MINIREVIEWS

Novel epigenetic-based therapies useful in cardiovascular medicine

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Abstract

Epigenetic modifications include DNA methylation, histone modifications, and microRNA. Gene alterations have been found to be associated with cardiovascular diseases, and epigenetic mechanisms are continuously being studied to find new useful strategies for the clinical management of afflicted patients. Numerous cardiovascular disorders are characterized by the abnormal methylation of CpG islands and so specific drugs that could inhibit DNA methyltransferase directly or by reducing its gene expression (*e.g.*, hydralazine and procainamide) are currently under investigation. The anti-proliferative and anti-inflammatory properties of histone deacetylase inhibitors and their cardioprotective effects have been confirmed in preclinical studies. Furthermore, the regulation of the expression of microRNA targets through pharmacological tools is still under development. Indeed, large controlled trials are required to establish whether current possible candidate antisense microRNAs could offer better therapeutic benefits in clinical practice. Here, we updated therapeutic properties, side effects, and feasibility of emerging epigenetic-based strategies in cardiovascular diseases by highlighting specific problematic issues that still affect the development of large scale novel therapeutic protocols.

Key words: Epigenetics; Cardiovascular diseases; Heart failure; Inhibitors of histone deacetylases; Antisense microRNAs

Core tip: Recent evidence suggests that specific epigenetic regulatory mechanisms play key roles in cardiac differentiation, homeostasis, injury response, and disease development. Drug therapies that work *via* epigenetic mechanisms are currently limited to antineoplastic agents; large controlled trials are required to establish whether

current possible candidate antisense microRNAs or histone deacetylase inhibitors could offer better therapeutic benefits in cardiovascular disease. We review recent findings on the epigenetic control of several cardiovascular diseases and the new challenges for therapeutic strategies in cardiovascular diseases.

INTRODUCTION

Cardiovascular diseases (CVDs) are the primary cause of death worldwide, with 17.5 million deaths from CVD in 2012 representing 31% of all global deaths that year. CVDs include a number of alterations affecting heart and vascular structures, such as heart valves, heart muscle (*e.g.*, cardiomyopathy), and pericardial and coronary artery diseases. All these conditions may result in cardiomyocyte loss, cardiac-remodeling with consequent heart failure (HF), and an increased risk of arrhythmias and death. Cardiac fibroblasts also have a pivotal role in HF[1]. Indeed, endothelial cell activation and inflammation promotes the transdifferentiation of fibroblasts to myofibroblasts which, after extensive collagen production, results in the release of chemokines and the activation of inflammatory cells, which in turn causes cardiomyocyte stiffness by contributing to HF pathogenesis[1]. Increasing evidence has shown that epigenetic mechanisms control and influence the expression of cell cycle central genes involved in human disease progression[2]. Toward this context, significant epigenetic and epigenomic findings have opened a new area of research by exploring the role of genetic heritability and environmental interaction in CVDs[3]. Some deregulated epigenetic steps are involved in the pathophysiology of CVDs[4]. Specific epigenetic regulatory mechanisms could impact on the endothelium, cardiac muscle, smooth muscle, and fibroblasts[5]. Thus, the pharmacological setting of these pathways might represent a specific target for CVDs. Due to the reversible nature of these modifications, researchers are continuously engaged in the development of novel epigenetic-based drugs (epidrugs) for CVD treatment[6,7]. The primary goal of future studies will be to allow for the identification of selective therapeutic molecules that have been conceived in order to act on specific epigenetic-related pathogenic events.

Here, we summarize the current knowledge concerning epigenetic-based strategies in CVDs by outlining novel therapeutic steps in clinical practice.

