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Epigenetics in dilated cardiomyopathy

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Abstract

Purpose of review—Characterized by enlarged ventricle and loss of systolic function, dilated cardiomyopathy (DCM) has the highest morbidity among all the cardiomyopathies. Although it is well established that DCM is typically caused by mutations in a large number of genes, there is an emerging appreciation for the contribution of epigenetic alteration in the development of DCM.

Recent findings—We present some of the recent progress in the field of epigenetics in DCM by focusing on the four major epigenetic modifications, that is, DNA methylation, histone modification, chromatin remodeling as well as the noncoding RNAs. The major players involved in these DCM-related epigenetic reprogramming will be highlighted. Finally, the diagnostic and the therapeutic implications for DCM based on new knowledge of epigenetic regulation will also be discussed.

Summary—As a rapidly expanding field, epigenetic studies in DCM have the promise to yield both novel mechanistic insights as well as potential new avenues for more effective treatment of the disease.

Keywords

chromatin; dilated cardiomyopathy; DNA methylation; epigenetics; histone; noncoding RNAs

INTRODUCTION

Cardiomyopathies encompass a heterogeneous group of heart diseases characterized by a spectrum of morphological and functional abnormalities in myocardium. Excluding myocardial remodeling associated with coronary artery disease, hypertension, valvular disease, and congenital heart disease, the clinical manifestations of cardiomyopathies can be classified into five main subtypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathies [1]. Most recently,

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Conflicts of interest

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left ventricular noncompaction cardiomyopathy (LVNC) has been classified. [2] Depending on clinical and genetic evidence of presentation pedigrees, each subtype can be sub-classified into familial and nonfamilial forms [3,4■■]. DCM is characterized by common morphological features in enlarged ventricle and loss of systolic function [5■]. Genetic contribution to DCM has been well documented and the currently identified DCM-related genes include those encoding cytoskeletal proteins, sarcomeric components, mitochondrial proteins, desmosomal structure, nuclear membrane-associated proteins, and RNA-binding proteins. Indeed, mutations of these genes are routinely screened as a part of the clinical diagnosis for familial DCM [5■,6■]. Despite of the progress, the genetic basis of a significant portion of the DCM patients remains unknown. Heterogeneity of disease phenotypes caused by mutations in the same gene raise points to complexity of factors involved in determining the clinical phenotype.

There is an emerging recognition that phenotypic traits are not only determined by genetic variants of coding sequences at DNA level but also contributed by the functional state of the genome, which mainly dictates how genes are expressed. Consequently, the epigenetic studies mostly focus on the regulatory mechanisms and the functional consequences of the changes in gene expression rather than the changes in gene sequences. Recent advancement has revealed a growing importance of epigenetic regulation and dysfunction in human physiology and diseases [7,8■]. In this review, we will focus on some of the recent progress and discuss four major epigenetic modifications implicated in DCM, namely DNA methylation, histone modification, chromatin remodeling as well as the noncoding RNAs. The major factors involved in DCM-related epigenetic modifications will be highlighted. Finally, the therapeutic implications targeting epigenetic regulators for DCM will also be discussed.

DNA METHYLATION

DNA methylation, in particular 5-methylcytosine (5mC) at CpG site, is one of the most pervasive covalent modifications to DNA in the human genome. CpG methylation is carried out by a family of DNA methyltransferases, including DNMT1, 3A, and 3B. Although DNMT3a and DNMT3b are responsible for de novo DNA methylation to establish a new methylation pattern to unmodified DNAs, DNMT1 functions to maintain established DNA methylation during DNA replication by copying the DNA methylation pattern from the parental DNA strand onto the newly synthesized daughter strand [9]. Although DNA methylation can be reversed in a passive manner on newly synthesized DNA strains with loss of DNMT1 activity, active DNA demethylation can be accomplished by different pathways. Deamination of an amine into a carbonyl group by activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex (AID/APOBEC) converts 5-methylated cystine into thymine. The resulting G/T mismatch induces the base excision repair (BER) pathway to correct it back to unmethylated Cystine residue. Alternatively, the ten-eleven translocation (Tet) enzymes, TET1, TET2, and TET3, can add a hydroxyl group onto the methyl group of 5mC to form 5hmC, which will be cleaved by thymine DNA glycosylase (TDG) [9]. (Fig. 1) In addition to these DNA methylation erasers, methylated DNA can also be recognized by several readers, including methyl-CpG-binding domain proteins (MBD), ubiquitin-like containing PHD and RING finger domain proteins (UHRF),

