower than that in stable coronary artery disease (CAD) patients. Patients exhibiting low expression of PRMT5 in peripheral blood are more susceptible to AMI, indicating that low expression of PRMT5 is a standalone risk factor for the occurrence of AMI. In addition to PRMT family, as the catalytic subunit of polycomb inhibitory complex 2 (PRC2), enhancer of zeste homolog (EZH2) can mediate the trimethylation of histone H3 at lysine 27 (H3K27me3) [105]. Evidence suggests that EZH2 contributes to diabetic podocytes injury and oxidative stress [106]. Wang *et al*. [107] revealed that MALAT1 could exacerbate myocardial injury and cardiomyocytes apoptosis in diabetic cardiomyopathy through regulating the miR-22/EZH2/ABA1 signal transduction cascade.

The intricate regulation of protein function through arginine methylation and other epigenetic modifications such as H3K27 trimethylation plays a pivotal role in the pathophysiology of IHD. Targeting these pathways, particularly through modulating PRMT and EZH2 activity, offers promising therapeutic strategies for mitigating cardiac injury, improving cardiac function, and ultimately reducing the burden of IHD.

m^6A RNA methylation and ischemic heart disease

m^6A RNA methylation may be highly correlated with the pathogenic stimuli in the process of IHD, such as oxidative stress, inflammation, and energy metabolism disorders [108–109]. Apoptosis is an important cause of acute myocardial injury, and inhibition of apoptosis can improve the MI [110]. While inhibition of autophagy can lead to increased apoptosis, together indicating that IHD is related to autophagy [111]. In addition, endothelial cells and fibroblasts also play vital roles in IHD [112].

Song *et al*. [113] examined the gene expression levels in the heart tissues of 10 pairs of MI patients and normal

subjects and discovered that METTL3 expression was markedly upregulated in cardiac tissues of MI patients in comparison to normal subjects. Similarly, the expression of METTL3 in cardiomyocytes undergoing hypoxia and reoxygenation and in myocardium of mice following hypoxia and reperfusion was significantly increased. Mechanistically, METTL3 reduces the expression of transcription factor EB (TFEB) and inhibits the lysosomal autophagy pathway by methylating the m^6A residues of the downstream target gene TFEB, thereby promoting cardiomyocyte apoptosis and myocardial ischemic injury. Moreover, Yang *et al*. [114] found that ALKBH5 in fibroblasts stabilized ErbB4 mRNA by means of an m^6A-dependent mechanism, actively regulating the healing process after MI. Other studies have shown that ALKBH5 also influences the stability of WNT5A mRNA through an m^6A-dependent mechanism, thereby affecting angiogenesis after ischemia [115]. Treatment hitting ALKBH5 as a target may become an emerging treatment alternative for ischemic disorders, particularly peripheral arterial disease. In general, the significance of m^6A RNA methylation in IHD has received increasing attention, and research and intervention on these molecules may provide new treatment strategies for IHD.

Given the emerging therapeutic potential of targeting m^6A RNA methylation in IHD, further research into the molecular mechanisms underpinning these modifications could lead to novel therapeutic strategies aimed at mitigating myocardial injury and enhancing recovery following ischemic events.

Cardiac hypertrophy

Cardiomyocytes can grow hypertrophically under stress stimuli like pressure overload or MI. Initially, this hypertrophic response is an adaptive reaction that enables increased contractile force to cope with the escalation of wall tension or workload. However, such adaptation may eventually lose the compensatory capacity and ultimately lead to HF [116–117]. Deregulation of expression of a range of genes and their protein products in cardiomyocytes induces cardiac hypertrophy (CH). In recent years, growing evidence has highlighted the fundamental roles of epigenetic mechanisms in managing gene expression related to the pathogenesis of CH [118].

DNA methylation and cardiac hypertrophy

Stenzig *et al*. [119] documented findings indicating that the expression of genes related to CH (*Nppa*, *Nppb*, *Acta1*, and *Atp2a2*) is negatively correlated with the degree of methylation with decreasing methylation at the promoter sites of genes along with increasing gene expression. Intervention with DNA methyltransferase inhibitor RG108 or MDSA prevents the weakening of cardiac contractility and prolongation of diastole caused by increased cardiac afterload, whereas another inhibitor AZA has no effect on cardiac function. RG108 mitigates the enhanced methylation within the promoter region of *Atp2a2* gene induced by ventricular afterload and transcription factors binding to CpG sites, bringing about abnormal transcription regulation. These results suggest that abnormal DNA methylation is engaged in the management of CH. Xiao *et al*. [120] found that the activity of DNA methyltransferase in the left ventricle treated with norepinephrine was enhanced, and the DNA methylation level of the whole genome was increased, while the expression of DNA methyltransferase was nearly undetectable in normal myocardium. Application of AZA decreased DNA methylation and reversed CH phenotypes with improved myocardial contractility. Huang *et al*. [121] found that long-term exposure to phenanthrene (Phe) increased CH, protein synthesis, intracellular Ca^{2+} concentration, release of CH markers (ANP, BNP, c-Myc), and DNA methylation level in the CpG islands of miR-133a promoter region and decreased miR-133a expression. Therefore, ncRNAs, especially miRNAs may also be worthwhile candidates for in-depth analysis as DNA methylation epigenetic markers for cardiac hypertrophy. These studies collectively highlight the profound impact of DNA methylation in the regulation of gene expression in CH and point to potential therapeutic targets, including the modulation of DNA methylation and non-coding RNAs, to manage the progression of CH.

