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REVIEW ARTICLE

Potential Roles of MyomiRs in Cardiac Development and Related Diseases

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Abstract: Muscle-specific miRNAs, which are known as MyomiRs, are crucial regulatory elements for cardiovascular development. MyomiRs are abundantly expressed in the myocardium and regulate certain aspects of physiological and pathological processes in myocardiocytes, including cardiovascular development, myocardial remodeling, and arise for cardiovascular diseases through different mechanisms, such as epigenetic pathways. Clinical and experimental studies have confirmed the myomiRs as promising diagnostic biomarkers for the early diagnosis of cardiac disorders. In this review, we have summarized recent findings in the field of epigenetic modulations of myomiRs and cardiac regeneration associated with cardiac diseases.

Keywords: MyomiRs, epigenetic, cardiac development, cardiac diseases, microRNA, cardiac regeneration.

1. INTRODUCTION

Cardiovascular diseases (CVD) such as heart attack, stroke, peripheral vascular disease, hypertension, and congenital heart defects are a major group of health problems worldwide, leading to enormous morbidity and mortality as well as economic problems [1]. Recently, remarkable efforts have been made toward understanding the cellular and molecular pathways involved in cardiovascular diseases and pathogenesis. Noteworthy, significant advancement has been achieved regarding current preventative treatments, early diagnosis, and novel therapies against cardiovascular diseases. However, further studies are in demand for getting better results [2].

Several studies indicate that microRNAs play a vital role in various biological processes mediated by the regulation of the expression of several mRNAs [3]. The diverse functions of most miRNAs are mediated through regulating physiological and pathological events in cardiovascular biology [4]. Accordingly, miRNAs can be considered as expression regulators for modulating gene expression during development and tissue homeostatic maintenance. The majority of mRNA molecules are targeted and silenced by direct interaction of miRNA, which ultimately destabilizes the mRNAs or inhibits protein synthesis [2, 5]. So far, it seems that more than half of miRNAs have been discovered in the human genome, which are expressed in a temporally and spatially regulated manner. On the other hand, little is known concerning the underlying molecular mechanisms that regulate miRNA expression; however, major attempts are in progress to identify the exact role of these molecular mechanisms. Some miRNAs are located within the introns of the genes and their expression is coordinated with the host genes [6]. The expression level of miRNAs, which are encoded and transcribed as individual genes, is controlled transcriptionally by cis-regulatory factors in the promoter region of the miRNA, similar to protein-coding genes. Therefore, the biogenesis of some miRNAs is regulated by transcription factors or RNA-binding proteins [2].

A functional heart is the first organ system to form during embryogenesis and its development is controlled by a complex regulatory network. It is reported that cardiac transcript factors, including GATA4, TBX1, MEF2C, SRF, and MHC genes, play crucial roles in the development of myocard, which are under the control of certain myomiRs, such as MiR-1/-133. The proliferation of cardiomyocytes can be regulated by miR-1/-133, which induces mesoderm formation and differentiation of embryonic stem cells [7, 8]. Abnormal development of the heart leads to a wide spectrum of fatal disorders [9]. Genetic background is one of the main factors that strictly regulates early morphogenesis and development of the heart [10]. In addition, the regulatory roles of miRNAs in heart contraction and conduction have been reported in a previously published study. These molecules modulate cardiac depolarization and repolarization by estab-

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lished regulatory networks [11]. MyomiRs are certain subsets of miRNAs that include different members as follows: miR-1-1/2, miR-133a-1/2, miR-133b, miR-206, miR-208a/b, miR-499, and miR-486 [12]. Several lines of studies have reported that different miRs (-1, -133, -208, and -499) are highly expressed in heart tissue in the early stages of heart development up to adulthood [13] (Table **1**).

miRNAs can be used as potential biomarkers for some cardiovascular disorders, although the therapeutic and diagnostic applications are still at early stage [1]. In this review, we focus on the role of myomiRs in cardiac development and the epigenetic role of the myomiRs in the establishment of cardiovascular diseases will also be explained.

2. BIOLOGY OF MYOMIRS IN HEART TISSUE

The most important myomiR in heart biology is miR-1, which has two isomers, including miR (-1-1 and-1-2). Although these isomers have the same sequence, they are encoded by different genes [11]. Overexpression of miR-1 can reduce the proliferation rate in ventricular heart muscle cells, which are accompanied with impaired cardiac excitation-contraction and induction of arrhythmia [7]. miR-1 is involved in the function of cyclin-dependent kinase-9 (Cdk9), whose up-regulation as the main part of the p300-GATA4 complex is related to myocardial cell differentiation [14]. Most of the studies have verified the upregulation of miR-1 in cardiogenesis in both fetal and adults [15]. Over-expression of miR-1 is interrupted by the membrane potential balance by inhibiting the Kir2.1, which induces heart conduction [16]. In contrast, down-regulation of miR-1 is reported in atrial fibrillation (AF), while the levels of Kir2.1 are elevated [17]. In addition, it has been observed that the overexpression of miR-1 impels cardiomyocytes apoptosis [18].

miR-133 is another member of myomiRs, which has a key role in the heart tissue. Human miR-133 is composed of two distinct isoforms as following; miR (-133a and -133b). miR-133a, like miR-1, is a cardiac-specific miRNA which exists abundantly in the heart tissue [19]. miR-133a is expressed in cardiomyocytes, while miR-133b is only expressed in skeletal muscles. Lack of miR-133 results in immature heart development and deficient function, which leads to disorganized sarcomeres, the elevation of apoptosis, lethal ventricular septal anomalies, and smooth muscle gene expression [20]. Epidermal growth factor receptor (EGFR) is downregulated by miR-133a, which prevents the formation of ectoderm during the differentiation of normal cells [21]. miR-133a is the most abundantly expressed myomiR in myoblasts [22] and exhibits contradiction functions in the differentiation of myoblasts toward myocytes [11].

miR-208 is a cardiac-enriched miRNA, which includes miR-208a miR-208b isomers. In humans, only miR-208a is expressed in the heart, while miR-208b expression is reported in both heart and skeletal muscles [13]. Unlike the role of miR-1 and -133 in the early phase of cardiogenesis, the role of miR-208 is obvious in the late stage of heart development that modulates cardiac myosin heavy chain (MHC) expression [23]. The expression level of miR-208b in fetal myocardium is extremely high, whereas its level is decreased in mature heart tissues. In contrast, the expression of miR-208a is increased during cardiogenesis and reaches the highest level in adulthood [24]. Knockout of miR-208a expression in mice causes upregulation of β-MHC and downregulation of THRAP1expressions, which lead to heart hypertrophy [24].

