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Histone Methylation Related Therapeutic Challenge in Cardiovascular Diseases

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The epidemic of cardiovascular diseases (CVDs) is predicted to spread rapidly in advanced countries accompanied by the high prevalence of risk factors. In terms of pathogenesis, the pathophysiology of CVDs is featured by multiple disorders, including vascular inflammation accompanied by simultaneously perturbed pathways, such as cell death and acute/chronic inflammatory reactions. Epigenetic alteration is involved in the regulation of genome stabilization and cellular homeostasis. The association between CVD progression and histone modifications is widely known. Among the histone modifications, histone methylation is a reversible process involved in the development and homeostasis of the cardiovascular system. Abnormal methylation can promote CVD progression. This review discusses histone methylation and the enzymes involved in the cardiovascular system and determine the effects of histone methyltransferases and demethylases on the pathogenesis of CVDs. We will further demonstrate key proteins mediated by histone methylation in blood vessels and review histone methylation-mediated cardiomyocytes and cellular functions and pathways in CVDs. Finally, we will summarize the role of inhibitors of histone methylation and demethylation in CVDs and analyze their therapeutic potential, based on previous studies.

Keywords: cardiovascular diseases, demethylation, methyltransferases, demethylases, histone-methylation

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INTRODUCTION

As a major trigger of mortality worldwide, the epidemic of cardiovascular diseases (CVDs) is predicted to spread rapidly in developing and developed countries along with the high prevalence of risk factors, including hypertension, diabetes, and obesity (1). In 2016, CVDs caused ∼17.9 million deaths globally (2). The mortality of CVDs worldwide is estimated to reach nearly 23.6 million in 2030 (3). Several risk factors, both genetic and behavioral, including diabetes, high blood pressure, high cholesterol, smoking, unhealthy nutrition, obesity, physical inactivity, aging, and arterial hypertension, account for the occurrence of CVDs (4). The clinical features of CVDs mainly include vascular inflammation, endothelial dysfunction, atherosclerosis, fibrosis, and thrombosis accompanied by multiple simultaneously perturbed pathways, such as cell death and acute/chronic inflammatory reactions (5).

The structural and functional abnormalities of the heart and blood vessels mainly cause CVDs. The heart is composed of several types of cells, mainly including cardiomyocytes and fibroblasts, and an intricate network of blood vessels made up of fibroblasts, connective tissues, smooth muscle cells, and endothelial cells [ECs; (6)]. Considering the complex composition,

the dysfunction of these cells in the heart and vasculature contributes to the pathogenesis of CVDs. CVDs might be triggered by multiple processes, such as mitochondrial dysfunction, reactive oxygen species formation, abnormal calcium homeostasis, deleterious phosphorylation signaling, proteostasis imbalance, dysregulated nutrient sensing, cellular senescence, stem cell exhaustion, genomic instability, telomere attrition, and epigenetic alterations (7, 8). With the rapid advance in biochemical, molecular, and high-throughput sequencing technologies, the dysregulated expression profiles of the human genome in CVD patients have focused on (9). However, dynamic alterations in the gene expression landscape can contribute to the progression of CVDs (10). The dynamic gene expression landscape is subject to different levels of regulation, including genetics, epitranscriptomics, transcriptomics, and epigenetics (11). Epigenetics provides the link between genetic programming and environmental influence that results in the expressed phenotype (12). Epigenetics plays a major role in the occurrence and progression of several CVDs, such as cardiac hypertrophy, heart failure, ischemic heart disease, aortic aneurysm, vascular calcification, and pulmonary hypertension, by mediating gene expression and cellular function (13). Furthermore, epigenetics implies the heritable alteration in the gene expression landscape without alterations in DNA sequence caused by the changes in nucleosome remodeling, which represents the architecture of chromatin and regulates the accessibility of DNA (14). The altered nucleosome remodeling is attributed to the interaction between the environment and the genome (15).

Preliminary studies have pointed to the complex association between CVDs and epigenetic modifications, including DNA methylation, histone modifications, and RNA-based mechanisms (16). Histone modification is the methylation, acetylation, ubiquitination, phosphorylation, SUMOylation, GlcNAcylation, carbonylation, and ADP-ribosylation of histones, H2A, H2B, H3, and H4 (17). Post-translational modifications (PTMs) in core histones effectively modulate the activation and inhibition state of downstream gene transcription (18, 19). For example, H3K4 methylation can activate the expression of α-MHC gene in the left ventricle (LV) compared with that in the right ventricle (RV) (20). Generally, PTMs can be added and removed by specific enzymes, including "writers," which add modifiers, and "erasers," which remove modifiers (21). Histone acetylation is added to lysine residues by histone acetyltransferases (HATs) and removed by histone deacetylases [HDACs; (22)]. The aberrant regulation of epigenetic regulators in PTMs is a predisposing factor for cardiac diseases (23). Considering the close involvement of epigenetics in the expression of genes associated with CVDs, the epigenetic mechanism and its critical role in modulating CVD progression should be determined (24). A better understanding of the modulatory mechanism in CVD development may contribute to the discovery of novel therapeutic targets to provide beneficial effects for patients. Pharmacologically targeting epigenetic modification for the treatment of CVDs has been developed and successfully tested in preclinical models.

Abbreviations: CVD, cardiovascular diseases; PTMs, post-translational modifications; LV, left ventricle; RV, right ventricle; HAT, histone acetyltransferase; HDAC, histone deacetylases; KMT, histone lysine methyltransferase; LSD, lysine-specific demethylase; HDM, histone demethylase; JHDM, Jumonji C-domain-containing family; SMYD, SET domain and MYND domain protein; JARID, Jumonji, and AT rich interactive domain 1D; FHL1, four-and-a-half LIM domains 1; TAC, transverse aortic constriction; EZH2, enhancer of zeste homolog 2; SMC, skeletal myocyte; UTX, ubiquitously transcribed tetratricopeptide repeat on chromosome X; LVH, left ventricular hypertrophy; MEF2C, myocyte-specific enhancer factor 2C; DMD, Duchenne muscular dystrophy; ROS, reactive oxygen species; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; EC, endothelia cell; NF-κB, nuclear factor kappa-B; VSMC, vascular smooth muscle cell; SET, Su(var)3–9, Enhancer of zeste, and Trithorax; MLL, mixed lineage leukemia protein; SETD7, SET domain containing 7; EHMT2/G9a, euchromatic histone-lysine N-methyltransferase 2; PRMT, protein arginine methyltransferase; DOT1L, DOT1 like histone lysine methyltransferase; WDR5, WD repeat-containing protein 5; KLF2, Krüppel-like factor 2; JMJD, Jumonji C domain-containing.

