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Epigenetic Regulation in Heart Failure

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Abstract

Purpose of review—To provide an overview, highlighting recent findings, of a major mechanism of gene regulation and its relevance to the pathophysiology of heart failure.

Recent findings—The syndrome of heart failure is a complex and highly prevalent condition, one in which the heart undergoes substantial structural remodeling. Triggered by a wide range of disease-related cues, heart failure pathophysiology is governed by both genetic and epigenetic events. Epigenetic mechanisms, such as chromatin/DNA modifications and non-coding RNAs, have emerged as molecular transducers of environmental stimuli to control gene expression. Here, we emphasize metabolic milieu, aging, and hemodynamic stress as they impact the epigenetic landscape of the myocardium.

Summary—Recent studies in multiple fields, including cancer, stem cells, development, and cardiovascular biology, have uncovered biochemical ties linking epigenetic machinery and cellular energetics and mitochondrial function. Elucidation of these connections will afford molecular insights into long-established epidemiological observations. With time, exploitation of the epigenetic machinery therapeutically may emerge with clinical relevance.

Keywords

Heart Failure; Epigenetics; Metabolism; Aging

Introduction

Heart failure (HF) is a complex and highly prevalent syndrome in which the myocardium is unable to meet the circulatory demands of the organism [1]. It is important to recognize the HF is a syndrome that arises as the culmination of a wide range of disease processes, including genetic disorders, ischemic disease, metabolic disease, and hypertension. Aging, diabetes, and obesity – three globally increasing trends across diverse populations – are major clinical risk factors for HF [2]. Multiple studies have reported increased HF

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Conflicts of Interest

None declared.

prevalence, severity, and mortality in these conditions [3–5]. Whereas robust associations exist between myocardial dysfunction and these environmental factors, mechanistic links among them are complex and incompletely characterized. In fact, some efforts to elucidate mechanisms of pathogenesis have been fruitful, with two novel pharmacological therapies emerging in recent months [6,7]. Despite this, HF is a relentlessly progressive disorder with mortality exceeding that of most cancers.

Failing heart undergoes structural and functional remodeling which entails substantial transcriptional reprogramming [8,9]. For this reason, research in the field has centered on mechanisms governing gene expression, including a number of transcription factors [1,8,10]. A notable feature of many of these transcription factors is that, under stress, their relative abundance does not change substantially while their activity is altered [8]. This suggests a role of posttranslational events, both direct modifications of the transcription factors themselves and modifications of chromatin to alter gene accessibility, in transcriptional reprogramming. In addition, regulation of transcript stability and transcript translation by microRNAs has garnered considerable attention [11]. Together, these observations suggest strongly that epigenetic regulation of gene expression is a major mechanism governing disease-related cardiac remodeling and HF pathogenesis [8].

Over the past two decades, details of epigenetic regulation in cardiac biology and pathology have been studied extensively, yielding insights into molecular mechanisms that govern multiple signaling pathways during pathologic remodeling (for details see [12–15]). More recently, questions regarding events which trigger changes in the epigenetic landscape during disease-related stress are being explored. Here, we highlight recent work revolving around this theme, focusing on metabolic milieu and aging, for each of four epigenetic mechanisms: 1) histone acetylation, 2) histone methylation, 3) DNA methylation, and 4) non-coding RNA. Actions of other epigenetic mechanisms, including ATP-chromatin remodeling enzymes, have been summarized elsewhere [16].

Chromatin acetylation

An intricate and highly conserved structure supporting reversible histone acetylation plays an essential role in epigenetic control within the eukaryotic genome [14,15,17]. The acetylation machinery comprises 3 distinct components: 1) Histone acetyltransferases (HATs, “writers”), enzymes which transfer acetyl groups to histone tails within chromatin, generally relaxing nucleosomal structure and increasing accessibility of genes to DNA-binding elements. In contrast, 2) HDACs (histone deacetylases) “erase” the acetylation marks, condensing chromatin and decreasing its local accessibility. The final component is 3) the BET family of bromodomain (BRD) proteins, which function as “readers” of those acetylation marks, facilitating protein complex formation required for appropriate gene regulation. Together, this elegant and orchestrated, three-component system is a highly dynamic and effective means of governing gene transcription.