miR-499 is composed of two isoforms, miR-499a and miR-499b. miR-499b is an antisense form of miR-499a [25]. Similar to miR-208, miR-499 has a regulatory effect on late cardiogenesis, including in the final generation of cardiomyocytes from myoblasts [11]. It has been demonstrated that an increase in miR-499 level in human fetal cardiomyocyte progenitor cells (CMPCs) in collaboration with miR-1 induces differentiation of cardiomyocyte progenitor cells and embryonic stem cells into cardiomyocytes [26]. Overexpression of the miR-499 in transgene mice can alter the expression of contractile activity (MYH7B and skeletal muscle α-actin (ACTA1) and conductivity (KCNH6 and Kv11.1), which leads to heart hypertrophy and cardiac impairments [27]. In a rat model, overexpression of miR-499 in cardiomyocytes influences pro-apoptotic regulatory molecules like Pdcd4 (programmed cell death protein 4), Pasc2 (phosphofurin acidic cluster sorting protein 2), and Dyrk2 (dual-specificity tyrosine-phosphorylation-regulated kinase 2), which have

Table 1. Genome context of myomiRs in cardiovascular biology.

MyomiRs	Pre-miRNA	Genome context	Mature miRNA	Clustered miRNA gene	Tissue specificity
miR-1	Has-mir-1-1 Has-mir-1-2	Intragenic Intragenic	Has-miR-1-5p Has-miR-1-3p	Has-mir-133a-2 Has-mir-133a-1	Heart/Skeletal muscle
miR-133a	Has-mir-133a-1 Has-mir-133a-2	Intragenic Intragenic	Has-miR-133a-5p Has-miR-133a-3p	Has-mir-1-2 Has-mir-1-1	Heart/Skeletal muscle
miR-208a	Has-mir-208a	Intragenic	Has-miR-208a-3p	?	Skeletal muscle
miR-208b	Has-mir-208b	Intragenic	Has-miR-208b-3p	?	Heart/Skeletal muscle
miR-486	Has-mir-486-1	Intragenic	Has-mir-486-3p Has-mir-486-5p	Has-mir-486-2	Heart/Skeletal muscle
miR-499a	Has-mir-499a	Intragenic	Has-miR-499a-5p Has-miR-499a-3p	Has-mir-499b	Heart/Skeletal muscle
miR-499b	Has-mir-499b	Intragenic	Has-miR-499b-5p	Has-mir-499a	Heart/Skeletal muscle

key functions in elevation of cell survivability [28]. Moreover, miR-499 protects the cardiac cells from apoptosis *via* Sox-6 downregulation [29]. It seems that the impact of miR-499 on proliferation and its anti-apoptotic properties is important during heart development and might be addressed as a therapeutic potential of miR-499 [11]. The most important role of both miR-208b and miR-499 in cardiogenesis is the downregulation of the fast muscle fiber transcription [30]. Furthermore, impairment in heart fibrosis and rhythm is followed by upregulation of miR-208a besides the reduction of GATA, HOPX (homeodomain-only protein) , and connexin-40, which have significant roles in intercellular conductance of heart muscles [24].

3. MYOMIRS AND HEART DEVELOPMENT

Various studies have verified the function of myomiRs in the development of cardiomyocytes. Blocking of all the miRNAs expression in the cardiovascular system unveils their importance in heart biology [2]. miR-1-1/miR-133a-2 are located as a bicistronic microRNA in human chromosome 20, and the miR-1-2/miR-133a-1 are clustered in the antisense strand within an intron of the mind bomb 1 gene in human chromosome 18. miR-133b/miR-206 is located on chromosome 1 of humans. The studies have reported that miR (-1, -133, and -208) are highly expressed in the early stages of heart development [13] (Fig. **1**). These miRNAs, along with other microRNAs, are involved in various heart diseases (Table **2**). The ventricular septal or conduction system defects are obvious following the knock-out of miR-1-2 in lethal mouse embryos [8]. It is assumed that the loss of the miR-133 family does not have any extreme consequence in cardiac embryogenesis. Nevertheless, the deletion of miR-133 can cause VSD and early postnatal death [31]. miR-1/-133 are growth suppressors, which are able to inhibit cardiomyocyte programmed cell death by downregulation of growth-related cardiac genes [32]. miR-133b is a crucial factor in controlling main fetal genes and remodeling genes of cardiac cells. These genes are involved in the initiation and development of common human cardiomyopathy [33]. In addition, assessment of miR-208a, miR-208b, and miR-499 expression levels during cardiac stress or in response to hypothyroidism indicated that their expression could lead to the reactivation of cardiac fetal gene program [30]. Recent studies have shown that the miR-1/miR-133 levels are regulated by serum response factor (SRF), factor myogenic differentiation (MyoD) (as the key gene involved in muscle reprogramming), myocardin, and Mef-2C [34]. miR-1 has a negative regulation in cardiac growth and differentiation by inhibiting HAND2 expression, which is involved in the development of the outflow tract and right ventricle [7, 34]. Moreover, miR-1 influences cardiogenesis by regulating the expression of Irx5 and Hand2 transcription factors. Irx5 protein regulates the expression of K^+ channel genes, such as K^+ voltage-gated channel subfamily D member 2 (Kcnd2), and determines the cardiac ventricular repolarization gradient [8]. IGF-1 regulates cardiac muscle tropism *via* IGF-1 and its receptor, which directly targets miR-1. Furthermore, Foxo3a regulates the expression of miR-1 for triggering a feedback loop between miR-1 expression level and the signaling pathway of IGF-1. In acromegalic patients with overproduced IGF-1, after aberrant synthesis of growth hormone, the expression level of miR-1 in myocardial is inversely related to cardiac mass and wall thickness [35]. miR-1 and miR-133 promote mesoderm differentiation in embryonic stem cells. Then, miR-133 inhibits and miR-1 promotes differentiation of mesoderm into cardiomyocytes [36]. miR-133 enhances the activity of SRF as a key transcriptional factor in the proliferation of cardio myoblast cells [18]. miR-208a and miR-208b express with Mhy6 and Mhy7 for mediation of α and β myosin heavy chain (Mhy) isoforms, respectively, in fetal and adult phase switching [24]. Moreover, it has been demonstrated that other microRNAs have key roles in the growth, development, and regeneration of cardiomyocytes by targeting myocardial transcriptional factors (Table **3**) (Fig. **2**). For instance, miR-130a, which is expressed at a high level in the heart, interferences in cardiac development *via* targeting the transcription factor Friend-of-GATA 2 (FOG-2) [37]. miR-195 is upregulated instantaneously after birth and prevents cardiomyocyte proliferation; it controls the expression of various cell cycle genes, such as checkpoint kinase 1 (Chek1). The upregulation of miR-195 leads to ventricular hypoplasia as well as VSDs [36]. miR-15b controls the ATP level in cardiomyocytes by targeting Arl2, a component of the ADP/ATP exchange in mitochondria [38]. The other microRNAs are miR-216, which involve vascularization during development, and miR (-138, -143 and -218), which regulate heart morphogenesis [39].