HISTONE METHYLATION MODIFICATION

Alterations at the epigenetic level that mediate chromatin structure are involved in the regulation of genome stabilization and cellular homeostasis (25, 26). In eukaryotic nuclei, DNA is wrapped around by four core histone proteins, namely, H2A, H2B, H3, and H4, which further forms nucleosomes and chromatin (27, 28). Histone modifications alter the structure of nucleosomes, regulate gene transcription, and mediate growth and disease pathogenesis (29, 30). The important and unique roles of these histone modifications have been reported by a number of studies (31, 32).

Histone methylation is an essential modification that can cause monomethylation (me1), dimethylation (me2), and trimethylation (me3) of several amino acids, thus directly affecting heterochromatin formation, gene imprinting, X chromosome inactivation, and gene transcriptional regulation (33). In general, lysine (Lys or K), arginine (Arg or R), and rarely histidine (His or H) are the most common histone methyl acceptors (30, 34, 35). Histone methylation only occurs at specific lysine and arginine sites of histone H3 and H4 (36). In histone H3, lysine 4, 9, 26, 27, 36, 56, and 79 and arginine 2, 8, and 17 can be methylated. By comparison, histone H4 has fewer methylation sites, in which only lysine 5, 12, and 20 and arginine 3 can be methylated (37, 38). However, the methylation of H2A and H2B in histone octamer has not been confirmed (**Figure 1**). Histone methylation can occur at distinct positions with divergent transcriptional activity (39). Histone methylation is often associated with transcriptional activation or inhibition of downstream genes (40, 41). The methylation of histone H3K4, R8, R17, K26, K36, K79, H4R3, and K12 can activate gene transcription (42, 43). However, the methylation of histone H3K9, K27, K56, H4K5, and K20 inhibits gene transcription, confirming the complexity of epigenetic regulation of histone methylation (44). Interestingly, under different conditions, the methylation of histone H3R2 can activate and inhibit transcription (33).

Histone methylation is a reversible process that promotes homeostasis in healthy organisms (36). Histone methyltransferases and histone demethylases promote monomethylation, dimethylation, trimethylation, or

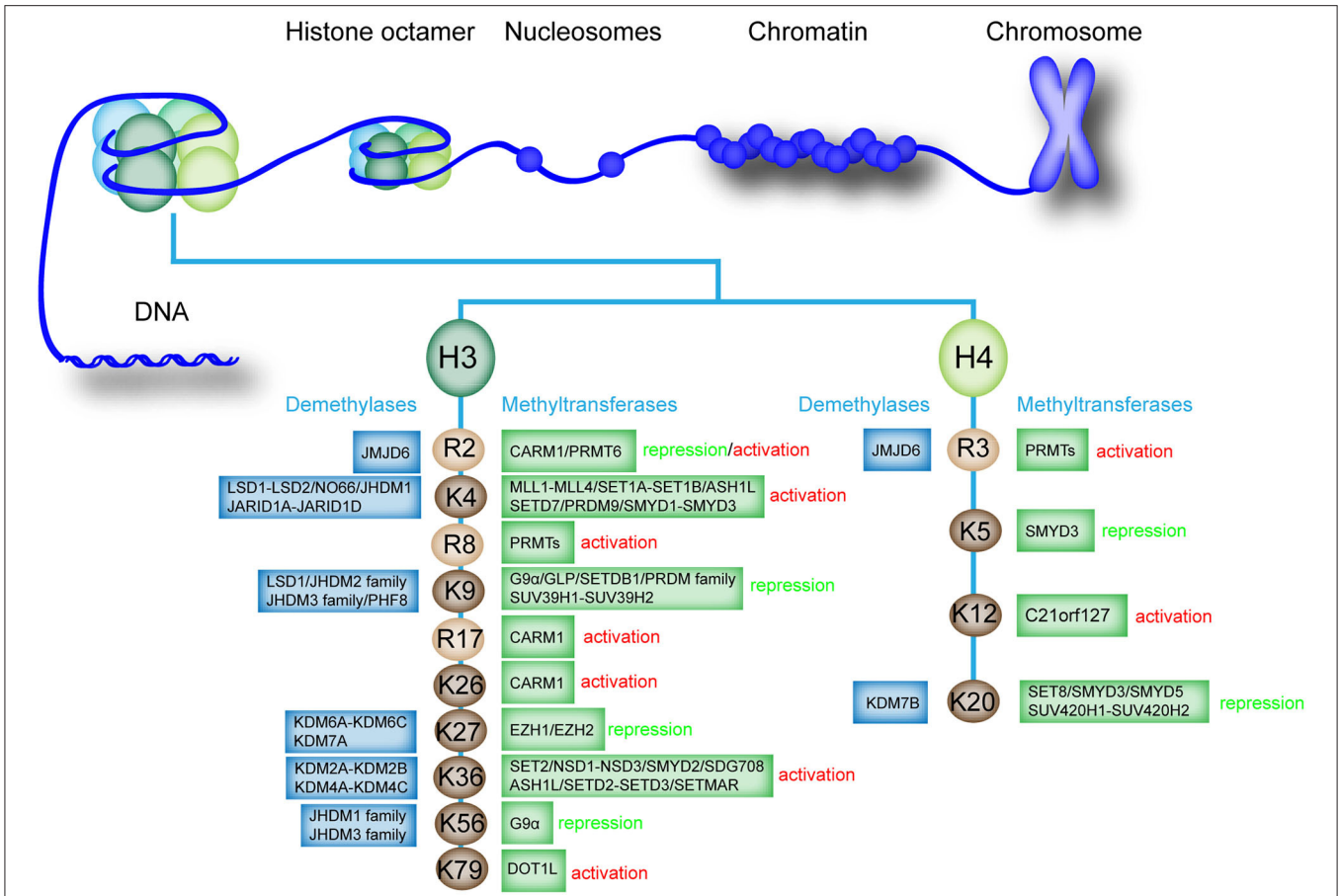

FIGURE 1 | Existing methylation sites in histones, the enzymes involved, and the effects on the transcription of downstream genes. The existing methylation sites and the histone methyltransferases and demethylases that catalyze monomethylation, dimethylation, trimethylation, or demethylation are listed. The effect of methylation modification at each site on downstream gene transcription is labeled as "activation" or "repression".

demethylation of histones (38, 45). Histone methyltransferases, particularly histone lysine methyltransferases (KMTs), are involved in the transfer of methyl group from S-adenosylmethionine to N-terminal tails of lysine residues present on histone (46). Histone demethylases such as lysine-specific demethylase 1 (LSD1) can regulate histone demethylation (47). Histone H3 and H4 can undergo methylation modification, and the methylation and demethylation of different sites are mediated by specific enzymes (**Figure 1**).