The simple, yet powerful, chemical nature of acetylation in “opening/closing” the chromatin architecture is such that the acetylation machinery serves as a global transcriptional co-activator or repressor [17,18]. Its indispensable role has been documented in normal

development and physiology, as well as in the pathobiology of many diseases, including cancer, inflammation, and HF [19,20]. Pioneering studies in the early 2000's elucidated the critical roles of HATs [21] and HDACs [22,23] in controlling the actions of several transcription factors, including GATA4, NFAT and MEF2, which are involved in maladaptive cardiac remodeling. Since then, the histone acetylation machinery has also emerged as a novel therapeutic target for various cardiac disease states, including HF. Table I summarizes currently available pharmacological tools that target chromatin acetylation, and other epigenetic mechanisms, in preclinical models of HF.

Acetylation links metabolism to genetic reprogramming

The relative switch in cardiomyocyte energy substrate utilization from fatty acids (FA) to glucose is the metabolic hallmark of HF remodeling [31,32]. In failing heart, this metabolic shift accompanies an uncoupling of glycolysis and pyruvate oxidation, resulting in inefficient energy production [33,34]. A key molecular event in this metabolic shift is the inactivating phosphorylation of pyruvate dehydrogenase (PDH), the rate-limiting enzyme of the Krebs cycle that mediates conversion of pyruvate to acetyl-CoA, by its kinase PDK (pyruvate dehydrogenase kinase) [35]. Increased activity of cardiac PDK, PDK4 specifically, has been documented clinically in conditions of chronic hemodynamic stress and chronic metabolic stress [36,37]. Mechanistically, persistent neurohormonal stimulation, increased FA signaling, and insulin resistance converge at a molecular level to activate PDK4 [38–40].

The importance of PDK4-triggered metabolic disruption in HF pathogenesis has been established in both preclinical and clinical studies [41–43]. Dichloroacetate (DCA), a small molecule inhibitor of PDK4, manifests efficacy in models of ischemic and pressure overload-induced HF, blunting pathological remodeling and partially restoring myocardial energetics [42]. Recently, evidence has emerged that these alterations not only affect myocardial energetics, but may also contribute to transcriptional reprogramming involved in maladaptive remodeling. DCA promotes re-entry of pyruvate into the Krebs cycle and results in increased intracellular acetyl-CoA (the substrate for HATs) and β -hydroxybutyrate (an endogenous class I HDAC inhibitor) [44]. These events, in turn, correlate with increases in histone acetylation in DCA-treated heart as well as increased gene expression, particularly among genes involved in transcriptional control. In fact, the role of intracellular acetyl-CoA levels as a “carbon-source rheostat” to transduce the cellular metabolic state into gene expression by controlling HAT activity has been noted previously [45–47].

Another metabolic cofactor is nicotinamide adenine dinucleotide (NAD^+), a major coenzyme involved in multiple enzymatic actions during energy production and cellular redox regulation [48]. Like acetyl-CoA, the intracellular pool of NAD^+ is sensitive to a variety of metabolic perturbations; it is known to respond to systemic conditions induced by aging, high-fat diet and diabetes [49], oscillatory changes in the circadian cycle [50], and the intracellular metabolic switch of FA oxidation-to-glycolysis within myocytes [51]. This important metabolic substrate is also an essential cofactor of class III HDACs, or sirtuins (Sirt) [52]. Sirtuins have been highlighted as an important regulator of the aging process from yeast to mammals [53–55]. In cardiovascular biology, sirtuins are held to be protective factors antagonizing “cardiac aging” diseases, such as coronary artery disease and HF [56–