and members of the zinc-finger proteins (ZFPs) [9]. Mutation of the repressive methyl-binding protein (MECP2), a member of the MBD family, causes Rett Syndrome, a X-linked genetic disease of mental retardation [10]. Despite of these ongoing DNA methylation and demethylation activities, in most normal tissues, the DNA methylation at CpG sites is long-lasting and stable. The distribution of methylated CpG is widespread in human genome, and is particularly prevalent in the gene body of highly expressed genes, transposable elements, as well as stretches (often longer than 200 base pairs) of DNA sequences enriched in CpG dinucleotide (so-called CpG islands, CGIs). In human genome, CGIs are a common feature of gene promoter. Although hypermethylation is thought to suppress transposon activity, methylated gene body is often associated with actively transcribed genes. In contrast, hypermethylation of CGIs in the promoter regions leads to long-term and stable gene repression by either recruiting transcriptional repressors or by masking the binding of transcriptional activating factors [11■]. The dynamic and orchestrated changes of DNA methylation either at global or individual gene level are critical for cell differentiation during normal development and diseases, including cardiomyocyte lineage determination, maturation, and diseases [12]. Therefore, DNA methylation is an important mechanism of epigenetic regulation.

DNA METHYLATION PROFILES IN DILATED CARDIOMYOPATHY

Using DNA captured by immunoprecipitation with an antimethylated cytosine antibody (MeDIP) and sequencing, Movassagh *et al.* reported the first genome-wide maps of DNA methylation from normal human hearts and end-stage cardiomyopathic (EsCM) hearts [13]. This study showed for the first time that DNA methylation was globally altered in association with cardiomyopathy, with changes particularly enriched in CpG islands [13]. In a separate study, Hass *et al.* [14] also examined the cardiac DNA methylation patterns in nonischemic idiopathic DCM heart. Both studies support the potential role of DNA methylation in cardiac gene regulation and the development of DCM. Indeed, based on the newly identified DCM-associated DNA methylation patterns, Hass *et al.* identified a number of genes with previously unknown roles in DCM, including Lymphocyte Antigen 75 and Adenosine receptor A2A. By validating their function in cardiac development and function using zebrafish model, the study provided a proof-of-concept evidence that DNA methylation mediated cardiac gene regulation can be a significant causal factor to the pathogenesis of DCM [14].

To further establish the correlation between DNA methylation and cardiac gene expression, Meder *et al.* recently reported a high-density epigenome-wide profiling of DNA methylation using both left-ventricular biopsies and whole peripheral blood samples from a total of 135 DCM patients. RNA deep sequencing and whole-genome DNA sequencing were also performed on the same samples in parallel [15■■]. By integrating these three datasets, 59 DCM-associated epigenetic loci are revealed where DNA methylation patterns are significantly associated with DCM. With a staged multiomics study design, a further set of 517 epigenetic loci are significantly linked with DCM and cardiac gene expression. Interestingly, they identified distinct epigenetic methylation patterns that are conserved between cardiac and peripheral blood, which demonstrated in principle the potential of using DNA methylation pattern as novel epigenetic biomarkers for DCM diagnosis [15■■]. This

study, as well as several other studies from smaller DCM cohorts [14,16■,17] support the overall recognition that DNA methylation-mediated epigenetic regulation of cardiac genes is an important molecular process in the onset of DCM.