Protein methylation and cardiac hypertrophy

Histone lysine methylation (HKM) is another common type of protein methylation, referring to the transfer of 1–3 methyl groups from SAM to lysine residues catalyzed by lysine methyltransferase and forming mono (Me1), di (Me2), or tri (Me3) methylated derivatives [122]. HKM mainly acts in promoting the opening of chromatin, increasing DNA accessibility, and initiating DNA transcription and RNA synthesis [123–124]. Multiple studies have demonstrated that HKM has a key function in the regulation of ventricular remodeling [125–126]. El-Nachef *et al.* [127] proved that H3K9me3 is necessary for cardiomyocytes cessation of the cell cycle and final stages of differentiation in adult cardiomyocytes. The loss of H3K9me3 in the adult heart prevents and reverses the exit of the permanent cell cycle and allows hypertrophic growth of the adult heart. G9a (also termed panchromatic histone lysine methyltransferase 2, EHMT2) is a histone methyltransferase (HMT), pertaining to the SET domain protein family, which mainly mono- or di-methylates K9 (H3K9me1 and H3K9me2) [128]. Studies have shown that G9a exerts a protective role in early myocardial

hypertrophy by repressing pro-hypertrophic gene expression, thereby mitigating the progression of pathological CH [129]. Moreover, the nuclear SET domain 2 (NSD2) is proved to promote ventricular remodeling governed by the regulation of H3K36me2 [130].

In recent years, researchers have revealed the impact of PRMTs in CH, in addition to HKM. Chen *et al*. [131] indicated that PRMT5 specifically interacts with GATA4 and negatively regulates CH, at least in part, through GATA4 arginine methylation. Cai *et al*. [132] then showed that Prmt5-induced H4R3me2s promoted β-catenin degradation by transcriptionally upregulating Filip1L expression, thereby improving CH. The lack of Prmt5 and the ensuing inhibition of H4R3me2s may promote the progression of pathological CH. Furthermore, a cardiac-enriched lncRNA, Chaer, which engages with the EZH2 subunit enhancer of PRC2, is necessary for CH [133]. To address these findings, larger studies are required to analyze the contribution of different histone modifications to the pathogenesis of CH.

m^{6}A RNA methylation and cardiac hypertrophy

A study determined the significance of mRNA m^{6}A methylation in the heart in a cell model of cardiomyocyte hypertrophy and a mouse model of CH [134]. The investigators discovered a significant increase in m^{6}A methylation in CH mice relative to sham-operated control counterparts. Knockdown of METTL3 expression inhibited cardiomyocyte hypertrophy under stress, while overexpression of METTL3 facilitated cardiomyocyte hypertrophy both *in vitr*o and *in vivo*. Moreover, the elevation of mRNA m^{6}A methylation orchestrated by METTL3 induced compensatory myocardial hypertrophy, while the decrease in m^{6}A caused abnormal cardiomyocyte remodeling and dysfunction [134]. Xu *et al*. [135] also found that m^{6}A reader YTHDF2 prevents CH by employing Myh7 mRNA decoy in an m^{6}A-dependent manner. Golubeva *et al*. [136] further confirmed that YTHDF2 is crucial for maintaining cardiac homeostasis. The absence of YTHDF2 results in pathological accumulation of MYZAP protein and induces CH, fibrosis, and dysfunction in mice. Another study revealed ALKBH5 as a novel factor in cardiomyocyte hypertrophy. ALKBH5 exhibits elevated expression in both cardiomyocyte hypertrophic responses induced by phenylephrine (PE) *in vitro* and *in vivo* pathological CH caused by transverse aortic coarctation (TAC) or high-fat diet (HFD). By activating the JAK2/STAT3 signaling pathway, ALKBH5 facilitates m^{6}A demethylation on Stat3 mRNA, which promotes the phosphorylation and nuclear translocation of STAT3. Consequently, this boosts hypertrophic genes transcription (e.g. Nppa) and contributes to the hypertrophic growth of cardiomyocytes [137]. Together, these findings emphasize the complex role of m^{6}A methylation in regulating CH and suggest that targeting the m^{6}A modification machinery might be an effective therapeutic avenue for combating CH and related pathologies.

Heart failure

HF is not a standalone disease entity but rather the culminating stage manifestation of heart disease progression. It ranks among the primary risk factors affecting the survival rate of patients with cardiovascular disease [138–139]. Diastolic and systolic insufficiencies are the main pathological characteristics of HF with dysfunction of the sarcoplasmic reticulum (SR) calcium ATPase as a causal factor [140–141]. Molecularly, SERCA2a is the key subtype of myocardial SR calcium ATPase, which is essential in the management of myocardial cell calcium homeostasis thereby myocardial relaxation and contraction [142–144]. As a key intracellular Ca^{2+} management protein, SERCA2a normally works by discharging calcium ions from the cytoplasm into the SR against the concentration gradient to maintain intracellular Ca^{2+} homeostasis. However, in many cardiac disorders including HF, the expression of SERCA2a is substantially downregulated, and SERCA2a replacement has been commonly accepted as an emerging approach for the management of HF [145–147]. Evidence exists for the role of methylation modifications in deregulation of SERCA2a in the setting of HF.

DNA methylation and heart failure

Movassagh *et al*. [148] used quantitative real-time PCR (qRT-PCR) and immunoprecipitation to study methylation of the genomic DNA of human left ventricular tissue (HF patients vs. healthy control subjects) and found that the 5′-end DNA methylation levels of three different genes (*AMOTL2*, *ARHGAP24*, and *PECAM1*) in HF patients were negatively associated with their expression levels.

DCM is one of the common cardiac diseases that are deemed to degenerate into HF [149]. Although many genetic mechanisms are known to cause DCM, the latest research documents that the onset age, manifestations, and clinical course of the disease in the population show significant differences, and this phenomenon cannot be explained by genetics. Haas *et al*. [150] examined the differences in DNA methylation on lymphocyte antigen 75 (*LY75*), tyrosine kinase cell surface receptor HER3 (*ERBB3*), homeobox gene B13 (*HOXB13*), adenosine receptor A2A (*ADORA2A*), and other unknown functional genes. Mass spectrometry and bisulfite sequencing revealed that DCM patients are related to abnormal DNA

methylation and deregulated expression of *LY75* and *ADORA2A* genes. Kao *et al*. [151] reported that tumor necrosis factor-α (TNF-α) promotes the expression of DNMT, increases the methylation modifications of the SERCA2a promoter region, reduces the expression of SERCA2a mRNA and protein, results in excessive intracellular Ca^{2+} accumulation, and contributes to the development of HF. Another investigation by Kulkarni *et al*. [152] revealed that in an animal model of HF, the degree of methylation in the *PITX2c* gene promoter region increased, accompanied by enhanced activity of methyltransferase (DNMT1) and decreased expression of *PITX2c* gene. According to these studies, DNA methylation is among the molecular and epigenetic mechanisms underlying HF, and thus inhibition of DNA methylation might be a valid strategy for HF management.