58]. Numerous experimental and clinical findings point to decreased Sirt activity (especially Sirt1, 3, 6, and 7) in aging and in metabolic disorders, as well as in cardiac hypertrophy and failure [59,60]. In particular, Sirt6 has been highlighted for its involvement in direct transcriptional control of an important hypertrophic growth pathway, IGF1/Akt [60]. Working with Sirt6 loss- and gain-of-function models, Sundaesan *et al* identified a critical role of Sirt6-dependent chromatin deacetylation in controlling the activity of c-Jun, a key regulator of Akt signaling-related genes. Further, Sirt6-mediated inhibition of another transcription factor, NFκB, regulates inflammation [59] and cardiac fibroblast differentiation [61]. Relevant to the link between the enzymatic activity of sirtuins and bioavailable NAD⁺ [62], hearts exposed to pressure overload, ischemic injury or metabolic stress manifest diminished levels of a key NAD⁺ salvage enzyme, nicotinamide phosphoribosyltransferase (Nampt) [63]. Indeed, agents that boost Nampt activity, and hence intracellular NAD⁺ levels, enhance Sirt activities and confer protective effects in heart [57,62]. In addition, increasing NAD⁺ synthesis by over-expression of NMNAT2 (nicotinamide nucleotide adenyltransferase 2) protects heart from angiotensin II-induced hypertrophy by activating Sirt6 [64]. These studies reveal the potential of targeting NAD⁺ metabolism to modulate Sirt-dependent epigenetic regulation in the heart.

While metabolism can impact the activity of the acetylation machinery, acetylation can act to impact metabolism. Down-regulation of HDAC6 activity results in decreased mitochondrial activity and increased autophagy [65,66]. The class IIb HDAC, HDAC6, is up-regulated in models of hypertension and atrial fibrillation [66,67], and mice lacking HDAC6 are protected against cardiac dysfunction induced by angiotensin II [68]. In these contexts, HDAC6-dependent control likely stems from cytoplasmic protein acetylation rather than histone modification.

Thus far, we have emphasized the maladaptive effects of obesity-, diabetes-, and age-associated metabolic changes in cardiac remodeling. In direct contrast, numerous reports have shown the beneficial effects of caloric restriction and exercise-elicited molecular changes (e.g. increased AMPK), yielding “anti-aging” molecular patterns: increased NAD⁺ levels, sirtuin activation, and increases in endogenous HDAC inhibitors [69–71].

In summary, recent findings lend strong support to the importance of reversible histone acetylation as a transducer of a wide range of environmental cues – hemodynamic, metabolic, and age-related – to govern transcriptional reprogramming of the cell. Key elements in this crosstalk are metabolic intermediates, such as acetyl-CoA, NAD⁺, and β-hydroxybutyrate, which also directly control the enzymatic activity of the acetylation machinery. Overall, mounting clinical and preclinical associations and growing molecular evidence support the role of epigenetic acetylation as an environmental liaison in the highly adaptive and plastic myocardium [72]. This simple, yet robust, biochemical principle of substrate availability ties metabolism to epigenetics in cardiac remodeling (Figure 1).

Chromatin methylation

Histone methylation can either activate or repress gene expression depending on the extent and site of methylation. Methylation occurs on lysine and arginine residues within histone 3

and histone 4 [73]. Genome-wide studies of histone methylation showed that trimethylation of histone 3 lysine 4 (H3K4me3) or lysine 9 (H3K9me3) is highly associated with HF in rats [74]. Cardiomyocytes isolated after one week of elevated afterload harbor increases in H3 methylation in 30% of the analyzed genes [75]. Hallmark gene expression in cardiac hypertrophy is associated with histone acetylation. However, a recent study reported that reduced methylation at H3K9 within the genes coding for ANF and BNP is required to promote their expression [76].

Just as with acetylation, histone methylation is reversible. There are two major families of demethylating enzymes, which include 32 histone demethylase enzymes [77]. The lysine-specific demethylase 4A (KDM4A) family, also referred as Jumonji domain-containing 2 (JMJD2A) demethylases, promotes cardiac hypertrophy and regulates gene expression via serum response factor and myocardin, transcription factors established to promote cardiac hypertrophy [30]. On the other hand, the methyltransferase cofactor PAXIP1 affects cardiac contractility via an H3K4me3 mark within the gene coding for the KCNIP2 potassium channel [78]. This histone demethylase family utilizes α -ketoglutarate (α -KG), a key Krebs cycle intermediate, as a cofactor [79,80]; this fact highlights another biochemical link between epigenetics (chromatin methylation) and metabolism and suggests that the chromatin methylome may evolve, just as does the acetylome, in various stress conditions.