EPIGENETICS INVOLVEMENT IN CVDs

DNA methylation as therapeutic target

DNA methylation is the most studied epigenetic modification and mainly involves methylation of CpG islands in the promoter genes. It has good long-term stability and is the most common modification involving the regulation of gene expression in the mammalian genome. All changes in methylation are modulated by specific catalytically-active enzymes, including "maintenance" methyltransferase (DNMT1) and "*de novo*" methyltransferase (DNMT3a and DNMT3b). DNMTs act by adding methyl groups to CpG residues, thereby modifying the accessibility of DNA to the transcriptional machinery. Altered regulation of cytosine methylation has been linked to CVD development and progression[8], as well as to cancer cell development[9]. In addition, DNA methylation has been shown to regulate biological processes underlying CVDs, such as atherosclerosis, inflammation, hypertension, and diabetes[10,11]. DNA methylation is also involved in essential arterial hypertension[12,13]. To date, DNA methylation remains an attractive target for CVD interventions, owing to its reversible nature. Dietary compounds, including polyphenols and catechins, act on DNA methylation processes[14,15]. In particular, some interesting clinical studies have shown that elevated consumption of polyphenols decreases global DNA methylation of peripheral leukocytes in humans with cardiovascular risk factors (NCT00511420 and NCT00502047)[16]. However, the role of nutrients in the evolvement of CVDs through the epigenetic link remains as yet studied. Conversely, the cardiovascular implication of pharmacological epigenetic compounds appears to be more direct and far-reaching. Indeed, some drugs are known to affect DNA methylation. Hydralazine, a vasodilator used to treat hypertension[17], is an example of compound that has been shown to inhibit DNA methyltransferase directly or by reducing its gene expression[18]. There are several clinical trials focusing on the use of hydralazine to combat hypertensive conditions (Table 1). Many of these completed trials have highlighted the beneficial effect of hydralazine on both hypertension and other cardiovascular conditions compared to other compounds. Several studies have shown that hydralazine might function by modulating the effect of purine-like compounds released from sympathetic nerve endings and/or by inducing an altered Ca^{2+} balance in vascular smooth muscle cells[19,20]; unfortunately, there are fundamental as-yet unresolved issues concerning this area of research that remain unclarified.

Procainamide is another drug that inhibits DNA methyltransferase I. It is a sodium channel blocker that belongs to the class of benzamides used against arrhythmias[21]. Clinical trials have evaluated this anti-arrhythmic drug in the acute treatment of monomorphous ventricular tachycardia with positive effects (Table 1). Nevertheless, recent evidence has shown toxic effects of procainamide on the lung after orthotopic cardiac transplantation[22].

Despite the use of the aforementioned drugs in cancer treatment appearing to have promising results[23], the implication of their epigenetic effects in CVDs requires further investigation in future studies.

Table 1 Interventional and randomized ongoing clinical trials on the use of hydralazine and procainamide in cardiovascular diseases

No.	Status	Condition	No. of enrolled patients	Intervention
NCT00684489	Completed	Hypertension	52	Hydralazine and other drugs
NCT02305095	Not open for participant recruitment	Heart failure	500 (estimated enrollment)	Hydralazine in combination with isosorbide dinitrate
NCT00661895	Completed	Hypertension	99	Hydralazine and other drugs
NCT00599235	Completed	Hypertension	30	Hydralazine, sildenafil, and placebo
NCT00223717	Recruiting participants	Hypertension	160 (estimated enrollment)	Hydralazine and other drugs
NCT01255475	Completed	Heart failure, cardiac failure, and congestive heart failure	21	Hydralazine/amlodipine and placebo
NCT01516346	Recruiting participants	Heart failure and congestive heart failure	54 (estimated enrollment)	Hydralazine, isosorbide dinitrate, and placebo
NCT01822808	Recruiting participants	Acute heart failure and left ventricular dysfunction	500 (estimated enrollment)	Hydralazine, isosorbide dinitrate, and placebo
NCT00000499	Completed	Cardiovascular diseases, heart diseases, hypertension, and vascular diseases	Not provided	Hydralazine, reserpine, chlorthalidone, and metoprolol
NCT02050529	Recruiting participants	Hypertension, Pregnancy induced	180 (estimated enrollment)	Hydralazine, labetalol
NCT01538875	Completed	Hypertension, Pregnancy induced	261	Hydralazine, labetalol
NCT00383799	Unknown	Ventricular tachycardia	302 (estimated enrollment)	Procainamide, amiodarone
NCT00000464	Completed	Arrhythmia, Cardiovascular diseases	115	Procainamide, quinidine, disopyramide, and other drugs
NCT00702117	Completed	Atrial fibrillation, tachycardia	123	Procainamide, ajmaline, flecainide
NCT00589303	Terminated	Atrial fibrillation, heart failure	27	Rhythm control drugs: Procainamide and other drugs
NCT00000556	Completed	Arrhythmia, atrial fibrillation, cardiovascular diseases	4060	Procainamide and other drugs
NCT01205529	Recruiting	Atrial fibrillation	750 (estimated enrollment)	Procainamide