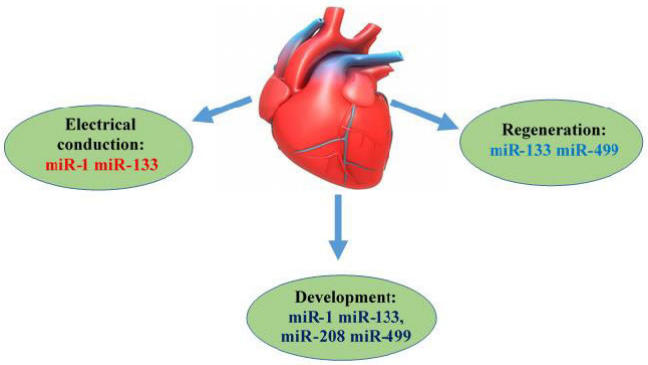

Fig. (1). The function of myomiRs in cardiac regeneration, development, and electrical conduction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. MYOMIRS AND HEART MORPHOLOGY

The first step for the development of an embryo is initiated by the maturation of cardiomyocytes to form an embryonic heart [40]. The procedure of cardiac myogenesis is controlled by a tight synchronized network of cellular and molecular interactions with effective roles of miRs on gene expression [20]. The genes and corresponding protein dosages are crucial factors in the formation and development of the heart. One percent of live human births consists of cardiac malformations as ventricular septal defects [41].

Table 2. Expression of myomiRs and the other microRNAs in cardiovascular diseases.

Cardiovascular Disease	miRNA	Up/down Regulation	References
Arrhythmia	**miR-1,** miR-328	up	[51, 52]
	miR-133	down	[55]
Myocardial Infarction	**miR-1,** miR21, miR-29b, miR-34a, miR-126, **miR-133,** miR-134, miR-192, miR-194, **miR-208,** miR-328, miR-423, **miR-486 ,miR-499**	up	[105-107]
	miR-106, miR-197 and miR-223	down	[48]
Heart Failure	miR-423-5p, miR-320a, miR-22 and miR-92b, miR-122, 423-5p, miR-210, **miR-499,** miR-622, miR-1, miR-21, miR-23, miR-29, miR-130, miR-195 ,miR-199, MiR-1254 ,miR-1306, **miR-208b**	up	[58-60, 108, 109]
	miR-18a, miR-27a, miR-30e, miR-26b, **miR-133**, miR-199a, miR-106a , miR-652	down	[110, 111]
Hypertension	**miR-1 ,**miR-21	up	[78]
	miRNA-143, miRNA-145, **miR-133**	down	[80]
Atherosclerosis	**miR-133a,** miR-135a, **miR-208a**	up	[86, 88]
	miR-126, miR-145, miR-155, miR-126, miR-17, miR-92a, miR-145 , miR-147	down	[86]
Congenital Heart Disease	miR-421, miR-181c	up	[9]
	miRNA-940, **miR-1,** miR-26a, miR-30b, miR-195, miR-141	down	[9, 112]

Table 3. Important target molecules of cardiovascular miRNAs in growth, differentiation, and regeneration of Cardiac Cells.

Target Molecules in Regeneration	Target Molecules in Differentiation	Target Molecules in Growth	MyomiR
MEF2C and αMHC 4E (Eif4e), Mef2a, Gata4, and HDAC6	YY1, HDAC4, Cx43, Pax3, Pax7, FZD7, FRS1and IGF-1R	BMP-10, SRF, Myocardin and Kcnmb1, Hand2	miR-1
AKT3	Chek1	BCL2	miR-15 family
SORBS2, PDZ and LIM domain 5 (PDLIM5)	GATA-4, MEF2c, TNI and β-MH*C*	PTEN, RECK and Bcl-2 Spry2, BTG2 and PDCD4	miR-21
LPA3 dependent PI3K/Akt pathway	Janus kinase 1 (JAK1) connexin-43 (Cx43/GJA1)	TOP1, topoisomerase I˙ APAF-1, IL6R, BLIMP-1	miR-23a
GATA2, PAK4, eNOS	GATA2, p21-activated kinase PAK4	-	miR-24
Bim	Wwp2, Fbxw7	Bim	miR-25
FBN1, COL1A1, COL1A2, ELN and COL3A1	YY1	Histone deacetylase 4, p85α, B-myb	miR-29 family
RhoBTB1	-	RhoBTB1	miR-31
ABCA1	-	CCND1, CDK6	mir-33 family
Sirt1, Cyclin D1*, Sema4b,* Bcl2 and Jag1	Vinculin, Sema4b, Pofut1 Sirt1 and Bcl6	Bcl2, Cyclin D1, and Sirt1	miR-34 family
MEF2C and α-MHC Akt, Cdc42, Rho-A and Nelf-A/WHSC2	MAML, IGF-1R, nPTB	BMP-10, Myocardin and Kcnmb1	miR-133a.b
TβRIII	EN1, EN2 and LMX1A, Hox-A11	-	Mir-181
FoxP1	Pola1, Cx43, Pax3, Pax7	Pax7	mir-206
MEF2C, CXCR4 and α-MHC	-	βMHC (Myh7) *Tbx5*, *Nkx2-5, and α-MHC*	miR-208
EZH2, XBP1	Ezh2	Mfn2	miR-214
$p27^{Kip1}$ and $p57^{Kip2}$	p27	p27, HIPK1, and HMBOX1	miR-221
IGFR1, Grb2, Ksr1 SuFu and Fus-1	MyoR	IGF1R	miR-378
PIM1 kinase	Pax7	-	miR-486
MEF2C and α-MHC	SOX6 and ROD1	Akt, MAPKs, Egr1, Egr2, Fos, Myh7 and Acta1	miR-499