In humans, the following two protein domains carry out lysine methylation: SET domain [named after three *Drosophila melanogaster* proteins originally recognized as containing this domain, namely, Su(var)3–9, Enhancer of zeste, and Trithorax] and the seven beta-strand (7βS) domain [non-SET-domain enzymes; (30, 31)]. These two families account for more than 200 enzymes with different amino acid residue specificity (48). Histone demethylases (HDMs) also include two groups in eukaryotes, including the LSD1 family and the Jumonji C-domain-containing family [JHDMs; (49)]. LSD1 is the first identified histone demethylase (50). HDMs in JHDMs include Fe^{2+}- and α-ketoglutarate-dependent hydroxylases, and seven phylogenetically distinct subfamilies were identified in this family (51).

In human cells, the methylation and demethylation of different histone sites are mediated by different enzymes, which precisely regulate histone methylation and gene expression (52). For example, various histone methyltransferases regulate the methylation of histone H3K4, such as mixed lineage leukemia protein 1 (MLL1)-MLL4, SET domain containing 1A (SET1A)-SET1B, and SET domain and MYND domain protein 1 (SMYD1)-SMYD3 (27, 36, 53, 54). Several histone demethylases mediate the demethylation of H3K4, such as proteins in the LSD family and Jumonji, and AT rich interactive domain 1D (JARID) family (55). We further summarized the methyltransferases and demethylases involved in the histone methylation regulation of different sites (**Figure 1**). Notably, the specific histone demethylase that regulates the demethylation of histone H3R8, R17, K26, K79, H4K5, and K12 has not been determined.

The crosstalk between miRNAs and histone modification forms closed epigenetic machinery loops. Histone modification may activate or inhibit miRNA expression. HDAC inhibition

TABLE 1 | The known methyltransferases and demethylases involved in CVDs progression.

Regulators	Actions	Effect
SMYD1/2/3	Methylation of H3K4, H3K36	SMYD1: Mice: Disrupted right ventricle formation and cardiomyocyte maturation; SMYD3: Zebrafish: Abnormal looping of heart tube, pericardial edema
COMPASS (Ash2, WDR5)	Methylation of H3K4	Involved in vasoconstriction, endothelial dysfunction, and development in numerous cardiovascular diseases
SETD7	Methylation of H3K4	Zebrafish: Developmental heart edema
MLL3	Methylation of H3K4me2	Patients with dilated cardiomyopathy
MLL2	Methylation of H3K4	Zebrafish: Abnormal development of the atria and/or ventricle, prominent bulging of the myocardial wall Mouse: Embryonic lethal, disorganized interventricular septum Human: Kabuki syndrome, congenital heart defects
G9a/EHMT2	Methylation of H3K9me2 and H3K27me3 (lesser extent)	Maintain cardiomyocyte homeostasis and interact with MEF2C to silence the fetal gene program in the adult heart Promote cardiac hypertrophy in stressed hearts
Blimp-1/PRDM	Methylation of H3K9	Mice: Ventricular septal defect and persistent arterial trunk
EHMT1/2	Methylation of H3K9	Protects mice from LVH induced by pressure overload
PRMT5	Methylation of H3R2, H2AR3, and H4R3	Regulate hypertrophic growth via GATA4
EZH2	Methylation of H3K27	Mouse: Failure of myocardial compaction, hypertrabeculation, and ventricular and atrial septal defects
NSD1	Methylation of H3K36	Sotos syndrome
DOT1L	Methylation of H3K79me	Reduction of DOT1L activity causes DCM
PTIP	Co-factor of H3K4 methylation Regulates the expression of Kcnip2	Misregulation of PTIP cause cardiac hypertrophy and failure
LSD1	Demethylation of H3K4	Mice: Ventricular septal defects, salt-sensitive hypertension
JMJD2A	Demethylation of H3K9me3, H3K4me3, and H3K27me3	Activate cardiac hypertrophy and alter cardiac gene expression
UTX (KDM6A)	Demethylation of H3K27	Regulate cardiac development
JMJD3	Demethylation of H3K27	Deficiency also leads to advanced atherosclerosis

upregulates miR-124 accompanied by the inhibition of the expression of downstream targets, such as CDK4, CDK6, and EZH2 (56). miRNA may also regulate histone modifications. HDAC1 is regulated by miR-34a via binding to the 3′-UTR of HDAC1 mRNA in the foam cells. The overexpression of miR-34a represses the expression of HDAC1 and increases the acetylation levels of H3K9ac, causing aberrant lipid accumulation in the foam cell (57).

HISTONE METHYLATION IN CVD PROGRESSION

Generally, histones are featured by their large quantity and various modification residues (46, 58). At least eight modifications have been identified in histones, and these modifications are catalyzed by distinct enzymes (59, 60). A genome-wide analysis depicted that 596 out of 1,109 differentially regulated genes harbor at least one histone modifier at the promoter region in adult mouse cardiomyocytes under hypertrophic remodeling, suggesting a key function in the epigenetic landscape in the transcriptome reprogramming of hypertrophic cardiomyocytes (27, 61). Histone modifications (e.g., methylation or acetylation) affect the progression of various forms of CVDs (22). The function of histone modification on target gene modulation specifically relies on cell types and epigenetic marks (62). Epigenetic modifications widely affect CVDs, and the epigenetic modifications involved in CVD progression are listed in **Table 1**.

Histone Methylation of Key Genes in Cardiomyocytes and Blood Vessels

Considering the close interaction among histone methyltransferases, demethylases, and the main regulators of muscle phenotype, the targeted cardiac genes are regulated by histone methylation (46, 63). A typical example of this interaction can be found in skeletal myocytes (SMCs). WDR5, a necessary component of the SET/MLL family of methyltransferases, regulates the expression of SMC-specific genes, including SM α-actin, SM22α, SM-MHC, and myocardia through the methylation of H3K4 on their corresponding promoters [**Figure 2**; (64)]. Ubiquitously transcribed tetratricopeptide repeat on chromosome X (UTX, a H3K27-specific histone demethylase), serum response factor (SRF), and other core cardiac transcription factors, such as Tbx5 and Nkx2.5, interact together. Their interaction synergistically modulates the expression of downstream genes, such as the atrial natriuretic factor (**Figure 2**). However, the inhibition of the UTX interaction between cardiac gene enhancers prevents cardiac differentiation [**Figure 2**; (65)]. In addition, increased histone acetylation and dimethylation are associated with increased expression of atrial

natriuretic peptide and brain-type natriuretic peptide in the LV. Therefore, ubiquitously expressed histone methyltransferases and demethylases have regulatory roles in modulating the expression of genes involved in CVDs. The interactions between histone methyltransferases, demethylases, and transcriptional factors also affect the expression of genes exposed to various stimuli. JMJD2A, a histone demethylase, interacts with SRF/myocardia to elevate the level of four-and-a-half LIM domains 1 (FHL1), a cardiac hypertrophy biomechanical stress sensor when exposed to transverse aortic constriction (TAC, **Figure 2**). JMJD2A promotes cardiac hypertrophy. MRTFs regulate the expression of downstream genes via their interaction with methyltransferases and demethylases when exposed to stimuli. In ECs, MRTF-A interacts with Ash2 and WDR5, the components of COMPASS, and is recruited to the ET-1 promoter, exerting critical functions in vasoconstriction and endothelial dysfunction in CVDs in response to Ang II stimulation (66, 67). SMYD1-mediated histone methylation modulates the expression of *Hand2* and *Irx4*, which are essential cardiac transcription factors for RV formation [**Figure 2**; (68, 69)]. Histone demethylase JHDM2A deficiency modulates the PPARγ pathway via H3K9 modification (70). Therefore, demethylases and methyltransferases are involved in the recruitment and interaction with transcription factors that play a vital role in CVD pathologies.

