Role of Epigenetics in Cardiac Development and Cardiovascular Diseases

Yanhan Dong#, Teng Sun#, Kun Wang, Jianxun Wang and Peifeng Li*

Institute for Translational Medicine, Qingdao University, Qingdao, China
#The authors contributed equally to this work

*Corresponding author: Peifeng Li, Institute for Translational Medicine, Qingdao University, Deng Zhou Road 38, Qingdao 266021, China, Tel: 86-532-82991791; **E-mail:** peifli@qdu.edu.cn

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-hydroxymethycytosine, 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 $\beta 1$ 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 Ca^{2+} 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].

References

1. Schiano C, Vietri MT, Grimaldi V, Picascia A, De Pascale MR, et al. (2015) Epigenetic-related therapeutic challenges in cardiovascular disease. Trends Pharmacol Sci 36: 226-235.

2. Jones PA, Archer TK, Baylin SB, Beck S, Berger S, et al. (2008). Moving AHEAD with an international human epigenome project. Nature 454: 711-715.

3. Abbott A (2010) Project set to map marks on genome. Nature 463: 596-597.

4. Schleithoff C, Voelter-Mahlknecht S, Dahmke IN, Mahlknecht U (2012) On the epigenetics of vascular regulation and disease. Clinical Epigenetics 4: 7.

5. Portela A, Esteller M (2010) Epigenetic modifications and human disease. Nat Biotechnol 28: 1057-1068.

6. Barres R, Osler ME, Yan J, Rune A, Fritz T, et al. (2009) Non-CpG methylation of the PGC-1alpha promoter through DNMT3B controls mitochondrial density. Cell Metab 10: 189-198.

7. Smith ZD, Meissner A (2013) DNA methylation: roles in mammalian development. Nat Rev Genet 14: 204-220.

8. Reik W, Dean W, Walter J (2001) Epigenetic reprogramming in mammalian development. Science 293: 1089-1093.

9. Wu H, Zhang Y (2014) Reversing DNA Methylation: Mechanisms, Genomics, and Biological Functions. Cell 156: 45-68.

10. Martinez SR, Gay MS, Zhang LB (2015) Epigenetic mechanisms in heart development and disease. Drug Discov Today 20: 799-811.

11. Smith ZD, Meissner A (2013) DNA methylation: roles in mammalian development. Nat Rev Genet 14: 204-220.

12. Hirasawa R, Chiba H, Kaneda M, Tajima S, Li E, et al. (2008) Maternal and zygotic Dnmt1 are necessary and sufficient for the maintenance of DNA methylation imprints during preimplantation development. Genes Dev 22: 1607-1616.

13. Okano M, Bell DW, Haber DA, Li E (1999) DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell 99: 247-257.

14. Gu TP, Guo F, Yang H, Wu HP, Xu GF, et al. (2011) The role of Tet3 DNA dioxygenase in epigenetic reprogramming by oocytes. Nature 477: 606-U136.

15. Chamberlain AA, Lin MY, Lister RL, Maslov AA, Wang YD, et al. (2014) DNA Methylation is Developmentally Regulated for Genes Essential for Cardiogenesis. J Am Heart Assoc 3: e000976.

16. Ziller MJ, Gu HC, Muller F, Donaghey J, Tsai LTY, et al. (2013) Charting a dynamic DNA methylation landscape of the human genome. Nature 500: 477-481.

17. Kaneda R, Takada S, Yamashita Y, Choi YL, Nonaka-Sarukawa M, et al. (2009) Genome-wide histone methylation profile for heart failure. Genes Cells 14: 69-77.

18. Buck-Koehntop BA, Defossez PA. (2013) On how mammalian transcription factors recognize methylated DNA. Epigenetics 8: 131-137.

19. Movassagh M, Choy MK, Knowles DA, Cordeddu L, Haider S, et al. (2011) Distinct Epigenomic Features in End-Stage Failing Human Hearts. Circulation 124: 2411-2422.