REGULATION OF DNA METHYLATION IN DILATED CARDIOMYOPATHY

Though DNA methylation is considered stable, aberrant patterns of CGI methylation are observed in diseases, which constitute more than 1 million tissue-specific differentially methylated regions (DMRs) [11■]. Knockdown of DNMT3a, but not DNMT1 or 3b, disrupted cardiomyocyte differentiation in mouse embryo [18■]. In pressure-overload induced mouse hearts as well as human hypertrophic hearts, DNMT3 expression is activated, which contributes to *Myh6* silencing and impaired contractility [19■]. Furthermore, treatment using a pharmacological inhibitor for DNMT attenuates pressure overload-induced heart failure [20■■], as well as norepinephrine-induced cardiac hypertrophy in rats [21]. However, the direct contribution of DNMTs in DCM remains to be demonstrated. It is demonstrated that MECP2 expression is necessary for heart development, but overexpression of MECP2 also leads to embryonic lethality associated with cardiac hypertrophy [22]. In addition, both Rett Syndrome patients and MECP2 mutant mice develop prolonged QT interval and lethal cardiac arrhythmia.[23,24]. MECP2 expression is repressed in both mouse hearts following transverse aortic constriction and human failing hearts, but its expression is recovered after unloading of left ventricular pressure, indicating MECP2 is involved in heart failure [25].

In summary, aberrant DNA methylation is significantly correlated with gene expression in DCM. But its specific contribution to DCM remains to be further explored. The functional significance of DNA methylation regulators in DCM should be better investigated in future studies.

HISTONE MODIFICATIONS AND EPIGENETIC CODE

Mammalian genomic DNA is organized as a macromolecule complex involving DNA, RNA, histone and nonhistone proteins at the chromatin level. As the basic functional unit of chromatin, each nucleosome contains 147 base pairs of DNA wrapped around a histone octamer that consists of two copies each of histone H2A, H2B, H3, and H4 [26]. A myriad of posttranslational modifications (PTMs) of histones play fundamental roles in transcriptional regulation by changing chromatin accessibility, stability, and architecture [27]. The currently documented PTMs of histone include acetylation, phosphorylation, methylation, deamination, β-*N*-acetylglucosamine, ADP ribosylation, ubiquitylation, and SUMOylation, each influences the transcriptional activation or suppression depending on the targeted modification sites [28]. Histone modifications have such a determining impact on the eventual output of the genome that they are often regarded as the so-called ‘histone code’ that dictate the function of genome in specific cellular, physiological, or pathological contexts.

HISTONE MODIFICATIONS IN DILATED CARDIOMYOPATHY

In a recent study by Ito *et al.,* a global change of histone modification was observed in the left ventricular tissue in end-stage nonischemic DCM patients, including a general reduction in the levels of H3 lysine 4 trimethylation (H3K4me3), H3 lysine 9 dimethylation (H3K9me2), and H3 lysine 9 trimethylation (H3K9me3) in the DCM heart tissue as compared with the normal heart tissues. Interestingly, partial reversal of these changes in histone modifications was detected following implantation of left ventricular assist device (LVAD) associated with a significant improvement in function. This finding suggests a close relationship between histone modification and DCM development [29■].

The mammalian homologue of yeast disruptor of telomeric silencing (DOT1L) catalyzes methylation at Lys 79 of histone H3 (H3K79). DOT1L expression is reduced in human DCM hearts and cardiac-specific knockout of DOT1L in mice also results in an increased mortality rate associated with DCM phenotype. Thus, changes in H3K79me level caused by loss of DOT1L expression may contribute to DCM development [30]. Similarly, a histone methyltransferase (HMT) named mixed lineage leukemia 3 (MLL3) is upregulated in human DCM hearts, leading to induced level of dimethylated histone H3 lysine 4 (H3K4me2) in DCM hearts [31■]. In a rat DCM model induced by furazolidone (FZ), a H3K9 histone methyltransferase G9a is significantly decreased associated with increased expression of cell adhesion molecules (CAMs) [32], highlighting yet another potential pathway affected by histone-modifying machinery in the onset of DCM.

Along with methylation, targeted acetylation of lysine residues in histones is also a major PTM event affecting chromatin function. The dynamic process of histone lysine acetylation and deacetylation is carried out by the opposite action of ‘writers’ or histone/lysine acetyltransferase enzymes (HATs/KATs) versus ‘erasers’ or histone deacetylases (HDACs). In general, histone acetylation activates while deacetylation represses transcription [33]. In humans, there are four classes of HDAC super family genes consisting of a total of 18 members [34]. The importance of HDACs in cardiac hypertrophy [35–38], heart failure [39–41], and diastolic dysfunction [42■■] have been extensively studied. For DCM, cardiac-specific knockout of both HDAC1 and HDAC2 results in neonatal lethality, accompanied by cardiac arrhythmias, dilated cardiomyopathy, and upregulation of genes encoding skeletal muscle-specific contractile proteins and calcium channels [40]. In a mouse DCM model expressing $cTnT^{R141W}$, transgenic expression of Dickkopf 3 (Dkk3) prevented the development of DCM phenotype, apparently by repressing noncanonical Wnt pathway including HDAC4 expression [43■]. However, our knowledge to the specific roles of histone acetylation in the pathogenesis of DCM is still incomplete.