Protein methylation and heart failure

The meticulous regulation of myocardial transcription is essential for adult homeostasis. The coordinated gene expression is modulated by DNA binding transcription factors and co-regulatory proteins [153]. During cardiac development, the activities of a range of write and erase histone methylation in the heart change the chromatin architecture and gene function through posttranslational modification of histone tails [154]. Recent studies have demonstrated changes in histone methylation across the whole genome in HF [80,155].

Stein *et al*. [156] pointed out that H3K4me3 is essential for Kcnip2 expression, which encodes the Kv channel interacting protein 2 necessary for cardiac repolarization. The Kcnip2 expression decreases in HF and is related to the decrease of H3K4me3 on the promoter. Beltran-Alvarez *et al*. [157] also determined that R526 methylation is the main posttranslational modification of either Nav1.5 arginine or lysine residue, and for the first time revealed the posttranslational modification of Nav1.5 purified from human heart tissues with end-stage HF.

The reactivation of fetal genetic programs in human HF is related to the epigenetic regulation of ANP and BNP promoter regions [158]. Regardless of the nuclear export of histone deacetylase 4 (HDAC4), the activation of ANP and BNP does not depend on elevated histone acetylation within these promoter regions, while HDAC4 controls the dynamic demethylation of lysine 9 of histone 3 (H3K9) and the dissociation of heterochromatin protein 1 (HP1) from the promoter region. This study by Mathias *et al*. [159]expands our grasp of the dynamic epigenetic regulatory mechanisms of human HF and could aid in developing new therapeutic targets.

m^6A RNA methylation and heart failure

The study of Mathiyalagan *et al*. [160] uncovered that the m^6A methylation levels of mRNAs in HF are markedly increased compared to those in normal heart for the first occasion. The expression of m^6A demethylase-FTO in human and mouse myocardium decreases in HF, resulting in heightened mRNA methylation and diminished SERCA2a expression. Overexpression of demethylase FTO diminishes the level of m^6A in the heart, which is accompanied by reduced myocardial fibrosis and enhanced angiogenesis. Apparently, m^6A demethylase FTO exerts a cardioprotective effect by upregulating the expression of SERCA2a in HF. Further studies have found that WTAP is implicated in development of the heart and exhibits reduced expression in both humans and mice with HF [161]. WTAP loss in the heart diminishes chromatin accessibility within the promoter regions of Mef2a (myocyte enhancer factor 2a) and Mef2c, resulting in a decline in mRNA and protein levels of these genes, along with a reduction in expression of their target genes. WTAP is necessary for the development and function of heart by sustaining chromatin accessibility of heart-related genes. Dysregulation of epigenetic modifications and atypica gene expression are pivotal processes of HF. Further research is necessary to enrich and deepen the comprehension of m^6A methylation functions in HF and the underlying mechanisms.

Atherosclerosis

Atherosclerosis is a sustained inflammatory disease of the coronary arteries. In recent years, multiple investigations have confirmed that epigenetic regulation such as DNA methylation and histone modification is a crucial mechanism in the development of atherosclerosis [163–164]. Though the relationship between RNA methylation, especially the m^6A modification of RNA, and atherosclerosis has not been fully delineated, findings from existing literature have highlighted the significance of RNA methylation in controlling atherosclerosis.

DNA methylation and atherosclerosis

Available studies indicate that epigenetic modifications of the genome render dysregulation of atherosclerosis-related genes, which has a major impact on the formation and progression of atherosclerosis [165–167].

A study reported in 1999 by Newman *et al*. [168] shed the first light on DNA methylation and atherosclerosis by showing that high levels of homocysteine in atherosclerotic patients inhibit the conversion of the methyl donor SAM, cause DNA hypomethylation accompanied by enhanced proliferation of vascular smooth muscle cells and fiber deposition, thereby

accelerating atherosclerosis. Subsequently, Hiltunen *et al*. [169] confirmed that DNA hypomethylation in neovascular intimal induced by damage exacerbates atherosclerosis. In a clinical trial with a 5.8-year follow-up of 286 individuals, Kim *et al*. [170] reported that global genomic DNA methylation in peripheral blood leukocytes was positively correlated with the incidence of CVDs (MI and stroke) and its contributing factors (hypertension, diabetes, and obesity). In addition, it has been documented that in patients with atherosclerosis, the CpG islands within the promoter sequences of the estrogen receptor-α (ER-α) gene are hypermethylated. ER-α is a growth inhibitory factor activated by estrogen, which has the protective effect of preventing the proliferation and migration of smooth muscle cells, as well as the generation of new intima. Huang *et al*. [171] showed that homocysteine in plasma is related to abnormal methylation of ER-α gene. High levels of homocysteine can cause hypermethylation of ER-α gene and proliferation of arterial wall vascular smooth muscle cells, and fall-off of arterial endothelial cells, which accelerates atherosclerosis. The mechanism may be related to vascular endothelial dysfunction due to high homocysteine, reduced NO-mediated vasodilation, and oxidative stress. Laukkanen *et al*. [172] indicated that the CpG methylation of the extracellular superoxidase (ec-sOD) gene promoter in the aortic arch of atherosclerotic rabbits and the percentage of 5mC DNA methylation in the overall genome are substantially decreased. The investigation by Zhu *et al*. [173] demonstrated that compared with contractile smooth muscle cells, the level of MCT3 in proliferative smooth muscle cells and its participation in lactic acid transport are significantly decreased. The methylation level of CpG island in the second exon region of the *MCT3* gene correlates with the degree of atherosclerosis. Liu *et al*. [174] confirmed the regulatory impact of the promoter methylation on the translation of *ALOX15* gene in cultured human monocytes, T lymphocytes and tumor cells.