Histone modifications as therapeutic target

Epigenetic alterations occur in the histone code, and so can modulate histone-DNA interactions and significantly influence chromatin structure by modifying the accessibility of transcriptional regulators to DNA-binding elements[24]. The most common modifications are lysine acetylation and methylation, arginine methylation, and serine phosphorylation. Histone acetylation is catalyzed by histone acetyltransferases (HATs), while histone deacetylation is carried out by histone deacetylases (HDACs)[25].

Inhibitors of histone deacetylases (HDACi) represent a significant group of epidrugs that could be highly relevant to the treatment of CVDs. Indeed, HDACi exert anti-proliferative and anti-inflammatory effects, and their cardio-protective therapeutic use has been recently confirmed in preclinical studies[26,27].

According to their chemistry, HDACi can be divided into four main groups: Hydroxamates, aliphatic acids, benzamides, and cyclic peptides. Hydroxamates like trichostatin A (TSA) and vorinostat (suberoylanilide hydroxamic acid, SAHA) serve as pan-HDACi and are generally most often used for preclinical studies[28-30].

Principal histone modifications and therapeutic targets involved in CVDs are reported in Table 2. Animal studies *in vivo* showed that TSA treatment improved functional myocardial recovery after myocardial infarction (MI) *via* a reduction in myocardial and serum tumor necrosis factor-α. Neo-angiogenesis was demonstrated in MI animals after receiving TSA treatment[31]. Taken together, these results indicate that HDACi could preserve cardiac performance and mitigate myocardial remodeling by stimulating endogenous cardiac regeneration[31]. HDAC inhibition was also shown to attenuate ischemic injury in the heart and other tissues. Pre-treatment with TSA resulted in improvements in post-ischemic ventricular function, with a reduction in infarct size in both early and delayed preconditioning models[32]. Despite the high activity of TSA, it was disqualified as a clinical drug due to its many side effects, such as non-transformed cell apoptosis and increased DNA damage[33].

Vorinostat was approved by the Unites States Food and Drug Administration (FDA) for the treatment of advanced cutaneous T cell lymphoma[34]. Suberoylanilide hydroxamic acid (SAHA/vorinostat) reduced myocardial infarct size in a large animal model, even when delivered in the clinically relevant context of reperfusion[35,36].

Aliphatic acids like valproic acid (VPA, 2-propylpentanoic acid) inhibits class I HDACs, causing accumulation of hyperacetylated histone tails (H3 and H4 histones) and other protein targets such as p53. VPA has anti-proliferative and pro-apoptotic activities. Lee *et al*[37] demonstrated the

Table 2 Histone modifications and therapeutic targets involved in cardiovascular diseases