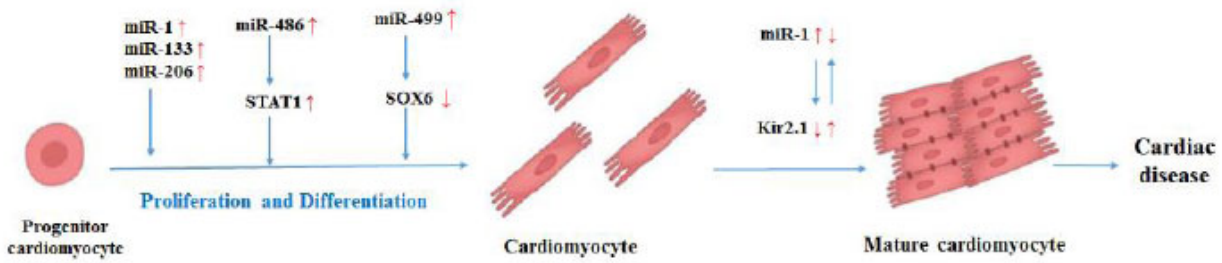

Fig. (2). The roles of myomiRs and related transcript factors in the development of cardiomyocytes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Cardiac-specific miRNAs, such as miR-1, are crucial factors in controlling physiological and morphological aspects of cardiac development [42]. miR-1 association with Notch ligand Delta 1 (Dll1) can determine cell fate choice in embryonic stem cell (ESC) and cardiac progenitor cells [43]. miR-1 provokes cardiac mesoderm induction and balances between proliferation and differentiation. Therefore, miR-1 facilitates the development of normal cardiac chambers and atrioventricular and ventricular conduction [42]. Deletion of miR-1-2 causes defects in the ventricular septum, which is responsible for fifteen percent of newborn deaths [44]. Mutated miR-1-2 provides depression of various genes, such as Hrt2/Hey2 (a member of the Hairy family of transcriptional repressors) and Hand1 (bHLH transcription factor), resulting in the elimination of VSDs in mice [45]. Hand1 is essential for ventricular development septation [46]. miR-1-2 also reduces the expression levels of Hand2 that advances ventricular cardiomyocyte expansion [8]. Cardiomyocytes stimulate smooth muscle genes and suppress them during the progression of cardiac development. The regulatory factors, which control the transition between immature and mature cardiomyocytes are not fully understood [20]; However, the expression of miR-1 is reported to be equal between differentiation and proliferation during cardiogenesis in cardiac regulatory proteins [7]. Myocardins are able to positively control the expression of miR-1/133a. Also, miR-1/133a regulates myocardin levels by a negative feedback loop that is essential for early cardiac development [20]. The effect of miR-208a overexpression in the adult heart was agreed upon by using a biogenic system that is under the control of the α-myosin heavy chain (αMHC) promoter. This system showed that overexpression of miR-208a does not cause embryonic lethality [24]. Mutated miR-208a can cause abnormalities in the sarcomere structure of 6-month-old infant, thereby reducing cardiac functions [36]. It has been shown that the ventricular growth and cardiomyocyte proliferation is related to the expression levels of miR-486 and STAT1 (Signal transducer and activator of transcription 1) as one of the proteins in ventricular growth and is mostly upregulated by miR-486 [47]. Finally, it has been shown that the cardiac progenitors can be differentiated into cardiomyocytes in the presence of mir-499, perhaps by inhibition of SOX-6 [26]. Overexpression of miR-499 in transgenic mice enlarged hearts and increased heart-to-body weight ratios. Whereas, at low levels of miR-499 expression, this phenomenon was not observed [48].

5. MYOMIRS IN ARRHYTHMIA AND CARDIAC ELECTRICAL CONDUCTION

Arrhythmia is determined *via* abnormal electrical activity in the heart, which is classified as dysrhythmia, tachycardia, bradycardia, and atrial fibrillation (AF). The cardiac electrical-conduction complex includes myocyte cells and different complexes of ion channels. Dysfunction (abnormal QT prolongation) may lead to arrhythmia in the conduction complex and sudden death. miR-1 and miR-133 are arrhythmogenic factor control components, which interfere with the expression of cardiac conduction-complex [49]. Various studies have shown that miR-1 expression is elevated in coronary artery disease of infarcted human and rat heart tissues [16]. The injection of miR-1 into the infarcted myocardium can slow cardiac conduction and cause arrhythmias, while knockdown of miR-1 inhibits arrhythmogenesis. These findings suggested that miR-1 is involved in the electrical arrhythmias and remodeling of the heart [16]. Two mechanisms are proposed for the potential arrhythmogenic activity of miR-1. The first is the repression of KCNJ2 (encodes Kir2.1 potassium channel subunit) and GJA1 (encodes Cx43 cardiac gap junction), which ultimately lead to slow conduction and depolarization of the cytoplasmic membrane and arrhythmia development. Indeed, it has been shown that removing miR-1 leads to the expression of KCNJ2 and GJA1 in infarcted rat hearts [16]. Another mechanism is calcium burst from sarcoplasmic reticulum that is mediated by CaMKII-dependent phosphorylation of the L-type Ca^{2+} channels and ryanodine receptors 2 (RyR2) [50]. The up-regulation of miR-1 has been shown in ventricular arrhythmia in the rat model, however, its downregulation has been shown in human myotonic dystrophy in both ventricular arrhythmia and conduction block [51]. Altering the distribution of gap junctions and the Cx43 levels in cardiomyocytes due to miR-1 up-regulation induces failure in the heart rhythm [52]. In contrast, down-regulation of miR-1 was noticed in hypertrophic hearts of murine [53]. Recent studies indicated that over-expression of miR-1 leads to arrhythmia by intruding on the intracellular trafficking complex. It seems that the trafficking-related gene Stx6 controls intracellular Ca^{2+} and

is involved in the occurrence of cardiac arrhythmia, which was regulated by miR-1 [54]. In contrast, miR-133 can act as a double-edged sword in the remodeling of cardiac electrical. miR-133 acts through various target genes and changes signaling pathways in cardiac remodelings, such as RhoA, Cdc42, HERG, and PI3K/Akt signaling pathways [55]. Meanwhile, miR-133 has a key role in abnormalities of cardiac conductance through suppression of ERG (ether-a-go-go-related) gene expression, which organizes a cardiac K^+ channel protein that has the key role in myocyte repolarization, which is related to congenital arrhythmias [49]. Fig. (**3**) summarizes the interactions between miR-1 and miR-133 and illustrates their effects on the arrhythmias.