20. Yang AS, Estecio MRH, Doshi K, Kondo Y, Tajara EH, et al. (2004) A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. Nucleic acids research 32: e38.

21. Girelli D, Russo C, Ferraresi P, Olivieri O, Pinotti M, et al. (2000) Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. N Engl J Med 343: 774-780.

22. Friso S, Lotto V, Choi SW, Girelli D, Pinotti M, et al. (2012) Promoter methylation in coagulation F7 gene influences plasma FVII concentrations and relates to coronary artery disease. J Med Genet 49: 192-199.

23. Turunen MP, Aavik E, Yla-Herttuala S (2009) Epigenetics and atherosclerosis. Biochim Biophys Acta 1790: 886-891.

24. Doyama K, Fujiwara H, Fukumoto M, Tanaka M, Fujiwara Y, et al. (1996) Tumour necrosis factor is expressed in cardiac tissues of patients with heart failure. Int J Cardiol 54: 217-225.

25. Torre Amione G, Kapadia S, Lee J, Durand JB, Bies RD, et al. (1996) Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 93: 704-711.

26. Kao YH, Lien GS, Chao TF, Chen YJ. (2014) DNA methylation inhibition: A novel therapeutic strategy for heart failure. Int J Cardiol 176: 232-233.

27. Marin-Garcia J, Akhmedov AT (2015) Epigenetics of the failing heart. Heart Fail Rev 20: 435-459.

28. Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997) Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature 389: 251-260.

29. Jenuwein T, Allis CD (2001) Translating the histone code. Science 293: 1074-1080.

30. Zhou VW, Goren A, Bernstein BE (2011) Charting histone modifications and the functional organization of mammalian genomes. Nat Rev Genet 12: 7-18.

31. Di Salvo TG, Haldar SM (2014) Epigenetic mechanisms in heart failure pathogenesis. Circ Heart Fail 7: 850-863.

32. Strahl BD, Allis CD (2000) The language of covalent histone modifications. Nature 403: 41-45.

33. Vaquero A, Loyola A, Reinberg D (2003) The constantly changing face of chromatin. Sci Aging Knowledge Environ 2003: RE4.

34. Bernstein BE, Meissner A, Lander ES (2007) The mammalian epigenome. Cell 128: 669-681.

35. Verdone L, Caserta M, Di Mauro E (2005) Role of histone acetylation in the control of gene expression. Biochem Cell Biol 83: 344-353.

36. Bannister AJ, Kouzarides T (2011) Regulation of chromatin by histone modifications. Cell Res 21: 381-395.

37. Selth LA, Sigurdsson S, Svejstrup JQ (2010) Transcript Elongation by RNA Polymerase II. Annu Rev Biochem 79: 271-293.

38. Marmorstein R (2001) Structure of histone acetyltransferases. J Mol Biol 311: 433-444.

39. Aggarwal VS, Morrow BE (2008) Genetic modifiers of the physical malformations in velo-cardio-facial syndrome/DiGeorge syndrome. Dev Disabil Res Rev 14: 19-25.

40. Voss AK, Vanyai HK, Collin C, Dixon MP, McLennan TJ, et al. (2012) MOZ Regulates the Tbx1 Locus, and Moz Mutation Partially Phenocopies DiGeorge Syndrome. Dev Cell 23: 652-663.

41. Montgomery RL, Davis CA, Potthoff MJ, Haberland M, Fielitz J, et al. (2007) Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. Genes Dev 21: 1790-1802.

42. Gottlieb PD, Pierce SA, Sims RJ, Yamagishi H, Weihe EK, et al. (2002) Bop encodes a muscle-restricted protein containing MYND and SET domains and is essential for cardiac differentiation and morphogenesis. Nat Genet 31: 25-32.

43. Delgado-Olguín P, Huang Y, Li X, Christodoulou D, Seidman CE, et al. (2012) Epigenetic repression of cardiac progenitor gene expression by Ezh2 is required for postnatal cardiac homeostasis. Nat Genet 44: 343-347.