Target	Epigenetic mechanisms	Condition	Organism/*in vitro, in vivo*	Effects	Ref.
TSA	Inhibition of HDAC4	Ischemic injury	Mouse, *in vitro* and *in vivo*	HDACi would be predicted to have a beneficial effect in the context of active ischemia	Granger *et al*[28] (2008)
TSA/VPA	Class I HDACs	Cardiac hypertrophy	Mouse, *in vitro* and *in vivo*	Therapeutic target for preventing or reversing cardiac hypertrophy and subsequent heart failure	Kee *et al*[29] (2006)
TSA	Inhibition of HDACs	Atrial fibrosis and arrhythmias	Mouse, *in vitro* and *in vivo*	Reversed myocardial fibrosis	Liu *et al*[30] (2008)
TSA	Inhibition of HDACs	Acute myocardial ischemia and reperfusion injury	Mouse, *in vitro* and *in vivo*	Improved cardiac functional recovery and antagonized myocardial remodeling in chronic myocardial infarction	Zhang *et al*[31] (2012)
TSA/SAHA	HDAC inhibitor	Myocardial infarct	Mouse, rabbit, *in vivo*	Reduced infarct size in a large animal model	Xie *et al*[35] (2014)
SAHA/sodium valproate	Inhibition of HDACs	Ischemic injury	Mouse, *in vitro* and *in vivo*	Potential therapeutic strategy for restoring compromised cardiac proteostasis	Wang *et al*[36] (2011)
VPA or tributyrin	Inhibition of HDACs	Infarct	Rat, *in vitro*	Attenuated ventricular remodeling after infarction	Lee *et al*[37] (2007)
MS-275A	Inhibition of class I/II HDACs	Infarct	Rat, *in vivo*	Significant reduction of infarct area observed	Aune *et al*[39] (2014)
Apicidin	Inhibition of class I HDACs	Cardiac hypertrophy and heart failure	Rat pups, *in vitro* Mouse, *in vivo*	Preserved cardiac function in the long-term	Gallo *et al*[42] (2008)
Curcumin	p300 HAT inhibitor	Heart failure	Rat, *in vitro*	Prevented deterioration of systolic function and heart failure	Morimoto *et al*[45] (2008)

TSA: Trichostatin A; HDAC: Histone deacetylases; HDACi: Inhibitors of histone deacetylases; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid.

attenuation of ventricular remodeling following MI *in vivo* when VPA or tributyrin was administered to rats 24 h after ligation of the left anterior descending artery. However, these short chain fatty acids are known to weakly inhibit HDAC activity with a number of off-target effects[38].

Benzamides are small molecules that are mostly active against class Ⅰ HDACs. Class Ⅰ HDACi is entinostat (MS-275A) and prompts protective effects against ischemia reperfusion injury in isolated rat heart. MS-275A is not effective against class Ⅱ b HDAC6[39]. Entinostat might be more advantageous than first-generation examples such as TSA, vorinostat, romidepsin, and VPA, as less profound side effects are observed[40]. Some studies have suggested that tranilast also has cardiovascular-protective effects[41]. Depsipeptide is a natural cyclic peptide that inhibits HDAC 1 and 2, and selectively modulates the expression levels of different genes such as c-myc, Hsp90, and p53. The cyclic peptide family includes other HDACi, such as apicidin. The apicidin derivative API-D is capable of reducing hypertrophy and, consequently, the transition to HF in mice subjected to thoracic aortic constriction. Treatment with this substance therefore establishes a relevant therapeutic approach for HF[42].

The cardiovascular protective effects of p300 HAT inhibitor curcumin have been demonstrated[43,44]. In a rat model of HF and primary cultured rat cardiac myocytes and fibroblasts, curcumin prevented ventricular hypertrophy and preserved systolic function[45].

RNA-based mechanisms as novel biomarkers
MicroRNAs are key regulators of gene expression acting at the post-transcriptional level. MiRNAs are implicated in the pathogenesis of several CVDs[46]. The modulation of miRNA expression could represent an innovative therapeutic approach to the treatment of cardiovascular conditions by targeting a single cell type or specific pathways, as demonstrated in an animal model[47,48]. Recently, several study population have investigated the involvement of transcriptionally regulated miRNAs as an attractive target for the treatment of several cardiovascular conditions (Table 3). Preclinical studies using antisense oligonucleotide (antagomir) -mediated knockdown have demonstrated the role of specific miRNAs in HF[47,49,50]. Indeed, it was shown that a single treatment with the infusion of a miR133 antagomir induced cardiac hypertrophy in mice[49]. Recently, Wahlquist *et al*[47] demonstrated that high levels of miR25 can depress cardiac function, although the inhibition of this miRNA by anti-miR25 effectively restores cardiac function in an HF mouse model. Interestingly, it was demonstrated that miRNAs secreted by cardiac fibroblasts may also act as mediators of cardiomyocyte hypertrophy *via* a paracrine mechanism[50]. During hypertension or pathological cardiac hypertrophy, reactivation of fetal cardiac genes such as atrial natriuretic peptide, (ANP)/B-type natriuretic peptide (BNP), and beta-myosin heavy chain (β-MHC) can occur. In a hypertensive mouse model, aldosterone-dependent inhibition of miR-208a can occur, resulting in β-MHC inhibition and an increase of cardiac hypertrophy[51]. It was also shown that therapeutic inhibition of miR-208a led to a reduction in cardiac remodeling, which coincided with a significant improvement in survival and cardiac function during heart disease[48]. Additionally, in hypertensive rat models, changes in β-MHC expression were observed