6. MYOMIRS AND MYOCARDIAL INFARCTION

"Acute myocardial infarction (AMI) occurs by total occlusion of the coronary arteries which accompanied by heart chamber dilation and the ventricular wall thinning. Also, myocardial tissue-damaging progresses is followed by apoptosis and fibrosis [56]. Notably, in other CVD, the levels of myomiRs are changed in AMI patients. For instance, it has been shown that the level of miR-1, which is correlated with infarct and left ventricular (LV) end-diastolic volume, is varied in AMI patients [57]. MiR (-1, -499, and -208) are used as sentient biomarkers for the diagnosis of sudden death in early acute myocardial infarction [58]. The level of miR-133, miR208, miR-486, and miR-499 (an exclusive cardiac tissue miRNA) are changed in Myocardial infarction [59, 60]. In the AMI, changes in miR-1 expression are related to the time and size of myocardial infarct [61]. Moreover, several studies demonstrated that the expression of miR-1 is correlated with the changes of infarct volume, LV ejection fraction and mortality, following MI. Hence, the miR-1 level can act as a diagnostic biomarker of AMI [62]. In contrast, the expression level of miR-499 is low in ASC individuals, patients with congestive heart failure, and even in normal subjects; thereby, it is a distinguishable marker between acute MI and other cardiac diseases [63]. A recent study indicated that an increase in serum creatine kinase-MB (CK-MB) and cTnI occurs following overexpression of miR-499 could be applied as diagnostic markers [63]. The normal transplanted CSCs to post-MI myocardium leads to the generation of mature cardiomyocytes by increasing miR-499. The clinical implications for the treatment of human heart failure could be decreased *via* the function of miR-499, which is overexpressed in regenerative cell grafts and stimulates the better rebuilding of heart mass [63-65].

7. MYOMIRS AND HEART FAILURE

Heart failure (HF) is the most serious heart condition with high mortality as the heart muscles cannot pump blood efficiently, failing to provide metabolic needs of the body. The main causes of HF are CAD, HTN, diabetes mellitus, AF, and valvular heart disease [66]. Structural defects, abnormality in function, prolonged arrhythmias, myocarditis, infections, and exposure to cardiotoxic drugs [67] or overload can lead to HF. MyomiRs, like the other miRNAs, have a key function in systolic HF. Increment in miRs, including miR-208b and miR-499, is strongly correlated with the incremental risk of HF or death [68, 69]. Kontaraki *et al.* (2013) confirmed that miR-208b and miR-499 enhance myocardial hypertrophy in the animal models. They showed that miR (-1, -208b, and -499) are upregulated while miR-133a is downregulated in peripheral blood mononuclear cells of pat-

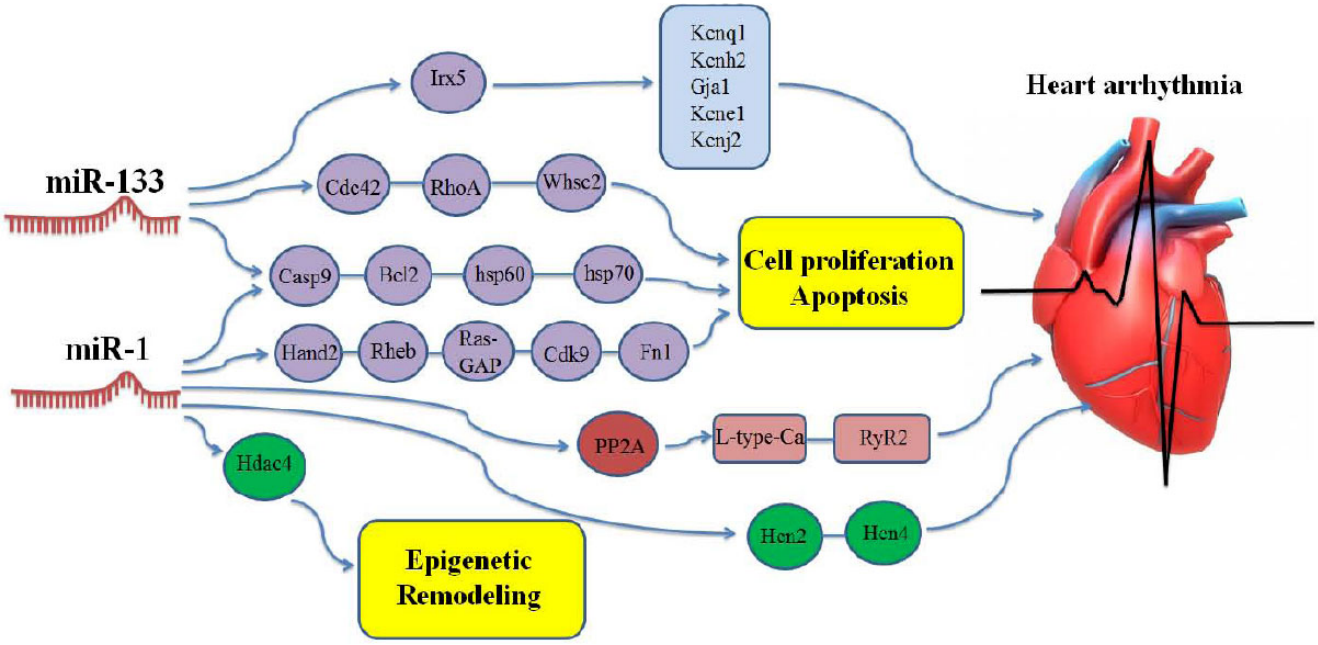

Fig. (3). The role of miR-1/miR-133 and corresponding target genes in heart arrhythmia. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tients with hypertension HF compared to controls. Moreover, in these patients, the expression level of miR (-1 and -133) was negatively correlated and the miR (-208b and -499) indices were positively correlated with left ventricular hypertrophy [70]. It was demonstrated that myomiRs have interference in Diabetic Heart failure (D-HF). A significant down-regulation of miR-1 was shown in the myocardium mouse model of type 1 diabetes mellitus, which is established by streptozotocin, whereas the expression levels of miR-499-3p and miR-208a were upregulated [71]. Wong *et al*. (2008) reported that miR (-1 and -133) remarkably increased in myocardial cells following hyperglycemic injury. MiR-1 targets IGF-1 and IGF-1 receptor [72]. Horie *et al.* (2009) showed an elevated level of miR-133 in hyperglycemic cardiomyocyte injury. MiR-133 has a critical role in metabolic control in cardiac myocytes by regulation of the expression level of GLUT4, which targets Kruppel-like transcription factor 15 (KLF15). Moreover, miR-133a/b targets KLF15 and is directly involved in this process [73]. MiR-133a/b can decrease the expression level of glucose transporter 4 and prohibit the uptake of glucose by insulin-induced myocardial cells [74]. It has been identified that miR-133a/b targets the human ether-a-go-go-related gene and KCNQI. These genes can interfere with the regulation of cardiac K^+ channels, which present in long QT syndrome patients with diabetes [71].

