Review Article

Role of non-coding RNA in cardiac remodeling

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Abstract: Studies conducted in the past decade have identified that a significant portion of the genome is "non-coded" instead accounts for non-coding RNAs (ncRNAs) including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), piwi-interacting RNAs (piRNAs), guide RNAs (gRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs). Evidences further indicate that these groups of ncRNAs contribute significantly to cardiac remodeling process including hypertrophy and fibrosis. In addition, several ncRNAs have been identified as biomarkers in cardiac disease. Thereby, ncRNAs are promising therapeutic targets for several cardiac pathologies/diseases. This review aims to discuss and summarize the molecular mechanisms and function of several classes of ncRNAs related to cardiac diseases.

Keywords: Non-coding RNA (ncRNA); cardiac remodeling, therapeutics

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Introduction

Cardiac remodeling is defined as an alteration of cardiac cells in response to mechanical, chemical, electrical signals and stress or pathological stimuli that culminate into cardiac dysfunction. The stress stimuli such as inflammation, oxidative damage, myocardial infarction (MI), pressure or volume overload can trigger cardiac remodeling leading to cardiac arrythmia and heart failure (HF). Cardiac remodeling is a complex process characterized by structural alteration and phenotypical changes including hypertrophy, apoptosis, necrosis, fibrosis, ventricular dilatation, vascular dysfunction resulting in HF (1-3). Reversing cardiac remodeling is, therefore, a key strategy for the treatment of HF. Recent work from multiple laboratories have highlighted the role of non-coding RNAs (ncRNAs) in cardiac remodeling and will be described in this review.

The ncRNAs are a class of RNA that does not encode for a protein and is previously thought as "junk" molecule. In fact, in humans, approximately 98% of the genome consists of ncDNA meaning ~2% of DNA sequences corresponds to protein coding exons with any functional relevance (4-6). Researchers have reported over the past two decades the importance of RNA research primarily dominated by microRNA (miRNA), a particular class of ncRNA. However, several other classes have been identified over the time and, they include long non-coding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs), circular RNAs (circRNAs), piwi-interacting RNAs (piRNAs), guide RNAS (gRNAs), small nuclear RNAs (snRNAs) (7). The ncRNAs regulate cellular or biological functions like proliferation, differentiation, inflammation, cell death and metabolism. In this review, we focus on the role of miRNA, lncRNA and circRNA and, their therapeutic use in cardiac remodeling.

miRNA in cardiac remodeling

miRNAs are single-stranded endogenous ncRNA of 19–23 nucleotides (nt), evolutionary conserved across different species and, modulate gene expression by targeting specific

gene(s) at the posttranscriptional level in a tissue-specific fashion. miRNAs bind mostly to the 3'-untranslated region (UTR) of target genes and inhibit gene expression translationally and/or by destabilizing the target mRNA (8). Although miRNAs were discovered first in *C. elegans* in 1993 (9) but the importance of their function was much later recognized in 2000 and research gained momentum thereafter.

The single stranded small miRNA is formed from its longer transcript called primary miRNAs (pri-miRNA) which is more than 1 kb in length and contain hairpin/stem loop (10). The pri-miRNA is further processed to precursor miRNAs (pre-miRNAs), 70-nt stem loop oligonucleotides, in the nucleus by the Drosha/DGCR8 complex (a type III RNase complex), then exported to the cytoplasm through the nuclear pore with the help of a protein called Exportin 5 and Ran-GTPase. Here, the pre-miRNAs are subsequently processed by Dicer/TRBP complex, to form mature double-stranded miRNAs (11,12). During the maturation process, the pre-miRNAs lose their terminal base pairs and their hairpin structure. The single-stranded form is a fully active mature miRNA; this is achieved by dissociation of the complex and association with Argonaute (Ago) which binds with RNA-induced silencing complexes (RISCs) and specifically binding with its target genes (11-13). Mature miRNAs can be released to the extracellular milieu within vesicles (i.e., exosomes) and communicate via miRNA-mediated cellular function. Finally, miRNA binds to the 3'-UTR of the mRNA and promote posttranslational degradation or downregulation of target gene.