Trithorax-group (TrxG) complexes and polycomb-group (PcG) complexes represent another layer of histone methylation regulation [81]. The PcG complex induces H3K27me3, which is associated with gene repression. On the contrary, TrxG induces H3K4me3 which, in turn, promotes gene activation [81]. These complexes are important for longevity and adult stem cell regulation [82]. Both complexes are essential for the proper development of the heart [83]. BMI1 is a member of the PcG complex required for proliferation of adult and embryonic stem cells [84]. BMI1 is also protective against dilated cardiomyopathy (DCM) and hypertrophy [85]. Interestingly, the anti-aging phenotype promoted by BMI1 is known to be mediated by the repression of the p16^(INK4a) senescence locus [86]. In this study, the aging locus p16^(INK4a) was reported to be active in patients with dilated cardiomyopathy, suggesting an association of aging and epigenetic changes in this disorder [85].

In Dahl salt-sensitive rats, acetylation of histone 3 or histone 4 does not correlate with the presence of heart failure [74]. On the other hand, ChIP-seq analysis of K4TM and K9TM marks in human heart revealed a strong correlation. Indeed, genes associated with K4TM and K9TM marks tended to be involved in molecular pathways governing heart function. About 30% of the genes implicated in heart failure were associated with disease-dependent K4TM or K9TM modifications. Interestingly, K4TM-associated transcripts that differ between healthy and failing hearts act on similar signaling pathways [74].

DNA methylation

The ability of DNA binding proteins to access DNA is regulated by methylation at position 5 of cytosine [87]. Indeed, this represents the most common epigenetic modification regulating gene expression [88]. Hypomethylation of a promoter prevents transcription factor binding or recruits repressor complexes resulting in gene repression, while hypermethylation results

in gene expression. This process is reversible and is regulated by DNA methyltransferases DNMT1, DNMT3A and DNMT3B [88]. DNMT1 binds to hemi-methylated DNA to maintain methylation patterns [89]. DNMT3A and B are responsible for *de novo* methylation patterns [90]. DNMT3A has been reported to play a role in the expression of signaling elements in HF, such as ERK1/2 [91]. Pathological cardiac remodeling is accompanied by activation of genes normally expressed during fetal development. Interestingly, methylation patterns regulated by DNMT3A in isolated cardiomyocytes after pressure overload are similar to those seen during development [92].

As discussed, HF-associated changes in gene expression touch multiple cellular functions required for cardiac remodeling [1]. DNA methylation, which regulates global gene expression, has been implicated in multiple cardiovascular diseases [92]. In a model of norepinephrine-induced hypertrophy, treatment with the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine blunted hypertrophic growth [93]. Epigenetic studies in end-stage cardiomyopathy provide evidence that DNA methylation is an important factor in regulating cardiomyocyte gene expression. Genes with hypomethylated promoters were marked by increased expression in failing heart compared with healthy controls [94]. Additionally, failing hearts harbor hypomethylation in satellite DNA regions which correlates with overall increased gene expression [95].

Studies of specific genes regulated by methylation in heart disease reveal a diverse range of epigenetic targets. For example, the promoters of lymphocyte antigen 75 (*Ly75*) and tyrosine kinase-type cell surface receptor HER3 (*ERBB3*) are aberrantly methylated in human diabetic cardiomyopathy [96]. These genes have implications in cardiac contractility and HF [96]. Hypermethylation of the angiogenic genes *PECAM1*, *AMOTL2* and *ARHGAP24* also correlates with their expression [97]. Methylation may also play a role in the fibrotic phenotype of HF. Smooth muscle cells treated with a methylation agent (DAC) manifest elevated expression of collagen type XVa1 [98].

Mitochondria have been considered the “machinery by which stimuli from the environment can translate into epigenetic regulation” [99]. An example is the regulation of S-adenosylmethionine (SAM), the substrate for methylation of DNA and histones. Mitochondria promote the abundance of SAM in both embryonic and post-natal growth conditions [100]. In heart, oxidative stress increases SAM abundance and promotes DNA methylation associated with pathological remodeling [101].

Thus far, the link between gene methylation and HF remains correlative. Additional studies are needed to determine whether DNA methylation changes are causative and/or consequential. This will be essential for their development as HF therapeutic targets.