8. MYOMIRS AND HYPERTENSION

Hypertension (HTN) is a medical condition in which blood pressure is elevated. In developed countries, up to 20% of people have high or uncontrolled blood pressure. Indeed, in the long term, high blood pressure is accompanied by high morbidity and mortality rates. Hypertension is a major risk factor for many disabilities, such as CAD, HF, AF, peripheral vascular diseases, chronic renal failure, stroke, blindness, and dementia [75]. Like the other mentioned conditions, the regulating role of microRNAs in blood pressure is documented [76]. For example, the expression of the angiotensin II type 1 receptor is negatively regulated by miR-155 at the post-transcriptional level. Hence, the increased level of miR-155 is found to be associated with decreased blood pressure by binding of miR-155 to Angiotensin II type 1 receptor at 3'-UTR region [77]. It has been reported that myomiRs have epigenetic roles in hypertension. The level of MiR-1 is over-expressed in patients suffering from HTN, whereas the level of miR-133 is decreased in the patients [78]. Fbln2 protein is secreted to the extracellular matrix and participates in heart and embryonic development. A recent study indicates that Fbln2 could be targeted by miR1 and declines Fbln2 protein in cardiac hypertrophy [79]. Moreover, it has been reported that miR-208 is down-regulated during the progression towards right ventricular failure. Down-regulation of miR-208 activates the complex mediator of transcription 13/ nuclear receptor corepressor 1 axis which causes inhibition of the Mef2 expression [80]. Da Costa Martins and De Windt. (2012) suggested that some microRNAs, such as miR-1, miR-133, and miR-26, have an anti-hypertrophic function whereas, the others, such as miR-208, miR-499, and miR-21, have the agonist ability of the hypertrophic response [48].

In this case, Kontaraki *et al.*, (2015) investigated the expression levels of miR (-1, -133a, -208b and miR-499) in peripheral blood mononuclear cells in patients with essential hypertension relative to healthy individuals. These microRNAs are related to left ventricular hypertrophy in subjects with crucial hypertension. Their results indicated that miR-1 and miR-133a levels decrease in the left ventricular (LV) mass index, confirming their anti-hypertrophic activity. Also, the expression level of miR (-208b and -499) increases with the LV mass index, which confirmed previous hypotheses of their action as hypertrophy agonists [48].

9. MYOMIRS AND PULMONARY ARTERY HYPERTENSION

In pulmonary artery hypertension (PAH), the elevation of the resistance and reaction of pulmonary vein components occur to remodel in the distal pulmonary arteries, which leads to right HF. Recently, Mondejar-Parreño *et al.* (2019) investigated the level of miR-1 expression in a rat model of PAH enhanced by the hypoxia and Su5416 and its effect on voltage-dependent potassium channel (Kv) channels, which have a critical role on PAH. Their results showed that the expression of miR-1 was increased; while, Kv1.5 channels were decreased in the lungs from a rat model of PAH. This suggested that miR-1 has a pathophysiological role in PAH [81]. In a study on the pattern of miRNAs of mild-to-severe human PH, some myomiRs, including miR-1, 133b and 208b, were tested. The results indicated that a remarkable decrease in the miR-1 expression has occurred in human moderate and severe PH subjects while miR-133b and miR-208b were considerably upregulated in all moderate PH. However, it observed further enhancement in severe PH patients [82]. miR-23a can suppress the expression of PGC1α protein, which is a co-activator of PPARγ and PGC1α. Also, MiR23a reduces the expression of CYC, SOD, NRF2, and HO1 genes in Idiopathic PAH [83]. MiR-23b, miR-130a, and miR-191 can increase in patients with PH, and these miRs can serve as prognostic markers in the initial stages of PH [82].

10. MYOMIRS AND ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease in which plaque builds up inside the coronary arteries. Cellular interactions in the endothelium between resident cells (smooth muscle cells and endothelial cells) and immune system cells (leukocytes) lead to plaque formation [84]. Indeed, impairment of blood flow and lipid transportation (as a driving force) appears to be obligatory in this process. Fibrous tissue provides the structural integrity of a plaque. When atherosclerotic plaque develops in the wall of the coronary arteries, it causes Coronary Artery Disease (CAD). In the study of miRNAs analysis from the plasma of CAD subjects and healthy controls, it was indicated that miR (-133 and -208a) were increased [85] in view of the fact that up-regulation of miR-133a, miR-208a, and down-regulation of miR

(-126, -17, -92a, and -155) occur in CAD [86]. The upregulation of miR-155 increases the pro-inflammatory stimulation and macrophage-specific miR-155 has the potential to be used as a biomarker in the treatment of atherosclerosis [87].

D'Alessandra *et al.*, (2013) identified that there is an increased expression of miR-1 and miR-133a/miR-133b in patients with stable angina (SA) or unstable angina (UA). They suggested that miR-1 along with miR (-126, and -485-3p) can be used in the classification of patients with SA compared with controls, while miR (-1, -126, and -133a) is classified perfectly with UA *versus* controls in >87% of cases [88]. However, no combination could distinguish between UA and SA, suggesting that these bio-markers probably reflect the atherosclerotic burden present in both UA and SA subjects [89]. miR-181b is recognized as an atheroprotective miRNA that negatively regulates distinct components of NF-κB signaling pathway [90]. MiR -145 can reduce plaque size and the number of macrophages. However, overexpression of mir-145 supports plaque retains by elevation in the number of VSMCs and reduction in the number of macrophages. Consequently, suppression of miRNA-145 could be used as an emerging treatment for atherosclerosis [91].