Protein methylation and atherosclerosis

The vascular endothelium is fundamental in maintenance of homeostasis of the cardiovascular system. Numerous studies have revealed that there is a close relationship between vascular endothelial dysfunction and the onset and progression of cardiovascular diseases, especially hypertension, atherosclerosis, and CHD [175]. Nitric oxide (NO), which is generated by the catalysis of L-arginine nitric oxide synthase (NOS), is the most important and well-known endogenous vasodilator factor, and one of the most important mediators to maintain vascular endothelial function [176]. Studies have shown that methyltransferases can catalyze the arginine site of the substrate to produce asymmetric dimethylarginine (ADMA), a potent endogenous NOS inhibitor. ADMA not only competitively inhibits NOS activity, reducing the NO production, but also induces "NOS decoupling," increasing the generation of oxygen free radicals, and subsequently causes vascular endothelial dysfunction [177–178]. ADMA has now been deemed as a new factor posing risks to cardiovascular disease.

Hypercholesterolemia is a recognized contributor to plaque formation and provides the low-density lipoprotein (LDL) cholesterol which is the cornerstone of lipopathy [179]. Evidence indicates a relationship between ADMA concentration and plasma LDL [180], and subjects with hypercholesterolemia show a lower L-arginine/ADMA ratio [181]. Ahmad A *et al*. [182] pointed out that patients suffering from early coronary atherosclerosis alongside endothelial dysfunction in the coronary arteries is independently related to plasma ADMA concentration. ADMA levels in atherosclerotic patients are significantly increased, but L-arginine levels are similar to subjects with normal endothelial function. Carotid artery intima-media thickness (IMT) is also commonly employed as an indicator for the evolution of atherosclerosis. Numerous studies have shown that, regardless of other risk factors in healthy participants, there is a strong correlation between elevated IMT and the elevation of ADMA [183–184].

Additionally, Wierda *et al*. [185] provided evidence that treatment with an anti-EZH2 antibody reduced the number of nuclei labeled with H3K27me3 in atherosclerotic plaques. EZH2 is capable of driving the atherosclerosis progression by modulating the transcription of ATP-binding cassette transporter A1 (ABCA1) [186]. Knockdown of GAS5 may promote the reverse cholesterol transport, mitigate lipid accumulation, and ultimately impede the advancement of atherosclerosis by diminishing the EZH2's transcriptional repression of ABCA1 due to histone methylation [187].

m^6A RNA methylation and atherosclerosis

Wu *et al*. [188] reported that the m^6A level in leukocytes but not the ^5mC level is declined as the plaque size and thickness of carotid artery increased in 207 atherosclerosis patients versus 142 controls matched for age and sex. Both the levels of leukocyte m^6A and serum LDL are related to the increase in plaque size and thickness of carotid artery. Mechanically, ox-LDL activates the translocation of HIF1α into the nucleus. Nuclear HIF1α binds to the ALKBH1-demethylated MIAT promoter and transcriptionally increases the expression of this lncRNA. Evidently, elevation of ALKBH1 expression in endothelium and leukocytes reduces m^6A level, acknowledged as a unique and sensitive biomarker for the advancement of atherosclerosis. Jian *et al*. [189] demonstrated that

METTL14 elevates the expression of FOXO1 through the enhancement of m^{6}A modification, which triggers the inflammatory response of endothelial cells and the formation of plaque in atherosclerosis. Reduced levels of METTL14 inhibits endothelial inflammatory processes and atherosclerosis. These findings suggest that METTL14 has the potential to be targeted for the clinical management of atherosclerosis. Zhang *et al*. [190] also provided further evidence for the role of METTL14 by displaying that METTL14 increases the pri-miR-19a m^{6}A modification and the formation of mature miR-19a to promote the process involving proliferation and invasion of endothelial cells in atherosclerosis. Moreover, Gong *et al*. [191] reached a conclusion that the METTL14-mediated m^{6}A modification of another lncRNA ZFAS1/RAB22A plays an essential role in atherosclerosis.

Emerging evidence indicates that m^{6}A modification is not only pivotal in atherosclerotic endothelial cells but also regulates inflammatory reactions orchestrated by macrophages. Li *et al*. [192] demonstrated that METTL3-dependent m^{6}A modification on Braf mRNA stimulates macrophage inflammatory responses and accelerates atherosclerosis in mice. Zheng *et al*. [82] reported that METTL14 regulates inflammation of macrophages via the NF-κB/IL-6 signaling cascade in atherosclerosis. Another study identified the RNA-binding protein Matrin-3 (Matr3) functioning as a suppressor of macrophage inflammation. Matr3 modulates the assembly of the METTL3-METTL14 complex, thereby inhibiting m^{6}A-driven mRNA decay, reducing signals promoting inflammation, and diminishing mitogen-activated protein kinase (MAPK) activation induced by ox-LDL [193]. Yu *et al*. [194] also found that leonurine activates the autophagic process in foam cells and metabolic restructuring, improving atherosclerosis through METTL3-mediated regulation of the stability of AKT1S1 mRNA. m^{6}A RNA methylation appears to have multifaceted roles in atherosclerosis, and targeting m^{6}A methylation may hold therapeutic promise in controlling the progression of atherosclerosis.