CHROMATIN REMODELING

One of the key consequences of DNA and histone modifications is the change of high-order architecture of the chromatin, which dictates the accessibility and the interaction of genes for transcription, replication or repair [44]. Carried out by a cohort of so-called ‘reader’ genes in an ATP-dependent manner, these chromatin remodelers regulate chromatin topology by moving, ejecting, or restructuring nucleosomes, leading to opening or closing at

specific genomic loci [45]. On the basis of conserved domains (such as bromo, chromo, etc.) for recognizing specific modification codes on DNA and histones, the human chromatin remodelers are divided into four subfamilies, including switching defective/sucrose nonfermenting (SWI/ SNF), imitation switch (ISWI), chromodomain, helicase, DNA-binding (CHD), and inositol-requiring 80 (INO80) [45]. In addition to these classic chromatin remodelers, chromatin architecture is also regulated by CCCTC-binding factor (CTCF) and high-mobility group protein B2 (HMGB2). Working in concert with histone modification and other chromatin features, these proteins regulate local chromatin accessibility and ultimately the transcriptional activities across genomic loci [46■].

CHROMATIN REMODELING IN DILATED CARDIOMYOPATHY

Using genome-wide chromatin conformation capture (Hi-C) and DNA sequencing, the global chromatin structure and genome accessibility are mapped and shown to be significantly changed in the mouse failing induced by pressure overload [47■■]. BRG1-associated factors (BAF) and polybromoassociated BAF (PBAF), both requiring BRG1 and BRM as the ATPase, are the two main SWI/ SNF complexes in mammalian genome. The Baf60C of BAF complex is necessary for the expansion of the anterior/secondary heart field during heart development [48]. Genetic inactivation of Baf60c leads to cardiac hypoplasia and pronounced cardiac dysfunction in mouse embryos [49■]. Likewise, the Baf180 of PBAF complex is also essential for cardiac chamber maturation [50]. Beyond their essential roles during cardiac development, the ATPase BRG1 and BRM are required for the maintenance of cardiomyocyte homeostasis by regulating mitophagy and mitochondrial dynamics [51■], as well as contractility[52■]. Brg1 is activated in certain patients with hypertrophic cardiomyopathy and promotes embryonic features in cardiomyocyte, including α-MHC, and β-MHC isoform switch [53]. Furthermore, a Brg1 interaction protein, microphthalmia-associated transcription factor (MITF), promotes GATA4 expression and cardiac hypertrophy [54]. In a recent study by Rosa-Garrido *et al.* [47■■], CTCF depletion in mouse heart selectively altered genome accessibility and long-range interactions of cardiac enhancers, resulting in a significant decrease in local chromatin interactions around these functional elements and a lethal heart failure phenotype. Specifically regarding DCM, conditional deletion of Baf60c in cardiomyocytes resulted in postnatal dilated cardiomyopathy phenotype with impaired contractile function involving Myocardin interaction [49■]. However, other knowledge of chromatin remodeling in DCM is still limited.

NONCODING RNAS

Other than genes coding for proteins, the vast majority (more than 98%) of human genome transcripts is noncoding RNAs (ncRNAs), which do not possess protein-coding capacities. On the basis of the transcript sizes, ncRNAs can be classified into small noncoding RNAs (<200nt), and the long noncoding RNAs (lncRNAs >200nt) [55■]. According to functions, ncRNAs can be further classified into housekeeping ncRNAs as part of the molecular processes in protein synthesis (e.g. tRNAs, rRNAs, and snoRNAs), genomic organization (piRNAs), and mRNA processing (SnRNAs). In addition, a large number of ncRNAs are involved in gene regulation, including miRNAs and lncRNAs [55■]. There is an emerging

recognition that ncRNAs play critical roles in epigenetic regulation during development, and their dysregulation can lead to major diseases [56]. ncRNAs are also demonstrating major potential as new diagnostic and therapeutic targets for cardiovascular diseases including DCM [57■■]. In DCM patients, structural genomic variants (SVs) are reported and can affect both coding and noncoding RNA expression, implicating the potential involvement of noncoding RNAs in DCM development [58■].