11. MYOMIRS AND CONGENITAL HEART DISEASE

Alteration of miRNA expression is seen in many congenital heart diseases (CHD). CHD, as a multi-gene genetic disease at birth, was eventuated by abnormalities in cardiovascular structure or function. miR-1, as the most abundant myomiRs, is strongly conserved in myocardial cells. Overexpression of miR-1 inhibits the synthesis of Hand2 and regulates cardiac morphogenesis. Therefore, it seems that abnormal expression of miR-1 leads to CHD [92]. On the other hand, Ferreira *et al.* (2014) reported that deletion of miR-133a-1 or 133a-2 had no abnormality in the mouse phenotypes, while the knock-down of both miR-133a-1 and miR-133a caused a fatal ventricular septal defect during the embryonic period of mice [93]. Thus, the abnormalities of miR-1/133 expression can lead to the development of CHD. Ventricular septal defect (VSD), as a discontinuation in the septal wall between the right and left ventricles, is reported approximately in 20-40% of CHDs. In a study by Li *et al.* (2013), it was found that the expression of miR-1 was decreased in CHD patient samples. The increasing of miR-1 level leads to an increase in its target genes transcription, including GJA1 (Gap Junction Protein Alpha 1) and SOX9 [23]. Although the deletion of either miR-133a-1 or miR-133a-2 did not have any critical results in the cardiogenesis [31], it seems that both miR-1 and miR-133 have a key role in the regulation of growth-related cardiac genes. There is not enough evidence about developmental defects in the other myomiRs-null animals belonging to the miR-208 family (miR-208a, miR-208b, miR-499) [24]. However, their over-expression can induce cardiac hypertrophy and conduction defects [32]. Loss of miR-17-92 cluster (miR-17, miR-18a, miR-19a, miR-19b-1, miR-20a, miR-92a-1) can increase incidence of VSDs and lead to the death of newborns [94]. Inhibiting ISL1 and TBX1 expression is a strategy to increase miR-17-92 cluster expression to overcome VSDs [32]. The analysis of ASD children has shown that hsa-let-7a, hsa-let-7b, and hsa-miR-486 are upregulated. Also, these miRNAs are detectable in maternal samples, which are applicable for predicting CHD risk in offspring [95]. The embryonic heart with ventricular septal defects and cardiac hypertrophy indicates overexpression for miR-195. MiR-195 can target CHEK1 as a cell cycle regulator and suppressing miR-195 results in a reduction of expression level for CHEK1 and increase the number of mitotic cardiomyocytes [36].

12. MIRNAS AS POTENTIAL THERAPEUTIC AGENTS

MicroRNAs are considered as a novel therapeutic modality in various diseases due to their resistance in circulation, high affinity, specificity, and low toxicity [67].

MicroRNAs are used for both replacement or inhibition therapy [96]. In replacement therapy, microRNAs mimic double-stranded miRNA (a synthetic RNA duplex; one guide strand to mature miRNA sequence, and the passenger strand) [97], miRNA precursor or miRNA-expressing DNAs. These miRNAs act as enhancers of miRNAs expression but are downregulated in diseases such as CVD [78]. Anti-miRNA oligonucleotides (AMOs), antagomirs, locked nucleic acid (LNA), antisense nucleotides peptide nucleic acids or miRNA sponges are used for blocking the suppressive function of miRNAs on the translation of protein. In modified oligonucleotide synthesizing methods, microRNAs were synthesized with the 2'-O-methyl, which elevate resistance against nucleases degradation [98]. In addition, a modification on the 3' and 5' ends of oligonucleotides *via* partial phosphorothioate backbone can protect synthetized microRNAs against degradation and elevate the protein binding and cellular uptake [99]. Beyond the mentioned modifications, 2'-fluoro and locked nucleic acid (LNA) also imparts more stability and binding affinity for microRNAs [99]. Lennox *et al.* (2013) showed that the combination of 2'-OMe and N, N-diethyl-4-(4-nitronaphthalen-1-ylazo)-phenylamine(ZEN) could decrease the toxicity of oligonucleotides [98]. Cardiac-specific down-regulation of the most important myomiRs (miR-1) has a potential treatment activity in the treatment of cardiovascular diseases, particularly CAD. In this case, we showed that inhibition of miR-1 expression by antisense-miR-1 significantly decreases apoptosis in the myoblast C2C12 cells [18]. Also, Tang *et al.* (2009) indicated that using antisense miR-1 oligonucleotides plays a protective role in cardiac pathology by inhibition of apoptosis and increases resistance to oxidative stress [100, 101]. Therefore, targeting of miR-1 can be useful in heart ischemia therapy and post-MI complications. Moreover, the implementation of Ischemic Preconditioning (IPC) can be accompanied by a cardio-protective effect. This mechanism of action beside mitochondrial function preserves the reduction of apoptosis and infarct size area.

As mentioned previously, a change in myomiRs level has been considered in different CVD. Hence, the serum and other body fluid levels of the micro RNAs can be detected using real-time PCR or microarray assay and be a key point of CVD diagnosis. Circulating miRNAs are stable nucleic acids [102]. In AMI, miRNA (-1, -133, -208b, and -499) may have the future for upcoming diagnostic markers. Moreover, the levels of miR-1 and miR-499 are increased in patients with HF [63]. It seems that myomiRs, especially miR-1, have been known as the main regulators during differentiation, proliferation, and apoptosis of cardiovascular cells. Moreover, the important role of myomiRs on cardiovascular diseases such as arrhythmia, remodeling processes, cardiac fibrosis, and hypertrophia was revealed. Therefore, myomiRs can be a candidate in different therapeutic strategies. Hence, identification of the details of myomiRs mechanisms in many cardiovascular disasters and focusing on antisense of myomiRs can be the goals of novel heart therapeutics.

Table 4. Advantages and disadvantages of myomiRs in cardiovascular diseases.