Crosstalk between different methylation modifications

The intricate interaction between DNA, RNA, and protein methylation is an emerging and critical area of research within the field of epigenetics and gene regulation. DNA methylation, protein methylation, and m^{6}A modification collectively form a complex epigenetic network through shared metabolic substrates, coordinated regulation of gene expression, and dynamic interactions. Studies have demonstrated that DNA methylation does not operate in isolation but also interacts with histone modifications [195]. For example, the trimethylation of histone H3 at lysine 36 (H3K36me3) has been shown to facilitate DNA methylation by promoting the binding of DNMT3 family enzymes to target chromatin regions. Conversely, histone H3K4 methylation can inhibit DNMT3 activity at promoter regions. When histones at these loci are unmodified, the ADD domain of DNMT3a recognizes them, indicating that specific histone marks, such as H3K4 methylation, can directly affect the activity of DNMT enzymes, leading to gene activation or repression [196–198]. Additionally, research has shown that at certain CpG sites, there is an inverse relationship between m^{6}A methylation and DNA methylation. This indicates that while mRNA may be stabilized and undergo proper translation dynamics due to m^{6}A methylation, DNA methylation also influences or reflects these changes at the transcriptional level [199]. Furthermore, the presence of certain microRNAs that regulate DNMTs points to a mechanism by which RNA methylation may influence DNA methylation patterns, further complicating the interplay between these modifications [200–201].

Briefly, the crosstalk between DNA, RNA, and protein methylation is vital for a comprehensive understanding of gene regulation. It represents a multifaceted regulatory network where modifications to one molecule can significantly impact the behavior of others. This interconnected system plays a crucial role in shaping transcriptional outcomes and cellular functions. A thorough understanding of the research progress regarding these three methylation modifications in the context of cardiovascular diseases, coupled with the integration of multi-omics data, will be essential for comprehensively analyzing the mechanisms and pathways involved in these epigenetic networks. Such insights will be critical for the development of novel therapeutic targets for cardiovascular diseases.

DNA methylation and protein methylation

Within the realm of disease, DNA methylation and protein methylation often occur simultaneously [8]. For instance, in breast cancer, both hypermethylation of tumor suppressor genes and alterations in histone methylation patterns are closely associated with malignant process [202–203]. Likewise, in diabetic nephropathy, a common complication of diabetes, alterations in DNA methylation are observed alongside modifications in histone marks [204].

The crosstalk between DNA methylation and protein methylation has become a major focus of research. A key discovery in this area is that protein methylation can influence the recruitment and activity of DNMTs [205]. For example, the trimethylation of histone H3 at lysine 36 (H3K36me3) has been shown to facilitate DNA methylation by promoting the binding of DNMT3 enzymes to target chromatin regions [197]. Conversely, histone H3K4 methylation can inhibit DNMT3 activity at

promoter regions. When histones at these loci are unmodified, the additional domain (ADD) of DNMT3a recognizes them, indicating that specific histone marks, such as H3K4 methylation, can directly affect the activity of DNMT enzymes, leading to gene activation or repression [206]. This highlights how active transcription, marked by specific histone modifications, can guide the establishment of DNA methylation. Moreover, DNA methylation itself can influence protein methylation patterns. By regulating the expression and activity of various histone methyltransferases and other chromatin-remodeling proteins, DNA methylation induces changes in histone modifications, which in turn affect protein methylation dynamics [196].

For example, in colorectal cancer, low-dose DNMT inhibitors (DNMTi), such as DAC, induce DNA hypomethylation but simultaneously trigger compensatory increases in EZH2-dependent histone H3K27me3, leading to gene silencing. When DNMTi is combined with specific EZH2 inhibitors, like TAZ, this compensatory mechanism is suppressed. As a result, calcium signaling pathways (NFAT:AP-1) are activated, viral mimicry effects are enhanced, and immune responses are boosted, ultimately inhibiting tumor growth [207]. Furthermore, Jackson *et al*. [208] demonstrated that embryonic stem (ES) cells lacking Dnmt3a and Dnmt3b exhibit severe DNA hypomethylation, impairing their ability to initiate differentiation upon withdrawal of leukemia inhibitory factor (LIF). While these cells remain viable and retain stem cell markers like alkaline phosphatase and Oct4, they fail to differentiate into hematopoietic or cardiomyocyte lineages. Interestingly, hypomethylated Dnmt cells show increased histone acetylation, particularly at histone H4 lysine-5, which correlates with differentiation arrest. However, restoring DNA methylation through Dnmt3a or Dnmt3b transgenic rescue reverses this acetylation and allows differentiation to proceed. Another study by Xu *et al*. [209] found that the enzymes Gcn5 and HDAC1 regulate histone acetylation at the promoter regions of GATA4 and Nkx2.5, while G9A and DNMT-1 control histone methylation and DNA methylation. These modifications are essential for the expression of key genes that drive cardiomyocyte differentiation. Notably, Gcn5 directs histone acetylation, replacing G9A and modifying H3K9 methylation at the GATA4 promoter. This modification reduces DNA methylation and promotes GATA4 expression, which is a critical factor in cardiomyocyte differentiation.

In summary, the interplay between DNA methylation and protein methylation is a crucial aspect of epigenetic regulation. Understanding this crosstalk is vital, as it offers valuable insights into how cells maintain gene expression stability and respond to environmental cues. Although research on the interplay between DNA methylation and protein methylation in disease remains limited, further exploration of these mechanisms holds significant potential for developing therapeutic strategies that target epigenetic modifications in diseases such as cardiovascular disorders.

DNA methylation and RNA methylation

Recent studies have shed light on the complex and intertwined interplay between DNA and RNA methylation, revealing their crucial role in regulating cell behavior and disease pathology. RNA methylation patterns can be a direct consequence of DNA methylation status, where methylated DNA influences the recruitment of RNA methyltransferases, subsequently modifying RNA transcripts. Conversely, changes in RNA methylation can exert feedback effects on gene expression at the DNA level [210–211]. For instance, studies by Melnik *et al*. [212] demonstrated that milk-derived miRNA-29 targets DNMT1, DNMT3A, and DNMT3B, leading to reduced DNA methylation, specifically at the *FTO* gene. This reduction in DNA methylation at CpG sites within the FTO promoter region enhances FTO expression, which in turn influences m^6A methylation dynamics and promotes transcriptional activity linked to adipogenesis and obesity. Additionally, another study highlighted the crosstalk between m^6A and DNA methylation, where ALKBH5-mediated hypomethylation of the m^6A mark on DNMT3B RNA resulted in increased DNMT3B levels, which subsequently caused hypermethylation of the E4F1 promoter. This hypermethylation inhibits E4F1 expression and contributes to nucleus pulposus cell (NPC) senescence [199].