miRNA in cardiac development

The first evidence of miRNA in the setting heart development was demonstrated in a mouse model of cardiac-specific deletion of DICER that led to embryonic lethality within the first four days after birth due to dilated cardiomyopathy (14). In addition, vascular smooth muscle-specific disruption of Dicer exhibited embryonic lethality at embryonic day 16 to 17 with massive internal hemorrhage and eventually led to dilated and thin-walled blood vessels due to impaired cellular proliferation. The blood vessels derived from these mice showed contractile dysfunction due to loss of actin fibers. Interestingly, the phenomenon is partly rescued by overexpression of miR-145 or myocardin (15). Moreover, several congenital heart diseases like small ventricular septal defects (VSDs), tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) are also associated with miRNA dysregulation.

miR-1 was the first miRNA that demonstrated a crucial role in cardiac development (16). Mice with increased miR-1 expression in the developing heart showed decreased cardiomyocyte proliferation and was mediated by inhibition of *Hand2*, a critical cardiomyocyte transcription factor (16,17). In contrast, depletion of miR-1-2 in mice resulted in embryonic lethality due to VSDs (18). Moreover, miR-1-1 was shown to be significantly dysregulated in patients with VSDs (19). In addition to the miR-1 family, several other miRNAs are reported to be involved in VSDs. Loss of both miR-17-92 and miR-106b-25 developed exacerbated cardiac malfunction including ventricular wall thinning and VSDs (20). miR-195, a member of the miR-15 family is involved in VSD. Cardiac-specific overexpression of miR-195 is associated with ventricular hypoplasia and VSDs in hearts on postnatal day P1 to P3 (21).

TOF, another congenital heart defect whose cause is primarily unknown. TOF is more often seen in children with Down syndrome or DiGeorge syndrome. The features include a hole in the heart, an obstruction between heart and lungs, pulmonary stenosis and right ventricular hypertrophy. The first study on ncRNA in TOF was reported by O'Brien *et al.* (22). They reported that sixty-one miRNAs and 135 snoRNAs were significantly dysregulated in children with TOF compared to healthy infants (22). miR-1 expression was significantly reduced but miR-421 was significantly upregulated. The study is interesting as it indicates that the alteration of miRNA/snoRNAs may influence differential splicing of a transcript resulting in faulty translation of a protein leading to the development of heart defect. A follow-up study by the same group showed the role of miR-421 in TOF targeted to SOX4, a key regulator in Notch pathway critical for cardiac outflow track (23). Another miRNA, miR-940 whose reduction may influence the development of track flow by targeting JARIAD1 (24). Connexin43, a gap-junction protein, essential for the formation of heart development and structures, was upregulated in TOF subjects (25). It is reported that miR-1 and miR-206 are significantly reduced in TOF patients and connexin 43 is a potential target gene (26). Another microarray study showed up-regulation of miR-424/424* and suppression of *HAS1*and *NF1* in right ventricular outflow tract biopsies of TOF patients indicated its' role in TOF (27).

miRNA in cardiac hypertrophy

Cardiac hypertrophy is defined by an increase in the size of cardiomyocytes, without increase in cell numbers. At the molecular level, cardiac hypertrophy exhibits an increased expression of certain fetal-type genes like *ANF* and β-*MHC* (28). Role of miRNA in cardiac hypertrophy was first documented by von Rooij *et al.* using cardiac-specific miR-208 transgenic and miR-208 knock-out mice (29). Knockout of miR-208 confers protection during aortic banding by targeting thyroid hormone receptor associated protein 1 (THRAP1). The first identified negative regulator of cardiac hypertrophy is miR-133 (30). Overexpression of miR-133 showed inhibition of pressure overload-induced cardiac hypertrophy targeting RhoA, Cdc42andNelf-A/WHSC2 (30). A subsequent article showed an anti-hypertrophic effect of miR-1 (31). Because miR-1 is an abundant miRNA in the myocardium, studies were conducted to test its efficacy at therapeutic stand-point. The study demonstrated that miR-1 prevents cardiac hypertrophy by suppressing heart and neural crest derivatives expressed 2 (Hand2), and by inhibiting the activity of insulin-like growth factor (IGF), twinfilin 1 or connexin 43 (32-35). The miR-378, another anti-hypertrophic miRNA, regulated cardiac hypertrophy by repression of Mapk1, Igf1r, Grb2, and Ras 1 (36). Over the period time, an overwhelming number of articles are published demonstrating pro- or anti-hypertrophy effect of miRNAs including miR-9, miR-21, miR-23a, miR-455, miR-199, etc. (37-41). Among them, miR-21 is very thoroughly studied miRNA over more than 15 years in many biological aspects including cardiac remodeling. Interestingly, the role of miR-21 in cardiac hypertrophy cautioned us about the use of anti-miRNAs as therapeutic. The small variation of 8 *vs.* 21 nt appears to have oligonucleotide chemistry preferences (42,43). Using miR-21 deficient mice and 8nt anti-miR-21 oligonucleotides, Patrick *et al.* demonstrated no development of cardiac hypertrophy and fibrosis when miR-21 null mice exposed to pressure overload and concluded that miR-21 has no role in cardiac hypertrophy (42). In contrast, Thum *et al.* showed that inhibition of miR-21 with 22- and 15-nt miR-21 oligonucleotides effectively inhibits myocardial and pulmonary fibrosis (43). Both studies were meticulously designed and elegantly executed but, questions remain about the ambiguity. Possible explanation may be due to off-target effect as two different sizes of nucleotides were used or a genetic deletion has influence in compensation effect.