In addition to cardiac genes, endothelial genes are also modulated by the combined regulation between transcription factors and histone methyltransferases and demethylases (71, 72). The interaction of epigenetic reader MECP2, H3K27 histone methyltransferase, enhancer of zeste homolog 2 (EZH2), and KLF2 triggers the inhibition of KLF2, which is a transcriptional factor responsible for the anti-inflammatory and antithrombotic surface via regulating numerous genes, including eNOS and thrombomodulin [**Figure 2**; (24)]. Additionally, the SMC phenotype switching in atherogenic conditions can be regulated by histone arginine methylation by targeting the transcription factor (73, 74). Protein arginine methyltransferase 4 mediates the upregulation of osteopontin through the dimethylation of R17 on histone H3, and this process promotes the recruitment of transcription factor USF1 (75, 76). The recruitment of USF1 is suppressed by arginine demethylase JMJD6 (77). Considering the sensitivity of ECs toward hypoxia, transcription factor interaction with epigenetic modification is also detected in hypoxia-induced upregulation of the glucose transporter, GLUT3, in ECs (78). The demethylase KDM3A is recruited to the transcriptional start site and enhancer regions of GLUT3 and facilitates the demethylation of H3K9 to induce GLUT3 expression in response to HIF1-α expression (78, 79). In addition, the interaction between HIF1-α and KDM3A has been confirmed by co-immunoprecipitation, and this process is inhibited by HIF1-α depletion (79). Thus, the interaction between HIF1-α and KDM3A modulates GLUT3 levels for the homeostasis of glucose levels, and this condition is required for maintaining energy supply under hypoxic conditions [**Figure 2**; (78)]. The demethylase LSD1 could serve as a repressor of Notch1, which specifically regulates cardiomyocyte proliferation within the trabeculae [**Figure 2**; (80)]. Based on these studies, histone methyltransferases and demethylases could modulate the expression of CVD-related genes by interacting with multiple transcription factors.

Role of Histone Methylases and Demethylases in CVDs

Histone methylases such as G9a, EZH2, MLL2, DOT1L, SMYD1-SMYD3, and SUV39H1 and demethylases such as LSD1-LSD2, JMJD2A, UTX, and JMJD3 modulate the transcription of various cardiovascular genes and play an important role in cardiovascular development and CVDs. For example, G9a mediates H3K9 dimethylation and further suppresses the expression of cardiomyocyte-related genes (81). SMYD1 is a modulator of cardiac transcription factors for RV formation (68). H3K27me3, one of the most established histone modifiers, is modulated by EZH2, UTX, and JMJD3, and affects CVD progress [**Figure 3**; (45, 82–84)]. UTX interacts with SRF and other core cardiac transcription factors to affect heart development. The inhibition of UTX interaction also suppresses cardiac differentiation (65). Considering the vital importance of these methylase and demethylase in cardiac development and function, aberrant expression and mutation of the histone methylation modifiers, which can be affected by living habits, genetic factors, environmental factors, and other CVD risk factors, are critical in the pathology of CVDs (**Figure 3**).

Histone Methylation in Atherosclerosis

EZH2 protects against cardiac pathology by inhibiting the expression of transcription factor Six1-a in cardiac progenitor cells (85). EZH2 plays a vital role in atherosclerosis (86). EZH2 overexpression leads to the development of atherosclerosis in $ApoE^{-/-}$ mice by catalyzing the methylation of DNMT1-mediated ATP binding cassette transporter A1, thereby inhibiting macrophage cholesterol efflux and promoting foam cell formation (87). JMJD3 depletion in foam cells suppresses pro-fibrotic pathways, an important hallmark for atherosclerosis (38). Myeloid JMJD3 deficiency also leads to advanced atherosclerosis (88). Histone modification alterations, such as reduction of H3K9 and H3K27 methylation levels, have also been observed in patients with atherosclerotic plaques and carotid artery stenosis (20). Along with the progression of atherosclerosis, H3K4 methylation accumulates in SMCs; H3K9ac and H3K27ac are also enriched in atherosclerotic SMCs and macrophages, thus supporting the elevated HAT activity of GCN5-like protein 1 and HAT KAT8 (89). Additionally, H3K9ac accumulates in atherosclerotic plaques in ECs (90).

Histone Methylation in Cardiac Hypertrophy

PRMT5 ameliorates cardiomyocyte hypertrophy and induces the methylation of H4R3me2 via the transcriptional activation of Filip1L and subsequent enhancement of β-catenin degradation [**Figure 2**; (63)]. PRMT5 deficiency contributes to the suppression of H4R3me2 and facilitates the progression of pathological cardiac hypertrophy (35). The depletion of muscle-specific SMYD1 (a H3K4 methyltransferase) leads to severe cardiac developmental defects [**Figure 3**; (91)].