The interaction between DNA and RNA methylation is also evident in the function of microRNAs (miRNAs), which regulate gene expression post-transcriptionally [213]. Dysregulation of miRNAs through methylation processes has been implicated in various pathological conditions, suggesting that these modifications act in concert to regulate cellular responses in disease [214]. Downregulation of miR-152 in glioma tissue has been linked to DNA hypermethylation, regulated by DNMT1. This interaction suggests that miR-152 expression influences DNA methylation and, in turn, its own regulation [215]. Furthermore, miR-29b regulates global DNA methylation by targeting DNMTs, acting both as a target and a key effector of DNA methylation. In patients with congenital heart disease (CHD), the expression of miR-29b-3p is negatively correlated with DNMT expression in cardiac tissue. Moreover, miR-29b-3p inhibitors can improve hypomethylation-related malformations in zebrafish myocardial tissue and restore DNA methylation patterns in cardiomyocytes, leading to enhanced cardiomyocyte proliferation and normalized gene expression. These findings suggest a bidirectional

regulatory relationship between miR-29b-3p and DNMTs in cardiomyocytes, supporting the potential for miRNA-based epigenetic therapy to normalize cardiomyocyte function [216].

The interplay between DNA and RNA methylation forms a dynamic and essential regulatory network that governs gene expression, cellular processes, and disease outcomes. Gaining a deeper understanding of the mechanisms driving this crosstalk holds significant promise for the development of innovative therapeutic strategies targeting these epigenetic pathways, especially in diseases such as cancer, cardiovascular conditions, and neurological disorders.

Protein methylation and RNA methylation

Evidence suggests that protein methylation can influence the RNA methylation process. Histone methylation contributes to chromatin structure and function, determining the transcriptional accessibility of RNA polymerase and thereby affecting the exposure of RNA to methyltransferases. In turn, RNA modifications can influence the fate and function of proteins. The m^{6}A modification of RNA can determine its interaction with reader proteins, which may include those that further regulate protein activity through subsequent post-translational modifications, thus forming a feedback loop between RNA and protein methylation [217–218]. Research on the impact of these modification crosstalks on diseases is continuously expanding.

Histone H3 trimethylation at lysine 36 (H3K36me3) is a hallmark of transcriptional elongation and plays a key role in guiding m^{6}A deposition on RNA. Studies have shown that m^{6}A is enriched near H3K36me3 peaks, and depletion of H3K36me3 reduces m^{6}A levels, indicating a strong correlation between these two modifications. In mouse ES cells, loss of H3K36me3 decreases m^{6}A abundance, resulting in increased stemness and altered gene expression regulation [219]. Furthermore, studies have shown that METTL3 can modulate the localization of the methyltransferase SETDB1 (also known as ESET or KMT1E) and its regulator TRIM28 (KAP1) on intracisternal A particle (IAP), suggesting that METTL3 catalyzes m^{6}A modification to recruit histone methyltransferase complexes, enhancing heterochromatin formation. These findings highlight the critical role of METTL3-mediated m^{6}A modification in regulating heterochromatin and its interplay with histone methylation in maintaining genomic stability in stem cells [220]. Additionally, Wang *et al*. [221] indicated that PRMT3 mediates the arginine methylation of METTL14, influencing its function and stability. Depletion of PRMT3 increases METTL14 levels, which in turn regulates m^{6}A modification of GPX4 mRNA. This upregulation enhances the sensitivity of endometrial cancer cells to ferroptosis by promoting GPX4 mRNA degradation, intensifying lipid peroxidation, and providing a potential strategy to overcome chemotherapy and radiotherapy resistance. In cardiovascular diseases, Zhen *et al*. [222] found that lysine acetyltransferase 2A (Kat2a) expression was upregulated in dilated cardiomyopathy (DCM), accompanied by reduced m^{6}A modification of Kat2a mRNA. The demethylase Alkbh5 decreased m^{6}A methylation on Kat2a mRNA, leading to its upregulation. Kat2a, in turn, promotes the expression of transferrin receptor (Tfrc) and heme oxygenase 1 (Hmox1) by increasing H3K27ac and H3K9ac enrichment at their promoters, driving ferroptosis in DCM. Additionally, Arcidiacono *et al*. [223] showed that METTL3 depletion in specific cardiac regions was associated with increased histone marks, such as H3K4me2 and H3K9me3, suggesting an interplay between RNA methylation and histone modifications that may influence cardiac gene regulation. Together, growing evidence emphasizes the intricate connection between protein and RNA methylation. These findings underscore the importance of understanding their interplay in disease pathogenesis and highlight the potential of therapeutic strategies targeting these modifications in cardiovascular diseases.

Clinical trials targeting methylation

With the continuous deepening of methylation research, clinical trials targeting methylation have been gradually launched in multiple disease areas. Alterations in DNA methylation occur during the early stages of carcinogenesis [224], rendering methylated ctDNA biomarkers an attractive approach for cancer screening. In cancer, clinical trials related to methylation mainly focus on cancer screening [225–228], early diagnosis of cancer [229–230], and prediction of efficacy and prognosis [231–233].

While in the field of cardiovascular disease, methylation-based clinical trials have primarily focused on validating diagnostic markers and developing risk prediction models (Table 1). Since 2010, advancements in DNA methylation chip technology have paved the way for new studies. Fiorito *et al*. [234] conducted epigenome-wide association studies (EWAS) and found that the methylation of genes involved in one-carbon metabolism and the homocysteine pathway, including those related to vitamin B12 metabolism, cystathionine-β-synthase, transaminase, and oxidative phosphatase activity, was negatively correlated with B vitamins intake. Additionally, hypermethylation of these genes in peripheral blood leukocytes of MI patients was linked to an increased risk of cardiovascular disease. Ek *et al*. [235] discovered that growth differentiation factor 15 (GDF-15) was highly expressed in cardiomyocytes of MI patients.