Mitochondrial DNA methylation

Cardiac metabolic activity is both unremitting and tightly regulated, and mitochondria play essential roles throughout [102]. Dysregulation of mitochondrial function is associated with accumulation of reactive oxygen species and defective energy production that together impact cardiac remodeling in several forms of disease [102]. While epigenetic changes are

mostly associated with nuclear DNA, recent studies suggest that epigenetic regulation of mitochondrial DNA (mtDNA) impacts mitochondrial function [99].

mtDNA lacks introns and is not arranged in histone-containing chromatin structures [103]. Interestingly, similar to nuclear DNA, mtDNA in humans has been shown to be methylated [104]. The demethylase DNMT1 localizes within mitochondria [105], and this enzyme is believed to have similar functions as its nuclear counterpart: to maintain methylation of CpG DNA regions. It is suggested that DNMT1 has additional roles in mitochondrial homeostasis, as it is activated by oxidative stress [105]. In addition, DNMT3A has also been localized to cardiomyocyte mitochondria, as well as mitochondria within skeletal muscle and neurological tissues; no known function for this protein has been established to date [106].

The study of mitochondrial epigenetics is nascent, and further in-depth analyses are required to unveil the impact of mtDNA methylation in heart disease. As an example, van der Wijst *et al.* suggested that mtDNA methylation affects transcription factor binding, such as that of Twinkle (TFAM), thereby impacting mitochondrial biogenesis and oxidative responses [103,107]. TFAM over-expression reduces the hypertrophic response elicited by volume overload and reduces oxidative responses in the heart [108].

While the causes and consequences of mtDNA methylation are yet to be understood, tracking mtDNA methylation as a biomarker is an attractive approach. A recent study proposed tracking mtDNA methylation in platelets as a marker of cardiovascular disease [109]. In this study, investigators compared the methylation levels of genes involved in the electron transport chain, ATP synthase and NADH dehydrogenase, from healthy patients with those from individuals with hypertension and atherosclerosis. Their screen revealed that patients with CVD have higher methylation levels in several mitochondrial genes [109]. Platelets have increased numbers of mitochondria and have greater ATP turnover than muscle cells [110]. As platelets lack nuclear DNA, mtDNA is the only genetic material. This is useful in light of previous studies that focused on nucleated cells, raising the possibility of contamination with nuclear DNA distorting measures of mtDNA methylation [109]. Of note, mitochondrial biomass and activity differ among different cell types. As such, mtDNA methylation could be associated with specific cell types or diseases.

Non-coding RNAs

Unlike the other epigenetic regulators, non-coding RNAs (ncRNAs) are nucleic acid-based molecules that control gene expression in a variety of ways, ranging from interference with transcriptional machinery, post-transcriptional silencing, and regulation of splicing [111]. In particular, the control of gene transcript decay mediated by microRNAs (miRNA) is of special interest to cardiovascular medicine, as a variety of miRNAs has been identified with important regulatory roles in numerous cardiac pathological conditions [11,112]. A large number of miRNAs exist within the cardiomyocyte, each one targeting unique sets of gene transcripts and promoting their degradation. Table II summarizes recent findings on roles of specific miRNAs in HF. As shown, many miRNAs alter expression during cardiac stress and mitigate pathological progression [111,113].

In addition to the studies revealing the pervasive importance of miRNAs, the concept has emerged of using circulating miRNAs as a biomarker to diagnose and prognosticate HF. Multiple clinical studies have been conducted to carefully characterize the miRNA profile in healthy versus advanced HF patients [146,147]. These clinical studies showed that miRNA profiles differ not only between HF and non-HF groups, but also between HF patients of differing ages and etiologies [129,148,149]. Similar types of study have been conducted in healthy groups exposed to exercise [122,150]. From these studies, it appears that profiles of circulating miRNAs are sensitive to environmental cues, such as metabolic health, aging, and hemodynamic stress. In so doing, these findings suggest that this epigenetic mode of gene regulation integrates the cellular environment with cardiac gene expression. Importantly, the accumulating clinical database of miRNA profiles across different etiologies, ethnicities, and age groups provides an interesting opportunity to engineer new diagnostic/prognostic tools for HF. For instance, Ellis *et al* [151] compared miRNA profiles in patients with chronic obstructive pulmonary disease and HF, identifying potential miRNAs that may aid in diagnosis of two diseases with similar clinical symptoms. Further, efforts to develop miRNA profiles that differentiate HF with preserved versus reduced ejection fraction (HFpEF vs. HFrEF) are underway [152–154], yielding subsets of miRNAs with diagnostic/prognostic value comparable to a currently used biomarker, NT-proBNP.