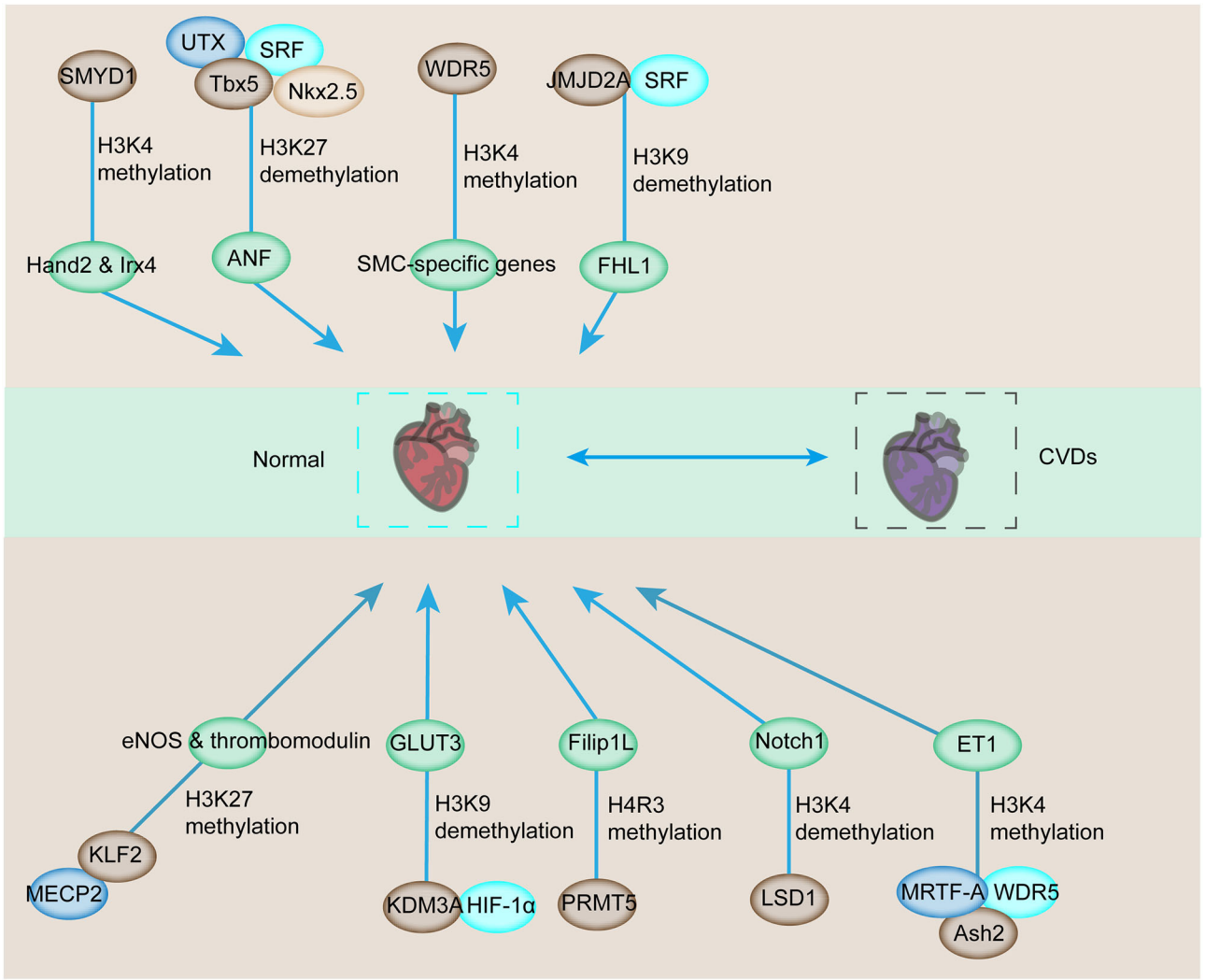

FIGURE 2 | Downstream target genes involved in cardiovascular development and CVDs are affected by histone methylation and related enzymes. The downstream genes involved in the regulation of cardiovascular development can be modulated by histone methyltransferase or demethylase for transcriptional activation or repression. The abnormal activation or repression eventually contributes to the progression of CVDs.

Furthermore, in adult heart diseases, SMYD1 is elevated to restrict hypertrophic growth by directly repressing a group of hypertrophy-associated genes, including TGFβ3 and NPPA (92). The misregulation of PAX transactivation-domain interacting protein, a cofactor of H3K4 methylation, causes cardiac hypertrophy and failure (93). JMJD1C is involved in pathological cardiac hypertrophy, in which its expression level increases, and H3K9 methylation decreases during cardiac hypertrophy in humans and mice (94). JMJD1C contributes to hypertrophic cardiomyocytes stimulated with Ang II (95). In addition, cardiomyocyte remodeling occurs with the help of H3K9me3 methyltransferase, SUV39H1 upregulation and the H3K9me3 demethylases, JMJD downregulation [**Figure 3**; (96)]. As a H3K9me2 dimethyltransferase, EHMT1/2 protects mice from left ventricular hypertrophy (LVH) accompanied by increased global H3K9me2 levels induced by pressure overload (97). G9a mediates cardiomyocyte homeostasis by repressing genes involved in cardiomyocyte function, including anti-hypertrophic genes through its methylation on histone H3K9 and interaction with EZH2 and transcription factor myocyte-specific enhancer factor 2C (MEF2C) (81).

Histone Methylation in Noonan Syndrome

The increased histone H3K4 methylation induced by haploinsufficiency of *RREB1* causes a Noonan-like RASopathy, which refers to the abnormal development in multiple part of the body including CVD, via SIN3A and KDM1A in human and murine cells (98). Moreover, disruption of the histone acetyltransferase MYST4 leads to a Noonan syndrome-like phenotype and hyperactivates MAPK signaling in humans and mice (99).