Table 1 Potential epigenetic targets and ongoing clinical trials in cardiovascular diseases

Category	Epigenetic target/marker	Related disease	Mechanism/role	Phase/type of study	References
DNA methylation	Vitamin B_{12}, CBS, transaminase, oxidase methylation	MI	Hypermethylation in leukocytes linked to increase MI risk	Observational cohort study	[234]
	GDF-15 methylation	MI	Expression level correlated with DNA methylation in peripheral blood	Clinical biomarker study	[235]
	Zinc Finger Homeobox (cg07786668), SMARCA4 (cg17218495)	MI	DNA methylation significantly associated with MI independent of risk factors	Epigenome-wide Association study	[236]
	Multiple DMPs	CHD	Blood DNA methylation signatures linked to CHD beyond traditional risk factors	Multi-cohort analysis	[237]
	EAA	Atherosclerosis	Accelerated epigenetic aging predicts future risk	Longitudinal cohort study (CARDIA)	[238]
	PCSK9 (CRISPR-dCas9–DNMT3A/3L-KRAB fusion)	Familial hypercholesterolemia	Permanent, reversible silencing of PCSK9; ~70% LDL-C reduction in NHPs	Phase I clinical trial for safety and efficacy	[239]
	PCSK9 (Chroma Medicine EE platform)	Hypercholesterolemia	Durable single-dose silencing; ~68% LDL-C reduction in NHPs	Preclinical to early clinical pipeline	[240]
Protein methylation	PRMT4/CARM1	MI	PRMT4 promotes apoptosis	Preclinical study	[103]
	PRMT5	Acute MI, stable CAD	PRMT5 linked to AMI risk	Clinical biomarker study	[104]
	EZH2 (H3K27me3 writer)	Atherosclerosis	MALAT1–EZH2 axis promotes apoptosis/inflammation; represses ABCA1	Preclinical study	[185–186]
RNA m^6A methylation	METTL3 (m^6A writer)	MI, CH	Promote apoptosis, inflammation, endothelial dysfunction	Preclinical study	[113,134]
	ALKBH5 (m^6A eraser)	MI, peripheral arterial disease	Stabilizes ErbB4, WNT5A mRNAs; enhances angiogenesis	Preclinical study	[114–115]
	FTO (m^6A eraser)	HF	Reduces m6A, restores SERCA2a expression, cardioprotective	Preclinical study	[160]
	METTL14 (m^6A writer)	Atherosclerosis	METTL14 elevates the expression of FOXO1; METTL14 increases the formation of mature miR-19a	Preclinical study	[189–190]
	WTAP (m^6A writer complex)	HF	WTAP is reduced in humans with HF	Preclinical study	[161]

They found that the expression level of GDF-15 in peripheral blood cells correlated with its methylation, showing significant differences between MI patients and controls. Nakatochi *et al*. [236] identified that methylation of the Zinc Finger Homeobox gene cg07786668 and the SMARCA4 gene cg17218495 remained significantly associated with MI, even after adjusting for traditional cardiovascular risk factors. These large-scale epigenomic studies have identified several DNA differential methylation sites associated with CHD and/or MI, providing valuable insights into the complex molecular mechanisms underlying these diseases. In further cohort studies, a multi-cohort analysis using high-dimensional multivariate models evaluated blood DNA methylation (DNAm) in 2321 American Indian adults and identified 505 differentially methylated positions (DMPs) associated with CHD in the StrongHeart study. These DMPs were then evaluated across other cohorts, including the Women's Health Initiative, the Framingham Heart Study, and the Atherosclerosis Risk in Communities Study, revealing common DMPs across multiple populations. Many of these common DMPs marked genes with well-established links to cardiovascular disease, indicating that blood DNAm is associated with CHD beyond traditional cardiovascular risk factors and exhibits complex epigenomic patterns across different populations [237]. Additionally, in a CARDIA study tracking DNA methylation patterns in young individuals using the Hannum and Horvath epigenetic clocks, it was found that epigenetic age acceleration (EAA) was significantly associated with future risk of atherosclerosis (HR = 1.32, $P < 0.001$) [238]. This promising finding is being expanded to a cohort of 100 000 individuals to further refine the prediction model. Building on the expanding body of biomarker and risk-prediction-oriented studies, CRISPR-based epigenetic editing has recently emerged as a transformative strategy and is now rapidly advancing

toward clinical translation. Among these approaches, a dCas9-based epigenetic editor fusing DNMT3A/3L with a KRAB transcriptional repression domain has been engineered to achieve durable silencing of PCSK9 without introducing permanent DNA sequence alterations. In transgenic mice and non-human primates (NHPs), a single lipid-nanoparticle (LNP) infusion produced near-complete PCSK9 suppression, approximately 90% reductions in circulating PCSK9 protein, and ~70% lowering of LDL-cholesterol (LDL-C), with effects lasting ⩾ 1 year. Importantly, the silencing was also shown to be reversible upon activation of a targeted demethylase [239–240]. These preclinical data provide strong mechanistic and pharmacological rationale for the first-in-human evaluation of CRISPR epigenetic editors. Complementary independent programs reinforce this trajectory. For instance, Chroma Medicine company has reported NHP studies using a PCSK9-targeted epigenetic editor, which achieved ~84% reductions in PCSK9 and ~68% reductions in LDL-C after a single administration at clinically relevant exposure levels, thereby strengthening the translational readiness of this approach for cardiovascular indications. For contextual comparison, non-epigenetic CRISPR gene-editing strategies have already produced first-in-human LDL-C-lowering outcomes. Notably, base-editing therapies (VERVE-101 and VERVE-102) that permanently inactivate hepatic PCSK9 have demonstrated dose-dependent, durable reductions in LDL-C in early clinical cohorts, with decreases ranging from ~39%–55% for VERVE-101 to ~53% on average (and up to ~69% at higher doses) for VERVE-102 [242,243]. Although mechanistically distinct from epigenetic silencing, these data highlight the overall clinical tractability of one-time, liver-directed CRISPR therapies targeting PCSK9.