MICRORNAS IN DILATED CARDIOMYOPATHY

MircoRNAs (miRNAs) are small ncRNAs with distinct molecular features. They are ~ 22nt in length, and target mRNAs via complementary binding most at their 3′ UTR, leading to either downregulation of target mRNAs or suppression of their translation. Although the source of miRNA precursors is diverse, from independent transcripts to intronic regions of coding genes, the biogenesis of functional mature miRNAs shares three essential factors, namely Drosha, DiGeorge syndrome critical region 8 (DGCR8) and Dicer [59■]. In a study by Jianfu *et al.*, Dicer expression is found to be significantly decreased in end-stage human DCM and failing hearts. More importantly, a significant increase in Dicer expression is also observed in the post-LVAD hearts with improved cardiac function [60]. In the same study, cardiac specific inactivation of Dicer in mice led to rapidly progressive DCM, heart failure, and postnatal lethality. The Dicer-deficient mouse heart showed misexpression of cardiac contractile proteins, profound sarcomere disarray, reduced heart rates, and decreased fractional shortening. In a separate study, DCM phenotype is also observed in the DGCR8 cardiac-specific knockout mice [61], although there are significant differences in transcriptomic signature and cardiac phenotype between the Dicer and the DGCR8-deficient hearts. Nevertheless, both studies demonstrate the critical roles of miRNAs in the onset of DCM.

Unlike mRNAs, most miRNAs are remarkably stable with extended half-life in tissue or serum and other biofluids, thus making them potential candidates as reliable biomarkers for cardiovascular diseases [62■]. miR-208 is a cardiac-specific miRNA derived from the intron 27 of the *MYH6* gene, which encodes the α-MHC protein. miR-208 is upregulated in endomyocardial biopsy tissues from DCM patients and is a strong predictor of worse clinical outcome [63]. A decrease of another miRNA let-7i in endomyocardial biopsy tissues is also a biomarker to predict poor clinical outcome in DCM patients [64]. In contrast, high circulating miR-185 levels appear to be associated with a favorable prognosis in DCM by repressing B-cell function [65■]. Furthermore, circulating miR-21, miR-26, miR-29, miR-30 and miR-133a are all shown to be correlated with interstitial fibrosis among DCM patients [66■]. Fan *et al.* [67] analyzed all the differentially expressed miRNAs in the plasma of a Chinese Han DCM cohort and demonstrated that the elevated miR-423–5p had distinguishing power for DCM diagnosis. More recently, miR-92b-5p in serum exosomes is also reported to serve as a potential biomarker for the diagnosis of DCM-induced acute heart failure [68■]. DCM is a common myocardial disease in young children, Shelley *et al.* compared the serum miRNA signature between the children with DCM who need transplant and the children with DCM who recover. They find two up-regulated (hsa-miR-155 and hsa-miR-636) and two down-regulated miRNAs (hsa-miR-646 and hsa-miR-639) are sufficient to diagnose children who can recover from dilated cardiomyopathy [69■]. Similarly,

Mehmet *et al.* compared the plasma miRNA expression profiles between a cohort of idiopathic DCM children and healthy control individuals. They also find miR-618, miR-875-3p, miR-205, miR-194, miR-302a, miR-147, and miR-544 are decreased whereas miR-518f and miR-454 are increased specifically in the DCM patients [70]. Finally, Meng *et al.* [71] reported that a combined change in the expression of mir-142–5p, mir-143-3p, mir-27b-3p, and mir-126-3p may serve as a potential diagnostic biomarker for childhood dilated cardiomyopathy. Although multiple studies have identified the correlation between miRNA expression changes and DCM, only a few reports establish their causal roles for DCM in more mechanistic details. Wino *et al.* [72] use a transgenic model to demonstrate that cardiomyocytes-specific expression of miR-30c leads to severe dilated cardiomyopathy after 6 months of age, perhaps because of mitochondrial dysfunction. Another recent study by Zeng *et al.* [73■] shows that down-regulation of miR-451a contributes to the activation and proliferation of $CD4^+$ T cells by activating the transcription factor c-Myc in the DCM patients. However, these findings of miRNA differential expression and functional association with DCM should be further validated through independent replicate cohorts.

