SciForschen
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ISSN 2379-769X

Journal of Heart Health

Review Article | Volume: 3.1 | Open Access

Role of Epigenetics in Cardiac Development and Cardiovascular Diseases

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Received date: 07 Jun 2016; **Accepted date:** 18 Oct 2016; **Published date:** 25 Oct 2016.

Citation: Dong Y, Sun T, Wang K, Wang J, Li P (2016) Role of Epigenetics in Cardiac Development and Cardiovascular Diseases. J Hear Health 3(1): doi http://dx.doi.org/10.16966/2379-769X.131

Abstract

Epigenetic mechanisms which comprise DNA methylation, histone modification, oxidative modification, and non-coding RNAs, are closely linked to cardiac development and dysfunction. However, the exact mechanisms remain unclear. More and more studies have represented altered DNA methylation or distinct changes in chromatin modifications within cardiovascular diseases including atherosclerosis, heart failure, myocardial infarction, and cardiac hypertrophy. Oxidative modification has also been uncovered involving in the cardiac physiology and pathophysiology. Among these mechanisms, microRNAs (miRNAs) have been widely demonstrated essential to cardiac development, pathology, repair, and as potential biomarker or therapeutic targets in the clinic. Most of the epigenetic changes control the development and progression of cardiovascular diseases through increasing or decreasing expression of cardiac-related genes. Nevertheless, how epigenetics lead to the changes of chromosome structure and their complex interplay still need further exploration. Here, we review recent findings on the epigenetic mechanisms and highlight their functions in heart development and pathology, which are expected to inform novel therapeutic targets for cardiovascular diseases.

Keywords: Cardiovascular diseases; Cardiac biology; DNA Methylation, Histone modification; Oxidative modification; microRNAs

Introduction

In the past few decades, with the rapid advancement in high-throughput sequencing of the genome and transcriptome, people have investigated many genetic changes associated with cardiovascular diseases. Recently, epigenetics such as DNA methylation, histone modifications, oxidative modification, and non-coding RNAs, that regulate gene expression without altering DNA sequences, add novel insight into the mechanisms behind heart disorder and regeneration. Epigenetic changes may explain why subjects with similar genetic backgrounds and risk factors can cause distinct clinical manifestation and therapeutic response for some particular diseases [1]. Additionally, Human Epigenome Project and International Human Epigenome Consortium have been launched to analyze epigenetics in cancer, diabetes, autoimmune diseases [2-5]. In this review, we focus on recent findings on the advances targeting epigenetic regulatory mechanisms underlying cardiac development and cardiovascular diseases, revealing novel therapeutic strategies in cardiovascular diseases.

DNA Methylation

DNA methylation is catalyzed by DNA methyltransferases (DNMTs) at the C5 position of cytosine residues within CG dinucleotides (CpG) [6], which is usually linked to poor genome stability and gene expression [7]. There are three DNMTs responsible for methylating DNA. DNMT1 maintains DNA methylation during replication, whereas DNMT3a and DNMT3b establish *de novo* DNA methylation [8]. On the contrary, three ten-eleven-translocation (TET) enzymes (TET1, TET2, and TET3) oxidize 5-methycytosine to 5-hydreoxymethycytosine, which are identified to mediate the initial process of DNA demethylation [9].

The development of heart is a complex process involving coordinated cellular proliferation, migration, differentiation, programmed cell death, and structural remodeling [10]. According to statistics, 60~80% CpG sites in the human genome are methylated [11]. Recent studies demonstrated that global hypomethylation and death in early embryo occured in DNMT1-null mice [12]. Meanwhile, DNMT3a and DNMT3b are proved necessary for mammalian development [13]. In addition, TET3-dificiency in mice led to embryonic developmental failure [14]. However, detailed knowledge is limited about DNA methylation in regulating cardiac development. Studies indicate that murine embryonic cardiac development is associated with increases or decreases in DNA methylation, particularly for some cardiac-specific genes [10,15].