Conclusion

The heart is a highly plastic organ, capable of undergoing extensive remodeling in response to various stimuli and cues within its environment [1]. In parallel to the remodeling process, substantial transcriptional reprogramming occurs in failing myocardium; the critical role of epigenetic regulatory mechanisms in mitigating these events has been previously identified [13]. Key components of the multifaceted epigenetic machinery are biochemically tied to cellular metabolism by substrates/cofactors required for their enzymatic actions [155,156]. Other biological systems, such as stem cells [46,51], also manifest this feature of epigenetic control, eliciting global genetic change through a simple metabolic switch. This inherent sensitivity of epigenetic mechanisms to cellular energetics and mitochondrial health is one reason why the epigenetic landscape of the heart under metabolic and aging stress manifests robust changes.

From a therapeutic perspective, these targetable gene expression regulators herald promise. Indeed, the benefits of targeting these epigenetic modifiers in pathological cardiac remodeling are several, with reported actions in inflammation, fibrosis, ischemic injury, and hypertrophy [14,15]. Our continued effort to decipher the biology of epigenetic change in heart may culminate in the development of novel therapeutics that effect clinical benefit.

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Key Points

- Evidence emerging from preclinical and clinical studies points to the importance of epigenetic mechanisms in the pathophysiology of heart failure.
- Key components of the epigenetic machinery are mechanistically linked to cellular metabolism.
- Epigenetic mechanisms transduce environmental cues into transcriptional changes in healthy and diseased heart.

Figure 1.

Epigenetic mechanisms transduce environmental cues into transcriptional reprogramming during HF. Aging and metabolic stress are associated with changes in the cardiac environment -- excess circulating FA, insulin resistance, and oxidative stress -- that lead to alterations in myocardial metabolism. Dysregulated cellular metabolism, in turn, provokes changes in metabolic intermediates, including NAD⁺, acetyl-CoA, β-hydroxybutyrate (β-OHB), S-adenosylmethionine (SAM), and α-ketoglutarate, each of which is also a key cofactor/substrate for the enzymatic actions of epigenetic editors. In addition, whereas a range of signaling events alters the abundance of the epigenetic editing proteins, these changes in metabolic intermediates alter the activity of the enzymes, as well. The resulting changes in the epigenetic landscape contribute significantly to HF-related reprogramming of the myocardium, working synergistically with hormonal and cytokine stimuli (which activate transcription factors that recruit epigenetic editors to specific loci) to promote pathological remodeling in HF.

Table 1

Therapeutic targets of epigenetic components in heart failure

Target	Trend in HF	Effect of Aging/Metabolism	Pharmacological agents	Functional outcome	Ref
Class I HDAC	Activity increases	Endogenous inhibitor level decreases in diabetes	Pan-HDAC inhibitors (TSA, SAHA, Valproic acid) Class I-specific inhibitors (Apicidin)	Rescue LV hypertrophy and cardiac function under mechanical and chemical stress; prevent I/R injury Prevent inflammation and fibrosis	[20,22,24]
Class II HDAC	Activity decreases	Decreased mitochondrial activity, increased autophagy	N/A	Genetic disruption leads to hypertrophy and cardiac malfunction	[23]
Class III HDAC	Activity and level decrease	Expression and activity decrease in aging and metabolic stress	NAD ⁺ precursors (NMN, NR, NA) Sirt activators (Resveratrol)	Improve cardiac aging phenotype; decrease oxidative damage; improved mitochondrial function	[25,26]
BRD protein	BRD4 level increase	Undefined	BET bromodomain inhibitors (JQ1, I-BET151, PHJ)	Rescue LV hypertrophy and cardiac function under mechanical and chemical stress Prevent inflammation and fibrosis	[27,28]
Histone demethylase	JMJD2A level increase	Undefined	JMJD inhibitors	Reduce inflammation; Need further characterization in heart	[29,30]
MicroRNA	Refer to Table II	Certain miR levels increase (195, 451, 29b), and some decrease (1, 133a) in metabolic stress	AntagomiRs, miR mimics, LNA (Specific for each miR)	Rescue LV hypertrophy and cardiac function under mechanical and chemical stress Reduce inflammation and fibrosis	[11]