Table 3 Recent evidence investigating the role of circulating miRNAs as biomarkers in several cardiovascular diseases

miRNAs	Sources	Conditions	Ref.
↑miR-339-5p, miR-483-3p	Plasma	LVI	Saddic *et al*[64] (2015)
↓miR-139-5b			
↓miR-145	Plasma	AMI	Gao *et al*[65] (2015)
↑miR-122, miR-140-3p, miR-720, miR-2861, miR-3149	Plasma	ACS, AMI	Li *et al*[66] (2015)
↑Let-7e, miR-15a, miR-196b	Plasma	AAA, Atherosclerosis	Stather *et al*[67] (2015)
↓miR-411			
↓ miR-125b, miR-320b	Plasma	AMI, CAD	Huang *et al*[68] (2014)
↓miR-21	Serum	CAD	Fan *et al*[69] (2014)
↓miR-31	Plasma	CAD	Wang *et al*[70] (2014)
↑miR-146a, miR-186, miR-208b, miR-499	Serum	ACS, Stable CAD, CV risk	Wu *et al*[71] (2014)
↑miR-210	PBMC	HF	Endo *et al*[72] (2013)
↑miR-21, miR-25, miR-92a, miR-106b, miR-126, miR-451, miR-590-5p	Plasma	AP, UA	Ren *et al*[73] (2013)
↔ miR-1, miR-208a, miR-423-5p	Plasma	AMI, CAD	Nabialek *et al*[74] (2013)
↑miR-30a, miR-210	Serum	HF	Zhao *et al*[75] (2013)
↑miR-337-5p, miR-433, miR-485-3p, miR-1, miR-122, miR-126, miR-133a/b, miR-199a	Plasma	AP, UA	D'Alessandra *et al*[76] (2013)
↔miR-17-5p, miR-92a, miR-145, miR-155, miR-208a, miR-375, miR-799-5p			
↓miR-103, miR-142-3p, miR-30b, miR-342-3p	Plasma	HF	Ellis *et al*[77] (2013)
↑miR-122, miR-200b, miR-520d-5p, miR-622	WB and serum	HF	Vogel *et al*[78] (2013)
↓miR-558			
↑miR-21, miR-133a, miR-423-5p, miR-499-5p	Plasma	HF, NSTEMI	Olivieri *et al*[79] (2013)
↔miR-1, miR-208a			
↑miR-133a	Plasma	AMI, AP	Wang *et al*[80] (2013)
↓miR-214	Plasma	AMI, AP, UA	Lu *et al*[81] (2013)

AAA: Abdominal aortic aneurysm; ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; AP: Angina pectoris; CAD: Coronary artery disease; CV: Cardiovascular; HF: Heart failure; LVI: Left ventricular ischemia; NSTEMI: Non-ST-elevation myocardial infarction; PBMC: Peripheral blood mononuclear cells; UA: Unstable angina; WB: Whole blood.

after treatment with anti-miR-208a that acted by reverting the levels of several miRNAs, including miR-16, -19b, and -20b[52]. Recently, the regulation of miR-208a and endoglin in AMI were investigated, with the authors demonstrating that the overexpression of antagomir-208a significantly inhibited the increase of myocardial endoglin and β-MHC protein expression induced by infarction[53]. In addition, pre-treatment with atorvastatin and valsartan, members of a drug class known as statins that are primarily used for the prevention of events associated with cardiovascular disease, can decrease myocardial fibrosis induced by AMI by attenuating miR-208a and endoglin expression[53]. Clinical evidence supports the different levels of miR-143, miR-145, miR-21, miR-133, and miR-1 expression in patients with essential hypertension, suggesting that these miRNAs can act in vascular smooth muscle cell phenotypic modulation and could represent potential therapeutic targets in essential hypertension[54]. It was found that the chronic restoration of miR-1 gene expression in an animal model reverted pressure-induced cardiac hypertrophy and prevented the adverse cardiac remodeling induced by pressure overload[55]. Recently, Han *et al*[56] found higher levels of miR-29a in patients with hypertension and left ventricular (LV) hypertrophy compared to patients with hypertension alone. MiR-29a levels were significantly associated with collagen type Ⅰ and Ⅲ and MMP-9 expression. The same authors, employing a mouse model of pressure overload, have shown that antagomir-29a significantly suppressed the hypertrophy of cardiomyocytes and reduced the expression of ANP