Large-scale studies have identified that DNA methylation is closely related to cardiovascular diseases, including Atherosclerosis, Coronary Heart Disease (CHD), Heart Failure (HF), Myocardial Infarction (MI), and Cardiac Hypertrophy. Ziller et al. [16] charted the dynamic DNA methylation landscape of human genome through high-throughput profiling of DNA methylome. Looking into the map, the cardiac-specific differentially DNA methylated regions were enriched for cardiovascular disease-relevant Single Nucleotide Polymorphisms (SNPs). Furthermore, in promoter regions of some cardiovascular disease-related genes, cytosine methylation prohibits binding of transcription factors, thus inhibiting expression of downstream genes [17,18]. For instance, a double homeobox transcription factor Dux4-associated CpG island displayed elevated DNA methylation and caused Dux4 repression in end-stage failing human hearts compared to healthy tissues [19]. Baccarelli et al. [20] found that lower LINE-1 (a repetitive element) methylation in peripheral blood leukocytes could be used as a biomarker for ischemic heart disease and stroke. In a follow-up study, Girelli et al. [21] explored that the polymorphisms of coagulation factor VII (F7) was linked with increased risk of MI in patients with coronary artery disease (CAD) [21]. After that, the same team investigated that the promoter methylation in coagulation F7 gene influences plasma FVII concentrations and relates to CAD [22]. It is well known that ApoE-/- mice represent histological

changes of atherosclerosis, meanwhile decreased DNA methylation is also detected [23], indicating that aberrant DNA methylation plays critical roles in disease progression. In patients with HF, levels of tumor necrosis factors (TNF-α) and angiotensin II (Ang II) were induced [24,25]. *In vitro* experiments, the DNA methylation inhibitors have been proved to suppress TNF-α- and Ang II-induced cardiac hypermethylation, exhibiting a novel therapeutic strategy for HF [26,27]. In some cases, gene-specific methylation is emerged as an epigenetic mechanism involved in the pathogenesis of cardiovascular diseases, and as a biomarker of increasing risk of cardiovascular diseases [27].

Histone Modifications

In the nucleus of cell, nucleosome is a fundamental primary unit of chromatin, comprised of DNA and histone octamers (formed with 2 copies each of the core histones H2A, H2B, H3 and H4) [28,29]. The histones can confer plasticity to chromatin packaging through dynamically modified or exchanged with variants [30,31]. Histone modifications usually occur at the N-terminal tails, including acetylation, methylation, phosphorylation, sumoylation, ubiquitination, biotinylation and ADP-ribosylation [32,33]. Histone modifications influence chromatin structure, thereby modulating histone-DNA interactions and gene regulation [32,34]. The most common modifications are acetylation, methylation, and phosphorylation. Generally, histone acetylation is catalyzed by histone acetyltransferases (HATs) on lysine residues, and results in transcriptional activation [35]. In contrast, removal of histone acetylation is accomplished by histone deacetylases (HDACs) [36]. Histone methylation often takes place at lysine and arginine residues of H3 and H4 histones, but does not alter histone charge [36]. Histone methyltransferases (HMTs) and demethylases regulate this process [37].

Epigenetic histone modifications have been confirmed to play a prominent role in normal and aberrant heart development. In mammals, MYST (Moz, Ybf2/Sas3, Sas2, Tip60) family is one member of HAT family [38]. Aggarwal and Voss et al. [39] observed that the cardiac phenotype of Moz-/- mice was similar to loss function of the transcription factor Tbx1 [39], which is essential for cardiac development. Further studies showed that Moz-/- mice reduced the H3K9 (lysine 9 of histone 3) acetylation and expression of Tbx1 [40]. In addition, the double knockout mice of HDAC1 and HDAC2 displayed heart defects and resulted in death early after birth [41]. Several lysine methyltransferases, such as SMYD1 [42], EZH2 [43] and DOT1L [44], have been extensively studied and proved to be essential for heart development by altering the expression of cardiac transcription factors.