LONG NONCODING RNAS IN DILATED CARDIOMYOPATHY

LncRNAs are emerging players in many layers of gene regulation and cardiovascular diseases [74■]. In DCM patients caused by Chagas diseases, an lncRNA myocardial infarction-associated transcript (MIAT) is upregulated in the cardiac tissue [75■]. In a rat model of DCM induced by adriamycin, Yanling *et al.* found the expression of lncRNA H19 was significantly upregulated in the myocardial tissues and H19 expression was sufficient to promote cardiomyocyte apoptosis in the DCM hearts [76■]. In one study, the global changes in lncRNAs were characterized using an lncRNA microarray and the differentially expressed lncRNAs between the DCM and the healthy human hearts were identified. By loss-of-function studies, three differentially expressed lncRNAs showed a functional impact in endothelial cells [77■]. Using RNA-sequencing method, Qiu *et al.* [78■] also identified differentially expressed lncRNAs in the cardiac tissues from transplanted hearts with DCM versus healthy donor hearts. lncRNAs are implicated in every step of gene regulation, from epigenetic modulation to RNA processing and translation, as well as interacting with miRNAs. It is a field with rapid progress in recent years, although many of the reports focus on cardiac hypertrophy and fibrotic remodeling [79■■,80■]. With more fundamental knowledge of the transcriptome changes associated with DCM, more functional and mechanistic studies of lncRNAs will be needed to explore the ever-expanding universe of ncRNAs in the pathogenesis of DCM.

TRANSLATIONAL PERSPECTIVES

With the rapid progress in our understanding of cardiac epigenetic regulation in DCM, there is tremendous expectation that novel therapeutic targets and tools will be developed for the disease. HDAC inhibitors targeting different sub-type of HDACs have been actively investigated for cancer treatment [81■]. Recent studies have also demonstrated a promising potential for their use to treat heart failure. Small molecule inhibitors targeting class II HDACs showed a dose-dependent blockage to cardiomyocyte hypertrophy induced by FBS, phenylephrine, or endothelin-1 [82]. In the AngII or aortic binding-induced cardiac

hypertrophy in mice and rats, nonspecific HDAC inhibitors Trichostatin A and Valproic acid, as well as a class I HDAC-selective inhibitor, SK-7041, could partially reverse preestablished cardiac hypertrophy and improved survival [83]. The antihypertrophy function of Trichostatin (TSA) was also observed in the pressure overload induced by thoracic aortic constriction (TAC) mice [84]. Another HDAC inhibitor apicidin (API-D) with selective activity for HDAC class I subtypes 1, 2, and 3 also demonstrated high potency to prevent cardiomyocyte hypertrophy *in vitro* and *in vivo*, and improved cardiac function following pathological stress [85]. All these studies suggest that HDAC inhibition is a viable therapeutic target that holds promise in the treatment of heart failure associated with DCM. In addition, members of the bromodomain and extraterminal (BET) family of bromodomain-containing reader proteins (BRD2, BRD3, BRD4, and testis-specific BRDT) associate with acetylated histones and facilitate transcriptional activation of pathological genes expression, leading to cardiac hypertrophy. Saptarsi group developed a selective bromodomain inhibitor, JQ-1, which significantly reduced the TAC-induced heart failure. This is a good example of targeting epigenetic modification readers to treat heart diseases [86].

In addition to the utilization of miRNAs as biomarkers for diagnostic purposes as discussed above, miRNAs can also be used as molecular targets or even therapeutic tools. Qifeng *et al.* identified miR-208b as an upregulated miRNA in the myocardium of both human DCM patients and a DCM mouse model with a Titin mutant. Using LNA-based miRNA to knockdown miR-208b, they demonstrated that antagonizing miR-208b prevented the transition from adaptive state to maladaptive remodeling in the DCM mice [87■]. DCM is a leading cause of mortality in the muscular dystrophy patients, and miR-669a downregulation in heart has been linked to the progression to severe DCM in the Sgcb-null dystrophic mice. Mattia *et al.* used an adeno-associated viral (AAV) vector to achieve long-term expression (more than 18 months) of miR-669a and improved the survival of Sgcb-null mice with a significant amelioration of DCM phenotype [88]. These studies demonstrate that miRNAs holds major promises as both potential therapeutic targets and reagents for clinical translation to treat DCM.