and β-MHC, suggesting a possible role of miR-29a as a therapeutic target[56]. Several preclinical studies showed the beneficial effects of antagomir-92a administration on small and large animal models before MI[57-59]. Inhibition of miR-92a by repeated intravenous injections of antagomir-92a induced angiogenesis and improved recovery of ventricular function in MI mouse model[57]. In MI large animal models, antagomir-92a treatment revealed cardio-protection against ischemia/reperfusion[58]. Recent evidence has demonstrated favorable post-ischemic myocardial repair after intravenous administration of antagomir-92a in adult large animal models[59]. Indeed, neovasculogenesis and the prevention of adverse ventricular remodeling, the major cause of contractile dysfunction and HF after MI, were observed after intravenous administration of antagomir-92a[59]. These results reveal a promising therapeutic approach for patients affected by MI. Progression of post-infarction LV remodeling in mice was studied by Tolonen *et al*[60], who observed that the inhibition of Let-7c was associated with decreased apoptosis, reduced fibrosis, and a reduction in the number of discoidin domain receptor 2-positive fibroblasts, while the number of c-kit+ cardiac stem cells and Ki-67+ proliferating cells remained unaltered[60]. Although Let-7c inhibitor injection improved cardiac function after MI, the safety of Let-7c inhibition has yet to be clarified due to its dualistic function that appears to have a causative role in various cancer diseases.

Circulating miRNA patterns are analyzed as potential disease specific biomarkers in CVDs in two observational

prospective studies on aortic aneurism in hereditary aortopathy syndromes (NCT02213484), coronary artery diseases, and myocardial infarction (NCT02076153). Three interventional randomized studies are focusing on the association between miRNA profile modifications and the administration of specific molecules like anti-platelet agents (NCT02071966) (NCT02447809) in coronary syndromes and anti-diabetics drugs in diabetic stable and unstable angina (NCT01331967).

CONCLUSION

To date, several epidrugs (such as vorinostat and panobinostat) have been approved for the treatment of cancer and myelodysplastic syndromes, and are therefore commercially available. However, no epigenetic drugs for CVDs have yet been actually approved by the FDA. Nevertheless, the opportunity to control genetic and epigenetic processes could be considered a promising and attractive tool in cardiovascular medicine. For this reason, the investigation of epigenetic-related mechanisms might help to explain how environmental and lifestyle factors can influence aberrant gene expression patterns over a lifetime that can result in increased cardiovascular risk. Preclinical experiments have identified some HDACi that could have future implications in the treatment of several cardiovascular conditions, including atrial fibrillation, cardiac hypertrophy, and HF. Ongoing human clinical controlled studies are emphasizing the ability of some drugs such as hydralazine and procainamide to act on DNA methylation in CVDs. However, the clinical experience with HDACi in CVDs is limited due to the observed toxic cardiac side effects in oncologic patients.

The study of the human genome will find biomarkers that might affect CVDs. It is likely that only epigenetic profiles obtained from large cohorts of patients with the same genetic mutations will be able to promote the development of surveillance programs and novel effective drugs for the transition of *in vitro* to *in vivo* treatments for the early stage of CVDs[61-63].

To date, few clinical trials have investigated the link between drugs and specific miRNA profiles, which might be considered as biomarkers for the classification of CVDs with scarce compliance to standard therapy and affected by the incidence of more aggressive clinical phenotypes. Unfortunately, antagomir in the area of cardiovascular disease has not yet been tested in clinical trials. However, the promising studies covered here reflect the open debate for possible future applications of miRNA therapeutics in CVDs.

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