44. Jones B, Su H, Bhat A, Lei H, Bajko J, et al. (2008) The histone H3K79 methyltransferase Dot1L is essential for mammalian development and heterochromatin structure. PLoS Genet 4: e1000190.

45. Papait R, Cattaneo P, Kunderfranco P, Greco C, Carullo P, et al. (2013) Genome-wide analysis of histone marks identifying an epigenetic signature of promoters and enhancers underlying cardiac hypertrophy. Proc Natl Acad Sci U S A 110: 20164-20169.

46. Napoli C, Paolisso G, Casamassimi A, Al-Omran M, Barbieri M, et al. (2013) Effects of nitric oxide on cell proliferation: novel insights. J Am Coll Cardiol 62: 89-95.

47. Fish JE, Matouk CC, Rachlis A, Lin S, Tai SC, et al. (2005) The expression of endothelial nitric-oxide synthase is controlled by a cell-specific histone code. J Biol Chem 280: 24824-24838.

48. Granger A, Abdullah I, Huebner F, Stout A, Wang T, et al. (2008) Histone deacetylase inhibition reduces myocardial ischemia-reperfusion injury in mice. FASEB J 22: 3549-3560.

49. Zhang L, Qin X, Zhao Y, Fast L, Zhuang S, et al. (2012) Inhibition of histone deacetylases preserves myocardial performance and prevents cardiac remodeling through stimulation of endogenous angiomyogenesis. J Pharmacol Exp Ther 341: 285-293.

50. Filippakopoulos P, Picaud S, Mangos M, Keates T, Lambert JP, et al. (2012) Histone recognition and large-scale structural analysis of the human bromodomain family. Cell 149: 214-231.

51. Anand P, Brown JD, Lin CY, Qi J, Zhang R, et al. (2013) BET bromodomains mediate transcriptional pause release in heart failure. Cell 154: 569-582.

52. Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, et al. (2010) Selective inhibition of BET bromodomains. Nature 468: 1067-1073.

53. Dawson MA, Kouzarides T, Huntly BJ (2012) Targeting epigenetic readers in cancer. N Engl J Med 367: 647-657.

54. Rasmussen HH, Hamilton EJ, Liu CC, Figtree GA (2010) Reversible oxidative modification: implications for cardiovascular physiology and pathophysiology. Trends Cardiovasc Med 20: 85-90.

55. Janssen-Heininger YM, Mossman BT, Heintz NH, Forman HJ, Kalyanaraman B, et al. (2008) Redox-based regulation of signal transduction: principles, pitfalls, and promises. Free Radic Biol Med 45: 1-17.

56. Martinez-Ruiz A, Lamas S (2007) Signalling by NO-induced protein S-nitrosylation and S-glutathionylation: convergences and divergences. Cardiovasc Res 75: 220-228.

57. Figtree GA, Liu CC, Bibert S, Hamilton EJ, Garcia A, et al. (2009) Reversible oxidative modification: a key mechanism of Na+-K+ pump regulation. Circ Res 105: 185-193.

58. White CN, Liu CC, Garcia A, Hamilton EJ, Chia KK, et al. (2010) Activation of cAMP-dependent signaling induces oxidative modification of the cardiac Na+-K+ pump and inhibits its activity. J Biol Chem 285: 13712-13720.

59. Pan S, Berk BC (2007) Glutathiolation regulates tumor necrosis factor-alpha-induced caspase-3 cleavage and apoptosis: key role for glutaredoxin in the death pathway. Circ Res 100: 213-219.

60. Li X, Li W, Gao Z, Li H (2016) Association of cardiac injury with iron-increased oxidative and nitrative modifications of the SERCA2a isoform of sarcoplasmic reticulum Ca-ATPase in diabetic rats. Biochimie 127: 144-152.

61. Zhang L, Chen CL, Kang PT, Garg V, Hu K, et al. (2010) Peroxynitrite-mediated oxidative modifications of complex II: relevance in myocardial infarction. Biochemistry 49: 2529-2539.