Together, these studies underscore the immense potential of methylation research. A deeper understanding of the mechanisms of cardiovascular disease methylation and the interactions between various methylations could not only enhance risk prediction models for cardiovascular diseases but also pave the way for new therapeutic strategies targeting epigenetic modifications.

Conclusions and perspectives

Epigenetics represents a fundamental and essential complement to the fundamental principles of molecular biology, which outlines the process of genetic information flow in a straightforward manner from DNA to RNA to protein. This conveys that genetic information can be manipulated by genomic and mRNA modifications to achieve more exact and adaptive expression, with the alterations in gene expression brought about by these modifications being heritable. Among the diverse forms of epigenetic modifications, methylations, including DNA methylation, RNA methylation, and protein methylation, serve a crucial function in controlling gene expression at various levels (chromatinic, transcriptional, post-transcriptional, and translational) across a range of physiologic functions and pathological conditions. To date, DNA and protein methylation in cardiovascular diseases has been extensively studied; yet, studies on

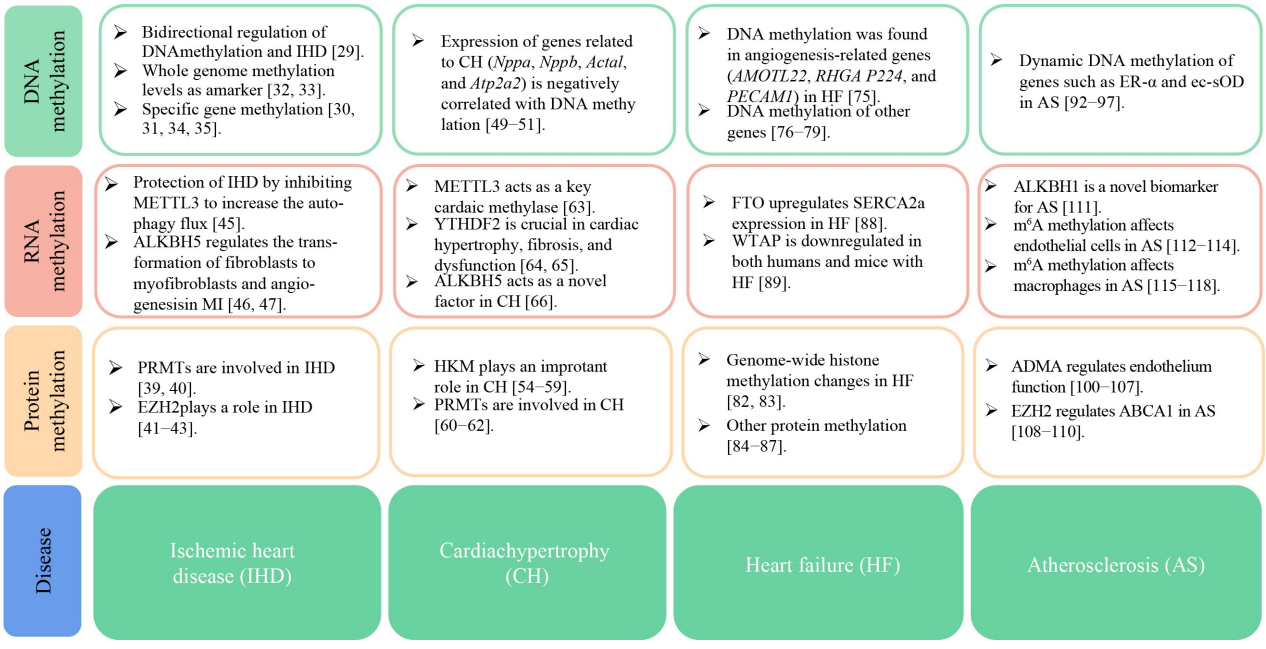

Fig. 5 Methylation modifications in cardiovascular disease. The mechanisms of DNA, RNA, and protein methylations in cardiovascular diseases in recent years including IHD, cardiac hypertrophy, HF, and atherosclerosis.

RNA methylation modifications in cardiovascular disease are still sparse (Fig. 5). Although the cross-regulatory mechanisms of methylation modifications remain to be fully elucidated, accumulating evidence has confirmed their potential as therapeutic targets in cardiovascular diseases. Nonetheless, the available data as described in this review article have set the theme that methylation modifications are indispensable part of the regulatory network in the development of cardiovascular disease of various types. Further in-depth investigations are absolutely required for a more profound understanding of the precise mechanisms of methylation modifications, the interrelationship, crosstalk, and coordination between different methylation processes, and their exact biological function and pathophysiological role in cardiovascular disease. Such understanding will foster the development of innovative approaches to better prevent and intervene in cardiovascular diseases. Combining epigenomic, transcriptomic, proteomic, and metabolomic data sets will help uncover hierarchical relationships between methylation modifications and their downstream effects. For example, longitudinal studies using single-cell or spatial transcriptomics to track methylation changes during disease onset, progression, and recovery could reveal critical phases for intervention. Furthermore, methylation signatures in circulating free DNA or extracellular vesicles warrant validation as non-invasive diagnostic or prognostic tools. Machine learning algorithms could enhance predictive accuracy by integrating multimodal epigenetic data. Developing organoid models or patient-derived iPSCs will facilitate personalized screening of methylation-modulating therapies. Additionally, utilizing the CRISPR-Cas9 system for precise epigenetic editing and combining methylation-targeted drugs with existing therapies may further improve therapeutic efficacy.

In summary, methylation modifications represent a multifunctional regulatory layer in cardiovascular disease, offering unprecedented opportunities for diagnosis, risk stratification, and treatment. By addressing current limitations and leveraging cutting-edge technologies, future studies can translate these epigenetic insights into tangible clinical advances, paving the way for precision medicine in cardiovascular health.

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Compliance with ethics guidelines

Conflict of interests Yuan Lin, Jennifer Wang, Xin Liu, Yong Zhang, and Baofeng Yang declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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