Growing researches have demonstrated that histone modifications are involved in the progression of cardiovascular diseases. Study of Papait et al. [45] discovered many changes of histone marks using ChIP-seq after heart transverse aortic constriction and enhancers underlying cardiac hypertrophy [45]. Nitric oxide (NO) is important for vascular tone and protects against atherosclerosis. In the endothelial cells, the endothelial nitric oxide synthase (eNOS) catalyzes the generation of NO [46], and its expression is modulated by histone modifications (acetylation of H3K9, acetylation of H4K12, and methylation of H3K4) at the proximal promoter site [47]. Recently, studies have found that HDAC inhibition could improve functional myocardial recovery after MI through facilitating phosphorylation of Akt-1 and decreasing active caspase 3 in mice [48,49]. In addition, proteins harboring bromodomains serve as "reader proteins" of histone modifications, which recognize and bind to the acetylated lysine (Kac) on histone tails [50]. Anand et al. [51] demonstrated that bromodomain proteins function mechanistically as pause-release factors of genes that are central to HF pathogenesis [51]. JQ1, a small molecule inhibitor of bromodomain proteins, is able to suppress HF progression *in vivo* by competitively displacing bromodomain proteins from Kac binding sites [52,53], confirming the essential role of bromodomain proteins in cardiac pathology. Taken together, these studies illustrate key roles of histone modification in heart development and disease. Further studies on the drugs such as HDAC inhibitors targeting histone methylation or acetylation are necessary for the treatment of cardiovascular diseases in the clinical.

Oxidative Modification

Oxidative modification is firmly implicated in the cardiac disorder [54]. Oxygen and nitricoxide which are referred to as ROS and reactive nitrogen species (RNS) are biologically critical cellular oxidants [54]. Excessive ROS and RNS cause cell damage through oxidative modification of marcromolecules including proteins and nucleotides (DNA and RNA). For proteins, methionine, tryptophan, tyrosine and cysteine residues can undergo oxidative modification, while only the oxidative modification of sulfhydryl group of cysteine has participated in signal transduction [55]. S-nitrosylation is the most important form of oxidative modification of proteins at sulfhydryl group, and is reported to be associated with heart diseases [55,56]. For example, glutathionylation of β1 Na^+-K^+pump subunit is increased by peroxynitrite (ONOO-), paraquat, or activation of NADPH oxidase stimulated by AngII, which inhibit Na^+-K^+pump activity in cardiac myocytes [57,58]. Caspase-3 is a critical cardiomyocyte apoptosis related protein and its oxidative modification participates in the apoptosis regulation. Caspase-3 glutathiolation attenuates necrosis factor-α induced endothelial cell death [59]. The levels of SECA2a oxidation/nitration are increased significantly in abnormal myocardium calcium homeostasis of diabetic rats. Further study indicates that iron exacerbates the diabetes-induced oxidative/nitrative modification of SERCA2a, which may lead to functional deficits in the myocyte associated with diabetic cardiac dysfunction [60]. Increased superoxide and nitric oxide production cause mitochondrial dysfunction in myocardial ischemia/reperfusion injury, of which the oxidative impairment decreases protein S-glutathionylation and increases protein tyrosine nitration at the 70kDa subunit, occur in the post-ischemic myocardium [61-63]. It is reported that polydatin protects cardiac function against burn injury by inhibiting sarcoplasmic reticulum $Ca2^+$ leak by reducing oxidative modification of ryanodine receptors [64]. Sirtuin 6 (Sirt6), a site-specific histone deacetylase that prevents development of cardiac hypertrophy and heart failure, could be oxidative modified. In detail, tyrosine 257 in Sirt6 is nitrated upon oxidative stress, and mutation of tyrosine 257 as well as abolishing the stimulation attenuate Sirt6 activity [65]. Besides, the protein actin, activating transcription factor/cyclic-AMP-responsive element binding protein (ATF/CREB), α4 VLA-4, c-Jun, creatine kinase, GAPDH, glutaredoxin, mitochondrial complex I, P50 subunit of NF-KB, protein kinase A, protein kinase C, PTP1B, Ras (G protein), ryanodine receptor, SERCA, and thioredoxin are susceptible to oxidative modification which involved in cardiovascular physiology and pathophysiology [54].

Additionally, oxidative modification of DNA and RNA is related to cardiovascular diseases. Besides 5- hydroxy thymine, 5-hydroxy methyl uracil, 5-Hydroxy-2-deoxycotosine and 8-hydroxyadenine, 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-OHdG) in DNA and 8-oxo-7, 8-dihydroguanosine (8-OHG) in RNA by ROS are two common forms of oxidative modification of nucleotides. The growing evidence has demonstrated that 8-OHdG and 8-OHG played an important role in heart pathophysiology. 8-OHdG and 8-OHG are most used as the biomarkers for monitoring oxidative damage and heart disease [66-70]. It is reported that 8-OHdG is implicated firmly in cardiovascular diseases including CAD, HF and MI. A significant increasing levels of 8-OHdG was observed in CAD, HF and MI patients compared to healthy control subjects [70]. Further study reveals that a high concentration of 8-OHdG caused by ROS induces atherosclerotic plaque formation through constructing a new lineage of smooth muscle cells, and then played a role in initiation