CONCLUSION

Although DCM has long been considered to be a cardiomyopathy caused by various genetic mutations, it is being recognized that epigenetic dysregulation also takes essential roles during the disease development [89■]. In this review, we discussed several major forms of epigenetic modulations, including DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs, in the pathogenesis and diagnosis of DCM (Fig. 2). In addition, we highlighted the translational potential of HDACs inhibitors and miRNA/lncRNA-based therapies for heart failure and DCM treatment. It is obvious that the knowledge about the epigenetics in DCM still remains largely preliminary. It is particularly urgent to validate the causal roles of many of the observed epigenetic changes in DCM. Finally, the universe of epigenetic regulation is still expanding rapidly with the discoveries of more types of epigenetic modulations in human genome, such as mRNA modifications and editing [90■,91■]. The ever-increasing complexity of the epigenetic regulatory network presents both challenges as well as exciting opportunities to better understanding the

principles underlying the development of DCM and the novel avenues for future diagnostic and therapeutic strategies.

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KEY POINTS

- Epigenetic regulation is an emerging layer of gene regulation with important contribution to cardiac physiology and pathology.
- DNA methylation, histone modification, chromatin remodeling and noncoding RNAs represent some of the major forms of epigenetic regulation in heart.
- Epigenetic landscapes are altered in dilated cardiomyopathy heart.
- Epigenetic signatures, particularly noncoding RNAs, can be used as molecular biomarkers of dilated cardiomyopathy.
- Epigenetic regulatory processes can be targeted for therapeutic development and noncoding RNAs can serve as therapeutic tools for dilated cardiomyopathy.

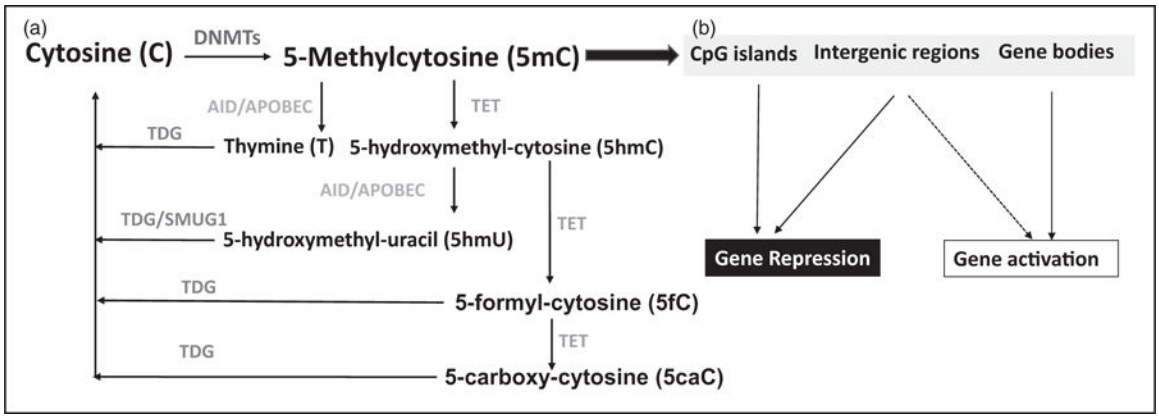

FIGURE 1.

DNA methylation and demethylation pathways. (a) DNA methyltransferases (DNMTS) catalyzes the transfer of a methyl group to the cytosine forming the 5-methylcytosine (5mC), which is the DNA methylation process. The demethylation of methylated DNA can be catalyzed by different mechanisms. The amine group of 5mC can be deaminated by AID/APOBEC, converting 5mC into thymine (T). Also the methyl group of 5mC can be modified by the addition of a hydroxyl group mediated by Tet enzymes to generate 5-hydroxymethyl-cytosine (5hmC). Then 5hmC can be chemically modified at two sites: the amine group and the hydroxymethyl group. AID/APOBEC can deaminate 5hmC to produce 5-hydroxymethyl-uracil (5hmU). And TET can further oxidize 5hmC to form 5-formyl-cytosine (5fC) and then 5-carboxy-cytosine (5caC). Eventually, Thymine, 5hmU, 5fC, and 5caCF are recognized and cleaved off to replace with a naked cytosine through the base excision repair pathway by TDG and/or SMUG1. (b) Functional impact of DNA methylation on gene expression. Hypermethylation in the CpG islands of promoters and intergenic regions tend to repress transcription activities. Hyper-DNA methylation in the gene bodies is correlated with a higher level of transcription in dividing cells, but not associated in slow growing or nondividing cells.