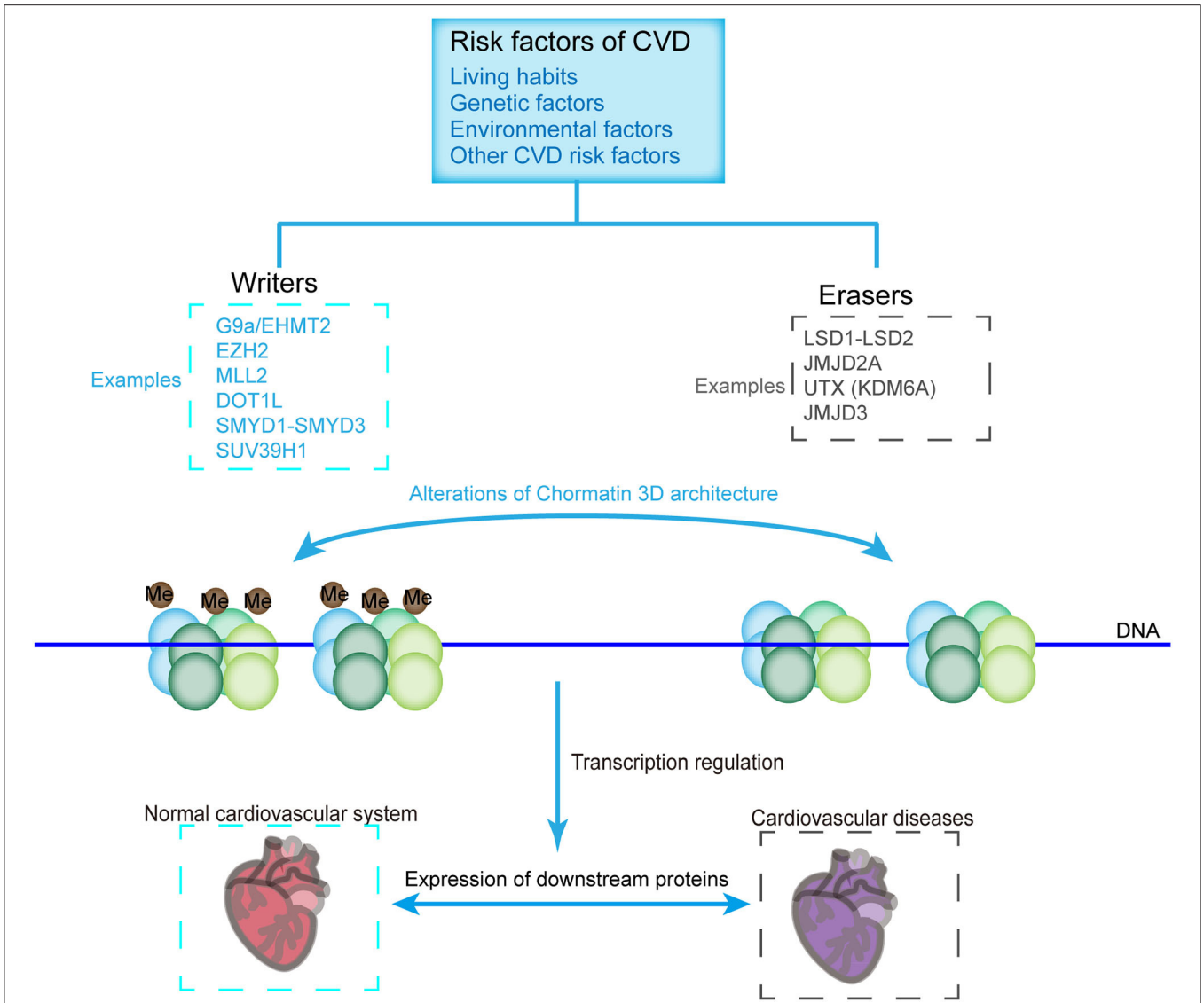

FIGURE 3 | CVD-related histone methyltransferases and demethylases. Chromatin constitutes two structural states, namely, the methylated **(Left)** and demethylated **(Right)** states, which are catalyzed by methyltransferases and demethylases, respectively. Histone methylation state affects the loosening of the nucleosome, thus allowing the binding of transcriptional machineries or inhibiting the accessibility of the transcriptional machinery to genes, which are critical for the pathology of CVDs. Methyltransferases and demethylases can be affected by environmental factors, living habits, genetic factors, and other factors of CVDs.

Histone Methylation in Dilated Cardiomyopathy

The overexpression of Rae28, which is involved in the protein regulator of cytokinesis 1 (PRC1) complex in cardiomyocytes, leads to apoptosis of cardiomyocytes, irregular myofibrils, and dilated cardiomyopathy (100). By contrast, H3K79me3 is added by the histone-lysine N-methyltransferase DOT1L, which is repressed during dilated cardiomyopathy (101). DOT1L-specific depletion in cardiomyocytes triggers the total depletion of H3K79me2/3 and finally the reduction of the dystrophin (DMD) gene, a membrane-associated protein involved in dilated cardiomyopathy and muscular dystrophy (102). Consistently, DMD protein level is reduced in DOT1L-ablated hearts, which displays dilated cardiomyopathy (102). Similarly, the decrease of H3K9me2/3 and increase of H3K4me2 are correlated with dilated cardiomyopathy and accompanied by increased levels of myeloid/lymphoid or mixed-lineage leukemia protein 3 in the LV (64).

Histone Methylation in Cardiac Development

H3K4 methyltransferase SMYD3 accumulates during the development of zebrafish heart, and SMYD3 knockdown results in severe defects, including pericardial edema and aberrant expression, of three heart-chamber markers in cardiac morphogenesis [**Figure 3**; (103)]. Therefore, histone methylation