62. Chen CL, Chen J, Rawale S, Varadharaj S, Kaumaya PP, et al. (2008) Protein tyrosine nitration of the flavin subunit is associated with oxidative modification of mitochondrial complex II in the post-ischemic myocardium. J Biol Chem 283: 27991-28003.

63. Chen YR, Chen CL, Pfeiffer DR, Zweier JL (2007) Mitochondrial complex II in the post-ischemic heart: oxidative injury and the role of protein S-glutathionylation. J Biol Chem 282: 32640-32654.

64. Jiang X, Liu W, Deng J, Lan L, Xue X, et al. (2013) Polydatin protects cardiac function against burn injury by inhibiting sarcoplasmic reticulum Ca2+ leak by reducing oxidative modification of ryanodine receptors. Free Radic Biol Med 60: 292-299.

65. Hu S, Liu H, Ha Y, Luo X, Motamedi M, et al. (2015) Posttranslational modification of Sirt6 activity by peroxynitrite. Free Radic Biol Med 79: 176-185.

66. Fiala ES, Conaway CC, Mathis JE (1989) Oxidative DNA and RNA damage in the livers of Sprague-Dawley rats treated with the hepatocarcinogen 2-nitropropane. Cancer Res 49: 5518-5522.

67. Shan X, Lin CL (2006) Quantification of oxidized RNAs in Alzheimer's disease. Neurobiol Aging 27: 657-662.

68. Lee CY, Isaac HB, Wang H, Huang SH, Long LH, et al. (2006) Cautions in the use of biomarkers of oxidative damage; the vascular and antioxidant effects of dark soy sauce in humans. Biochem Biophys Res Commun 344: 906-911.

69. Gao X, Tsou YH, Garis M, Huang H, Xu X (2016) Highly Specific Colorimetric Detection of DNA Oxidation Biomarker using Gold Nanoparticle/Triplex DNA Conjugates. Nanomedicine 12: 20101-2105.

70. Kroese LJ, Scheffer PG (2014) 8-hydroxy-2'-deoxyguanosine and cardiovascular disease: a systematic review. Curr Atheroscler Rep 16: 452.

71. Binková B, Smerhovský Z, Strejc P, Boubelík O, Stávková Z, et al. (2002) DNA-adducts and atherosclerosis: a study of accidental and sudden death males in the Czech Republic. Mutat Res 501: 115-128.

72. Martinet W, Knaapen MW, De Meyer GR, Herman AG, Kockx MM (2002) Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques. Circulation 106: 927-932.

73. Karamanlidis G, Nascimben L, Couper GS, Shekar PS, del Monte F, et al. (2010) Defective DNA replication impairs mitochondrial biogenesis in human failing hearts. Circ Res 106: 1541-1548.

74. Frustaci A, Russo MA, Morgante E, Scopelliti F, Aquilano K, et al. (2015) Oxidative myocardial damage in human cocaine-related cardiomyopathy. Eur J Heart Fail 17: 283-290.

75. Ding Q, Markesbery WR, Chen Q, Li F, Keller JN (2005) Ribosome dysfunction is an early event in Alzheimer's disease. J Neurosci 25: 9171-9175.

76. Zhan Y, Dhaliwal JS, Adjibade P, Uniacke J, Mazroui R, et al. (2015) Localized control of oxidized RNA. J Cell Sci 128: 4210-4219.

77. Wang JX, Gao J, Ding SL, Wang K, Jiao JQ, et al. (2015) Oxidative Modification of miR-184 Enables It to Target Bcl-xL and Bcl-w. Mol Cell 59: 50-61.

78. Yan S, Jiao K (2016) Functions of miRNAs during Mammalian Heart Development. Int J Mol Sci 17: E789.

79. Wang J, Liew OW, Richards AM, Chen YT (2016) Overview of MicroRNAs in Cardiac Hypertrophy, Fibrosis, and Apoptosis. Int J Mol Sci 17: 749.