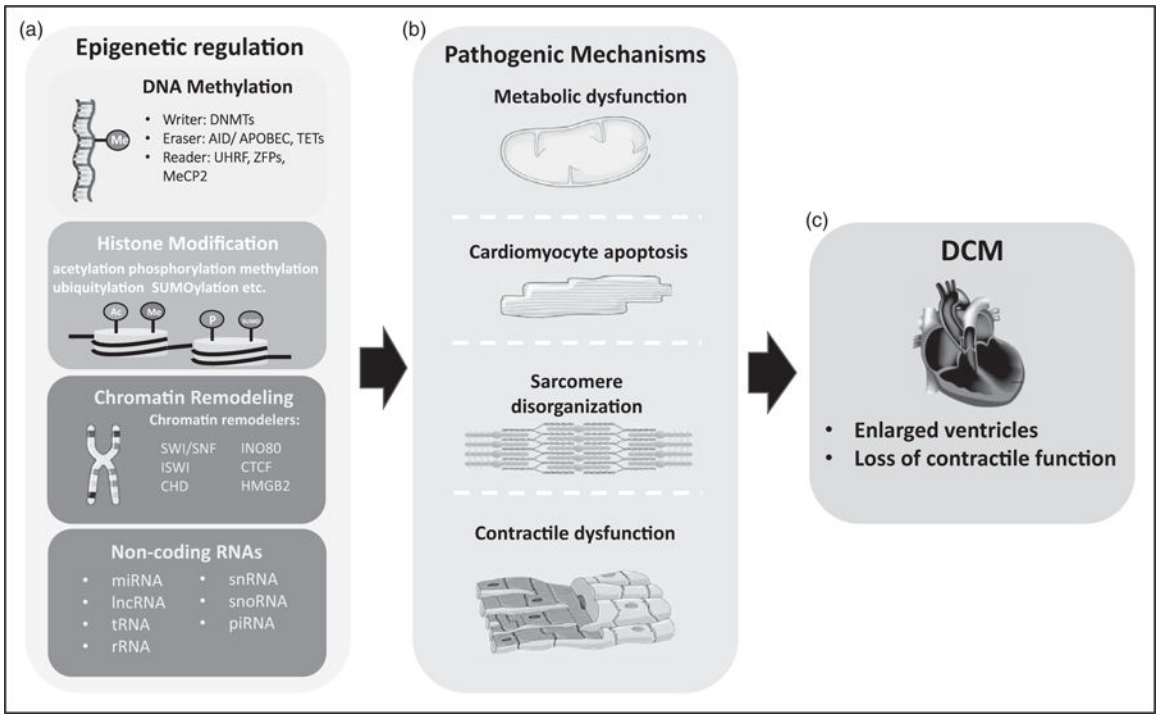

FIGURE 2.

Epigenetics in dilated cardiomyopathy. (a) DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs are the main key epigenetic regulatory processes and players, (b) Specific pathogenic processes of DCM implicated by epigenetic regulation, including metabolism dysfunction, cardiomyocyte apoptosis, sarcomere disorganization, and contractile dysfunction. (c) These converging features contribute to phenotype of DCM. (Depiction in panels a and b partially derived from online materials from Smart Service Medical Art under Creative Commons https://creativecommons.org/licenses/by/3.0/) Links to the figures - https://smart.servier.com/smart_image/dna-14/; https://smart.servier.com/smart_image/chromosome-9/; https://smart.servier.com/smart_image/mitochondria-7/; https://smart.servier.com/smart_image/cardiomyocyte-9/; https://smart.servier.com/smart_image/muscle-9/ https://smart.servier.com/smart_image/cellules-coeur/.