MyomiRs	Advantage	Disadvantage
miR-1	- An anticardiac hypertrophy effect by suppressing HAND2, and by inhibiting the activity of GF-1 and extracellular matrix remodeling factor, twinfilin 1 [113]. - The overexpression of miR-1 has lasting therapeutic potential in pathological cardiac remodeling [79] . - miR-1 expression can reduce fibrosis and apoptosis, and improve calcium signaling [79, 113]. - miR-1 is muscle specific miRNA, the most favorable miRNA in the early and accurate diagnosis of acute myocardial infarction (AMI) [107].	- Overexpression of miR-1 in the embryonic period gives rise to ventricular septal defect and heart failure in mice [7]. - Upregulation of miR-1 in patients with CAD and rats with experimental myocardial infarction [16]. - Overexpression of miR-1 causes an increase in H_2O_2-induced cardiomyocyte apoptosis [101]. - miR-1 was upregulated in myocardium hearts of patients who died of MI [53].
miR-133 family	- miR-133 is one of the major anti-fibrotic microRNA and knockout of miR-133a-1/2 leads to the progression of severe myocardial fibrosis and HF[31, 113]. - Overexpression of miR-133 leads to a decrease in pressure overload-induced fibrosis and apoptosis [114]. - Overexpression of miR-133a avoids early cardiac fibrosis in diabetes [114]. - Induction of miR-133 expression causes a decrease in cardiomyocyte apoptosis by negative regulation of Casp3 and Casp8 expression and results in protecting cardiomyocytes from cell death [115]. - miR-133a has a regulatory effect on Casp9 that leads to the beneficial effect of the post-ischemic condition [100]. - miR-133 is expressed highly in the vasculature and reduced after vascular injury and proliferates VSMCs [116]. - miR-133 has therapeutic potential for vascular diseases by reducing the proliferation of VSMCs and inhibition of transcription factor Sp-1 [116]. - miR-133 can be used as a diagnostic and prognostic biomarker in these patients throughout the acute ischemic period [117].	- miR-133 dysregulates during hypertension, vascular calcification, atherosclerosis, and aneurysmal disease [117]. - miR-133 is further increased in patients with coronary artery disease. [118]. - Downregulated miR-133 detected in the hypertension patients is compared with the healthy control group.
miR-208 family	- miR-208a is detectable in plasma in patients with AMI and is presumably originated from the heart and reflects necrotic myocytes [107]. - miR-208a has the anti-myocardial hypertrophy effect and is upregulated during myocardial hypertrophy [119].	- miR-208 family are the main miRs promoting cardiomyocyte hypertrophy [113, 120]. - Inhibition of miR-208a expression recovers cardiac function and survival [120]. - The level of MiR-208a is upregulated in CAD [118]. - miR-208a directly causesthe isoform switch from α-MHC to β-MHC that characterizes pathologic hypertrophy and HF. Also, miR-208a creates the expression of β-MHC in stressed hearts [113].
miR-486	- miR-486 level is reduced by both acute and chronic exercise [118]. - miR-486 regulates cardiomyocyte apoptosis by using the p53-activated BCL-2 in the mitochondrial pathway [121].	- Levels of miR-486 were significantly higher in AMI [122]. - miR-486 was significantly upregulated in children with atrial septal defects (ASD) [95].
miR-499 family	- Overexpression of miR499 reduces cardiomyocyte apoptosis in heart failure [123]. - miR-208a has the anti-myocardial hypertrophy effect and is upregulated during myocardial hypertrophy [119].	- miR-499 are elevated after acute myocardial infarction (MI) [124]. - miR-499 is increased with viral myocarditis [124].

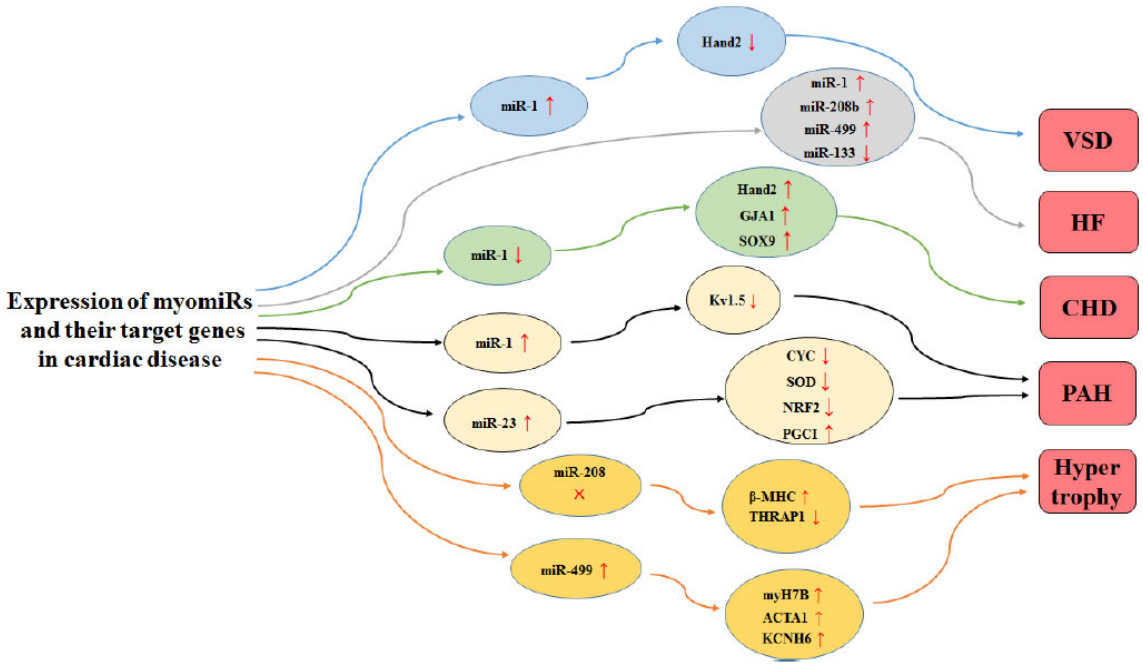

Fig. (4). The schematic representation of myomiRs expression and their target genes in cardiac disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

The contributing functions of cardiac-specific miRNAs (myomiRs) in the developmental process of the heart are well-defined. Among myomiRs, miR-1 and miR-133 display the most prominent activity in cardiovascular biologies such as proliferation, differentiation, metabolism, physiology, and myocardial diseases [103]. Thus, they appear to be potential targets for therapeutic interventions in cardiovascular diseases [104]. As shown in Fig. (**4**) and Table **4**, in some cardiac diseases, up-regulation or down-regulation of myomiRs can regulate vital physiological events [52, 80]. Considering the stability of myomiRs and their resistance to endogenous RNases, these regulators can be utilized as effective diagnostic biomarkers in cardiac disorders. However, regardless of the fact that the application of miRNas as routine diagnostic markers needs high technology and skill, more investigations regarding their specificity and optimization are required.

CONSENT FOR PUBLICATION

This is the review work of the authors. The work described has not been submitted elsewhere for publication, in whole or in part, and all authors listed carried out the manuscript writing. Moreover, all authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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