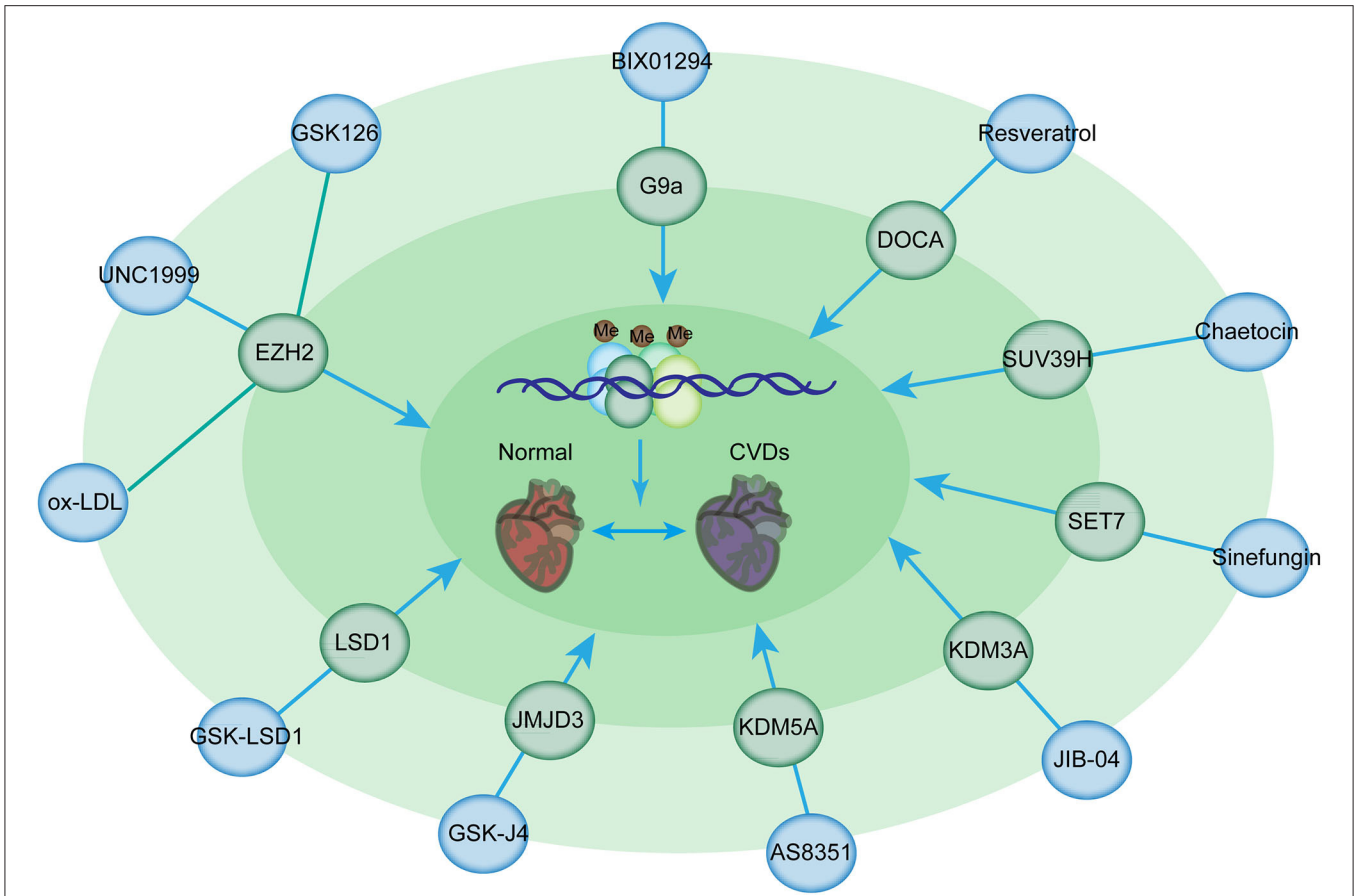

FIGURE 4 | Histone methylation-modifying inhibitors and their targets for the prevention of CVDs. Histone methylation-modifying inhibitors are indicated in bold together with their respective targets. Each compound specifically targets the enzymes involved in methylation regulation, thus affecting chromatin accessibility and binding of transcription factors critical for CVDs. These alterations modulate the expression of downstream genes in CVDs.

plays a critical function in the development of the heart, and its abnormal function leads to severe CVDs.

Histone Methylation in Diabetic Cardiovascular Complications

Epigenetic modifications are critically involved in the long-lasting and detrimental effects of hyperglycemia on the cardiovascular system. Hyperglycemia induces aberrant changes in H3K4me2 and H3K9me2 in human monocytes. Monocytes from T2D patients exhibit SETD7-dependent epigenetic alterations (H3K4m) on NF-kB p65 promoter (104). Adverse epigenetic remodeling driven by SETD7 was associated with endothelial dysfunction and oxidative stress (105). The inhibitor of SETD7 alleviates the burden of CVD in patients with diabetes.

Histone Methylation in Congenital Heart Defects

The mutations in epigenetic regulation are vital factors for the occurrence of congenital heart defects (106, 107). The decreases in heterochromatin H3K27me3 and its methyltransferase EZH2 are accompanied by Hutchinson–Gilford progeria syndrome, exhibiting atherosclerotic CVD phenotypes at an early age (108).

Histone Methylation in Cardiac Ischemia/Reperfusion Injury

In response to cardiac ischemia/reperfusion (I/R) injury, histone, and methyltransferase G9a protein levels increased in caveolin knockout mice (109). The expression levels of MLL2 and G9a increased in advanced atherosclerosis compared with early atherosclerosis (37). Su(var)3–9 methyltransferase is associated with the pathogenesis of myocardial infarction (110). SUV39H1 deficiency or inhibition attenuates I/R-induced infarction and improves heart function in mice possibly by influencing reactive oxygen species (ROS) levels in a SIRT1-dependent manner (110). The mechanism underlying the epigenetic change in cardiac regulation needs to be elucidated to develop effective therapeutic strategies for CVDs.

Combined Modulation of Histone Methylation and Acetylation in CVDs

Histone methylation and acetylation modification work together during the development of CVDs (46, 111, 112). For instance, nitric oxide (NO), which is produced by endothelial nitric oxide synthase (eNOS), is a major antiatherogenic factor in the blood vessel (113, 114). The activation of histone modifications, H3K9 and H4K12 acetylation, and H3K4 methylation are enriched at the proximal promoter site of NOS3 in ECs but not in SMCs, thus explaining the different expression patterns in ECs and SMCs (115). SMYD2 exhibits transcription repression on an SV40-luciferase reporter (116). The dimethylation of histone H3 lysine 36 by SMYD2 is accompanied by its interaction with Sin3, a HDAC1-containing complex, implying orchestrated regulation of methylation and acetylation [**Figure 3**; (117)].

Histone Methylation-Mediated Cellular Functions and Pathways in CVDs

Histone modification affects many cellular pathways essential for the normal function and development of the heart and blood vessels (110, 118–120). The methyltransferase SET7 induces the upregulation of NF-κB p65 as a result of enhanced monomethylation of H3K4 in aortic ECs (121). SET7 can also be mediated by transient hyperglycemia, triggering H3K4me1 and further activating NF-κB p65 and NF-κB-dependent inflammatory genes in ECs, thus suggesting its critical role in hyperglycemia-mediated vascular complications (105, 122). SET7 may act as a promising target for the prevention of atherosclerotic vascular disease in patients with cardiometabolic disturbances (122, 123). In addition, H3K4me1 is correlated with the expression of oxidant genes (iNOS and COX-2) and elevated plasma levels of ICAM-1 and MCP-1 (124). EZH2 ablation or enzymatic inactivation in the fetal heart decreases cardiomyocyte proliferation and increases apoptosis and lethal congenital malformations (85, 86). Although the function of the paralog gene EZH1 can be disregarded during early cardiac development, this function is essential for neonatal heart regeneration (125). EZH1 overexpression leads to cardiac regeneration in 10-day-old mice, which usually have non-regenerative heart (126). MLL2, a methyltransferase that is widely expressed in adult tissues, functions in embryonic development (127–132). As a H3K36-specific methyltransferase, HYPB (also known as SETD2 and KMT3A) homozygous disruption leads to embryonic lethality at E10.5–E11.5 caused by severe vascular defects in the embryo, yolk sac, and placenta (133). DOT1L catalyzes the methylation of histone H3K79 and modulates transcriptional elongation, cell cycle progression, somatic reprogramming, development, and DNA damage repair (134–138).

THERAPEUTIC POTENTIAL OF EPIGENETIC INHIBITORS AS CARDIOVASCULAR DRUGS

Considering that epigenetic modification plays an important role in the progression of CVDs, small-molecule epigenetic drugs against CVDs should be developed. The reversible nature of epigenetic modifications allows the modulation and restoration of phenotypes via some inhibitors or dietary restrictions (139–142). In comparison with the other types of epigenetic inhibitors, the inhibitors of histone methylation have not been extensively researched and remain an undeveloped source of pharmacological interventions.