80. Zhao Y, Samal E, Srivastava D (2005) Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. Nature 436: 214-220.

81. Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, et al. (2007) Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell 129: 303-317.

82. Meder B, Katus HA, Rottbauer W (2008) Right into the heart of microRNA-133a. Genes Dev 22: 3227-3231.

83. Liu N, Bezprozvannaya S, Williams AH, Qi X, Richardson JA, et al. (2008) microRNA-133a regulates cardiomyocyte proliferation and suppresses smooth muscle gene expression in the heart. Genes Dev 22: 3242-3254.

84. Ren XP, Wu J, Wang X, Sartor MA, Qian J, et al. (2009) MicroRNA-320 is involved in the regulation of cardiac ischemia/reperfusion injury by targeting heat-shock protein 20. Circulation 119: 2357-2366.

85. Cordes KR, Sheehy NT, White MP, Berry EC, Morton SU, et al. (2009) miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. Nature 460: 705-710.

86. Cheng Y, Liu X, Yang J, Lin Y, Xu DZ, et al. (2009) MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation. Circ Res 105: 158-166.

87. Singh MK, Lu MM, Massera D, Epstein JA (2011) MicroRNA-processing enzyme Dicer is required in epicardium for coronary vasculature development. J Biol Chem 286: 41036-41045.

88. Bronnum H, Andersen DC, Schneider M, Sandberg MB, Eskildsen T, et al. (2013) miR-21 promotes fibrogenic epithelial-to-mesenchymal transition of epicardial mesothelial cells involving Programmed Cell Death 4 and Sprouty-1. PLoS One 8: e56280.

89. Bronnum H, Andersen DC, Schneider M, Nossent AY, Nielsen SB, et al. (2013) Islet-1 is a dual regulator of fibrogenic epithelial-to-mesenchymal transition in epicardial mesothelial cells. Exp Cell Res 319: 424-435.

90. Wang K, Lin ZQ, Long B, Li JH, Zhou J, et al. (2012) Cardiac hypertrophy is positively regulated by MicroRNA miR-23a. J Biol Chem 287: 589-599.

91. Yang J, Nie Y, Wang F, Hou J, Cong X, et al. (2013) Reciprocal regulation of miR-23a and lysophosphatidic acid receptor signaling in cardiomyocyte hypertrophy. Biochim Biophys Acta 1831: 1386-1394.

92. Lin Z, Murtaza I, Wang K, Jiao J, Gao J, et al. (2009) miR-23a functions downstream of NFATc3 to regulate cardiac hypertrophy. Proc Natl Acad Sci U S A 106: 12103-12108.

93. Liu F, Li N, Long B, Fan YY, Liu CY, et al. (2014) Cardiac hypertrophy is negatively regulated by miR-541. Cell Death Dis 5: e1171.

94. Wang K, Long B, Zhou J, Li PF (2010) miR-9 and NFATc3 regulate myocardin in cardiac hypertrophy. J Biol Chem 285: 11903-11912.

95. Clark AL, Maruyama S, Sano S, Accorsi A, Girgenrath M, et al. (2016) miR-410 and miR-495 Are Dynamically Regulated in Diverse Cardiomyopathies and Their Inhibition Attenuates Pathological Hypertrophy. PLoS One 11: e0151515.

96. Liu JJ, Zhao CM, Li ZG, Wang YM, Miao W, et al. (2016) miR-218 Involvement in Cardiomyocyte Hypertrophy Is Likely through Targeting REST. Int J Mol Sci 17: 848.

97. Raut SK, Singh GB, Rastogi B, Saikia UN, Mittal A, et al. (2016) miR-30c and miR-181a synergistically modulate p53-p21 pathway in diabetes induced cardiac hypertrophy. Mol Cell Biochem 417: 191-203.

98. Wang JX, Jiao JQ, Li Q, Long B, Wang K, et al. (2011) miR-499 regulates mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1. Nat Med 17: 71-78.

99. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, et al. (2008) MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 456: 980-984.