and progression of atherosclerosis [71,72]. In heart failure, a decreased number of mitochondrial DNA as well as a decline in its protein level are in agreement with the increased 8-OHdG concentrations, which indicates that 8-OHdG probably regulates heart failure through targeting mitochondrial DNA [70,73]. 8-OHdG also contributes to cocaine-related cardiomyopathy through regulating cardiomyocyte apoptosis and necrosis [74]. Oxidative modification of RNA has been demonstrated associated with aging and neurodegenerative diseases. The oxidation of ribosomal RNAs participated in Alzheimer's disease [75,76]. However, there is little report that oxidation of RNA function in cardiovascular system except one. Wang et al. [77] found that small RNA microRNA-184 could be oxidatively modified by ROS to form 8-OHG which leaded to the mismatch of microRNA-184 with Bcl-xL and Bcl-w involved in the regulation of cardiomyocyte apoptosis and ischemia/reperfusion injury.

MicroRNAs

MicroRNAs (miRNAs), a class of approximately 22-nucleotide non-coding RNA, function in regulating of gene expression in a variety of biological processes including cell proliferation, differentiation, damage, death and carcinogenesis. MicroRNAs also played a significant role in development, disease, aging and regeneration. With regard to cardiovascular system, microRNAs serve as a critical regulators implicated firmly in heart development and diseases [78,79].

During early heart development, the mammalian embryonic heart is mainly derived from four major cell types including cardiomyocytes, endocardial cells, epicardial cells, and neural crest cells. MicroRNAs participate in regulating the proliferation, differentiation, and survival of these cells [78]. MiR-1 inhibits cardiac growth and differentiation through targeting transcription factor HAND2 which is important for ventricular cardiomyocyte expression [80]. Overexpression of miR-1 inhibits cardiomyocytes proliferation, while knockout of miR-1 affects cardiac morphogenesis [81,82]. MiR-133 negatively regulates cardiomyocyte proliferation through inhibiting Cyclin D2 and Serum Response Factor [83]. Mir-320 induces apoptosis in cardiomyocytes by inhibiting heat-shock protein 20 [84]. Mir-143 and miR-145 are critical regulators in promoting the differentiation and proliferation of vascular smooth muscle cell from cardiac neural crest cells through targeting a network of transcription factors including *Klf4*, Myocardin, and *Elk*. The dedifferentiation decreases miR-143 and miR-145, while over expression of miR-143/145 enhances the differentiation of vascular smooth muscle cell [85,86]. During epicardial development, miR-21, miR-31, miR-103/107, miR-155, and miR-200 have been demonstrated playing important roles [87-89].

MicroRNAs participate widely in heart diseases including myocardial hypertrophy and myocardial infarction [79]. MiR-23a is known as its powerful function in myocardial hypertrophy regulation. MiR-23a expression level is upregulated in response to hypertrophy stimulation. Then MiR-23a initiates cardiac hypertrophy through different pathways such as inhibiting transcription factor Foxo3a and targeting lysophosphatidic acid. MiR-23a transgenic mice exhibit exaggerated cardiac hypertrophy upon treatment with phenylephrine, endothelin-1 or transverse aortic banding [90,91]. MiR-23a functions downstream of NFATc3 related cardiac hypertrophy pathway [92]. Besides MiR-23a, myocardial hypertrophy regulation network consists of many other MicroRNAs such as miR-541, miR-9, miR-218, miR-30c, miR-181a, miR-410, and miR-495 [93-97]. MicroRNAs play an important role in myocardial infarction. MiR-499 has been demonstrated inhibits myocardial infarction by negatively regulating both calcineurin and dynamin-related protein-1, and exhibits cardioprotective effects [98]. MiR-21 promote cardiac fibrosis by targeting extracellular regulated kinase inhibitor sprout homolog 1 (Spry1), and then exacerbate myocardial infarction [99].

Acknowledgments

This research was supported by China Postdoctoral Science Foundation (2016M592134), and National Natural Science Foundation of China (81270160).

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