Among these inhibitors, GSK126 is a potent and highly selective methyltransferase inhibitor for the histone methyltransferase EZH2 [**Figure 4**; (143)]. Given that myeloid EZH2 deficiency in mice leads to improvement in chronic inflammatory disorders such as CVDs, GSK126 has been used to reduce macrophage pro-inflammatory responses (143). Moreover, EZH2 plays an important role in atherosclerosis. EZH2 induces lipid accumulation when stimulated with ox-LDL and macrophage activation and inflammation in THP-1- and RAW264.7-derived macrophages (144). The overexpression of EZH2 in mice can augment the atherosclerosis plaque size by repressing the expression of Abga1/Abcg1 (145). Therefore, GSK126 has a potential therapeutic effect of GSK126 in atherosclerosis treatment. Notably, statins can reduce EZH2 expression levels in ECs, suggesting that they can serve as the potential therapeutic target in atherosclerosis treatment (145, 146). Additionally, the inhibition of EZH2 by UNC1999 significantly inhibits VSMC proliferation induced by PDGF-BB and neointima formation caused by wire-guided common carotid injury, mediated by the enhanced transcription of the cyclin-dependent kinase inhibitor p16INK4A [**Figure 4**; (147)]. Inhibition of EZH2 activity by its inhibitor, UNC1999, or knockdown of EZH2 by its shRNA, leads to VSMC loss, while overexpression of EZH2 facilitates VSMC growth, therefore promoting a tear in the inner layer of the aortic wall, which allows blood to enter into the wall of the aorta, as evidenced by fragmentation of elastic fibers and VSMC loss (148).

G9a is responsible for the homeostasis of cardiomyocytes by mediating H3K9 dimethylation to inhibit the expression of cardiomyocyte-related genes and the formation of a complex with EZH2 and MEF2C (149). TAC mice, which were administered with BIX-01294 (a G9a inhibitor), had improved cardiac function and prevented the development of hypertrophy (150). BIX01294 promotes the expansion of adult cardiac progenitor cells without changing their phenotype or differentiation potential, suggesting that this drug can be used to generate large numbers of native cardiac progenitor cells for the treatment of cardiac disease (150). Furthermore, EPZ005687, a selective inhibitor of Ezh2, significantly inhibits the progression of pulmonary arterial hypertension induced by TAC (151). Resveratrol is beneficial for deoxycorticosterone acetate salt-induced hypertension, a risk factor for cardiac disease, partially by suppressing H3K27 methylation in the blood vessels (152). Additionally, Su(var)3–9 methyltransferase is associated with the pathogenesis of myocardial infarction (110). SUV39H is upregulated in neonatal rat ventricular myocytes in cardiac ischemia/reperfusion injury (114). Chaetocin is a promising epigenetic inhibitor for H3K9 methyltransferase SUV39H (153). The administration of chaetocin preserved changes in histone methylation and improved survival in a rat model of

high-salt-diet-induced heart failure, suggesting the beneficial effects of methyltransferase inhibitors for the treatment of heart disease (154). Furthermore, the intraperitoneal administration of chaetocin improves survival and decreases infarct size in C57/BL6 mice following myocardial infarction (155). Chaetocin therapy also suppresses the expression of MMP9, which is responsible for the destabilization of plaque (156). Thus, further investigations are needed to determine the potential use of this compound in CVDs. Sinefungin, a SET7 inhibitor inhibits the heightened production of TNFα and IL-6 in a dose-dependent manner following stimulation with LPS in an atherosclerotic disease mouse model (157).

KDM3A, a specific H3K9me2 demethylase, results in LVH and fibrosis induced by pressure overload (158). KDM3A promotes TAC-induced hypertrophic remodeling *in vivo* (158). JIB-04, a pan KDM inhibitor, prevents pressure overload-induced LVH and fibrosis (159, 160). JIB-04 inhibits KDM3A and the expression of proteins involved in myocardial fibrosis (159). It also protects mice against I/R injury (160). AS8351 is a KDM5B inhibitor that can induce and sustain active chromatin marks to facilitate the induction of cardiomyocyte-like cells (161). JMJD3 plays a pivotal role in hypertrophy (162). The overexpression of JMJD3 promotes cardiomyocyte hypertrophy; JMJD3 silencing or the administration of GSK-J4 (its inhibitor) suppresses ISO-induced cardiac hypertrophy (163). Another example showed IOX1, a JMJD2A inhibitor, suppressed the proliferation and migration of VSMCs induced by angiotensin II by regulating the expression of cell cycle-related proteins and can therefore serve as a potential therapeutic agent in the treatment of atherosclerosis (164). In addition, the inhibition of LSD1 with GSK-LSD1 in mice prevents the development of fibrosis, an EMT-mediated process, in the heart and dilatation, thus preventing heart failure (165).

Although the critical functions of histone PTMs in CVDs have been revealed, much work is needed to comprehensively illustrate the function of these proteins in various processes and their utilization in therapeutic applications. Currently, no epigenetically active agents have entered clinical trials for CVDs. Further investigations on the potential use of epigenetically active compounds are urgently needed for the treatment of CVDs.

CONCLUSIONS AND FUTURE PERSPECTIVES

Epigenetic modifications, such as DNA methylation, histone methylation, and acetylation, are promising therapeutic strategies for the treatment of CVDs (166–170). Despite the recent advances in epigenetic modifications in CVDs, the potential epigenetic inhibitors for CVD therapy have not been identified. Furthermore, a better understanding of the mechanism of epigenetic modification that regulates CVD progression is urgently needed to develop new strategies for the treatment of CVDs. Further studies are needed to improve the pharmacology of these potential inhibitors, because a non-specific inhibitor would cause unnecessary suppression or activation of a set of genes, causing adverse outcomes. Considering the high resemblance in the modifications on different histone proteins, the design of a highly selective inhibitor that targets a particular protein remains a challenge. Building on the foundation of currently available knowledge will help us to take full advantage of the incredible therapeutic capacity of epigenetic drugs.

Considering the complexity of the pathogenesis of CVDs, the important role of epigenetics, especially histone methylation, should be determined. In general, histone methylation mainly regulates the transcription of downstream genes that are closely related to cardiovascular development or affect the activity of related signaling pathways. Histone methylation can also cooperate with acetylation and other modifications to precisely regulate gene transcription. A deep understanding of the related processes will help us to clarify the regulatory mechanism of cardiovascular development and the pathogenesis of CVDs. It can also provide a theoretical basis for the next step of screening important therapeutic targets and developing related inhibitors.

With the use histone methyltransferase or demethylase inhibitors for CVD treatment and intervention, we should still focus on the various abilities of these inhibitors to activate or inhibit multiple gene transcription, causing complex, and potential side effects of related inhibitors. We should use transcriptomics and proteomics to analyze their pharmacological mechanism carefully to achieve the best therapeutic effect. Another important problem is that the inhibitors of histone methyltransferases and demethylases generally lack specificity. The next important task is the design of specific inhibitors for a certain enzyme based on different methyltransferases or demethylases by using specific three-dimensional structural analysis methods and combined with pharmacological approaches. The best therapeutic effect on CVDs can be achieved by precisely regulating the histone methylation or demethylation of a specific site.

AUTHOR CONTRIBUTIONS

YiL and YY conceptualized and wrote the manuscript and created Figures. YY and YingL contributed to the writing of the manuscript. YY and R-XY reviewed and modified the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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