Abbreviations: Left Ventricular (LV); Ischemia/Reperfusion (I/R); Trichostatin A (TSA); Suberoyl+Anilide+Hydroxamic Acid (SAHA); Nicotinamide Mononucleotide (NMN); Nicotinamide Riboside (NR); Nicotinic Acid (NA); Locked Nucleic Acid (LNA); Not available (N/A)

Table II

MicroRNAs in heart failure

miR	Trends	Targets	Functional outcome	Ref
181c		Bcl2, mtCOX1	Impaired mitochondrial morphology	[114,115]
340		Dystrophin	Eccentric hypertrophy	[116,117]
214		PPAR δ , XBP1, NCX1, CAMKIID	Hypertrophy, impaired Ca ²⁺ handling, decreased angiogenesis	[118,119]
212/132	Increase in HF	FoxO3	Hypertrophy, fibrosis, decreased autophagy	[120]
208a		MSTN, THRAP1	Pathologic myosin isoform switch	[121,122]
539		O-GlcNAcase	Increased O-GlcNAcylation	[123]
221		p27	Hypertrophy, decreased autophagy	[124]
34a		NAMPT, PNUTS	Fibrosis, increased oxidative stress, cell death	[125–127]
199a/b		DYRK1A, PPAR δ	Stress-induced hypertrophy	[119,128,129]
195	Increase in HF and in aging/metabolic stress	Sirt1, Bcl2	Hypertrophy, diabetic cardiomyopathy	[130]
451		CAB39, RAC1	Lipotoxicity, diabetic cardiomyopathy	[131]
29a		MCL1, COL1A	Fibrosis, hypertrophy	[132–134]
29b		IGF-1, LIF	Fibrosis	[135]
30	Decrease in HF	CTGF	Fibrosis, cardiac matrix remodeling	[136]
126		SPRED1, PIK3R2	Decreased angiogenesis, right ventricular HF	[137]
25		SERCA2A, HAND2	Disrupted Ca ²⁺ handling, impaired contractility	[138,139]
133a	Decrease in HF and in metabolic stress	RhoA, CDC42, Cyclin D, SRF	Hypertrophy, fibrosis, cardiac matrix remodeling	[140–143]
1		Calmodulin, MEF2A, NCX2, ANXA5	Impaired contractility, hypertrophy	[144,145]

Abbreviations: B-cell lymphoma 2 (Bcl2); Mitochondrial cyclooxygenase 1 (mtCOX1); Peroxisome proliferator-activated receptor delta (PPAR δ); X-box binding protein 1 (XBP1); Sodium-calcium exchanger 1 (NCX1); Calcium/calmodulin-dependent kinase type II delta (CAMKIID); Forkhead Box O3 (FoxO3); Myostatin (MSTN); Thyroid hormone receptor-associated protein 1 (THRAP1); O-linked N-acetylglucosamine (O-GlcNAc); Nicotinamide phosphoribosyltransferase (NAMPT); Phosphatase 1 nuclear targeting subunit (PNUTS); Dual-specificity tyrosine-phosphorylation regulated kinase 1A (DYRK1A); Calcium-binding protein 39 (CAB39); Ras-related C3 botulinum toxin substrate 1 (RAC1); Myeloid cell leukemia 1 (MCL1); Collagen type I alpha (COL1A); Insulin-like growth factor 1 (IGF-1); Leukemia inhibitory factor (LIF); Connective tissue growth factor (CTGF); Sprouty-related, EVH1 domain containing 1 (SPRED1); Phosphoinositide-3 kinase, regulatory subunit 2 (PIK3R2); Sarcoplasmic reticulum calcium ATPase 2A (SERCA2A); Heart and neural crest derivatives expressed 2 (HAND2); Ras homologous, member A (RhoA); Cell division cycle 42 (CDC42); Serum responsive factor (SRF); Myocyte enhancer factor 2A (MEF2A); Annexin A5 (ANXA5)