miRNA in cardiac fibrosis (CF)

CF is a proliferative remodeling disease and is a highly debilitating process that eventually leads to organ dysfunction. CF occurs as an imbalance of extracellular matrix (ECM) proteins turnover and the underlying molecular and morphological correlate of CF is disruption of myocardial structure via uncontrolled deposition of ECM proteins which include collagens, matrix metalloproteinases (MMP), etc. in the interstitium and perivascular region of the heart (44-46). As a result, myocardial stiffness occurs which alter the mechanics of the heart and impair the function. The role of miRNAs in CF is well-documented. Apparently, the initial studies demonstrated by Thum *et al.* (43) indicated the role of miR-21 in CF targeting extracellular regulated kinase inhibitor sprouty homolog 1 (Spry1) (43). But, an elegant study led by Eric Olson's group showed the expression of miR-29 family members (miR-29a, miR-29b and miR-29c) negatively correlated with ECM production and fibrosis in MI model (47). The miR-29 family is also referred to as "fibro" miRs because of its ability to promote tissue fibrogenesis (48). The miR-29 family is consistently downregulated in many organ fibrosis like renal, lungs and liver and their reduction correlate with upregulation of ECM-related genes leading to activating fibrogenic or fibrosis signaling pathway (49-52). In addition to miR-29 family, several other miRNAs have been reported in CF targeting various fibrotic genes and TGF-β signaling in fibrogenesis. Our group has previously reported the role of miR-26a in CF targeting connective tissue growth factor (CTGF) and collagen I, respectively (53). Moreover, we showed a transcription factor (NF-κB)-mediated modulation of miR-26a both *in vitro* and *in vivo* models. Another downregulated miRNA in MI-induced CF is miR-24 (54). Lentivirus-mediated delivery of miR-24 precursors reduced fibrosis and decreased cardiac fibroblast differentiation by targeting furin (54). The role of miR-133a and miR-30 in fibrosis has been determined and, this established an important function of these miRNAs in CF (55-57). A critical event in CF is the transformation of CF to an active CF phenotype or myofibroblasts (58,59). Myofibroblasts is the specialized CF formed by irreversible acquisition

of expression of alpha-smooth muscle actin (α-SMA) (59,60) and inhibition of myofibroblasts may be effective to prevent CF. Recent studies including ours indicate a critical link between miRNA dysregulation and myofibroblast activation (61,62). Both studies used locked nucleic acid (LNA) technology to specifically inhibit miRNAs, miR-125b and miR-130a, *in vivo* and rescued angiotensin II-induced CF (61,62). MiR-433, another fibroblast-enriched miRNA identified through MI-induced miRNA array analysis showed consistent upregulation in MI and dilated cardiomyopathy models (63). Over expression of miR-433 in cardiac fibroblast elicits fibroblast differentiation and myofibroblast activation targeting AZIN1 and JNK1. Reduction of both the molecules activating TGF-β1 and ERK/p38 pathway respectively, activating Smad3 leading to CF (63). Adenovirus-mediated (AAAV-9) *in vivo* inhibition of miR-433 showed reduction in CF and improved cardiac function following MI (63). These studies may indicate a future use of these miRNAs for the treatment of human cardiac fibrosis.

LncRNAs in cardiac remodeling

Long noncoding RNAs (lncRNAs) are autonomously transcribed RNA (~200 nt) with poor primary sequence conservation. However, the promoter sequence of lncRNAs in many cases are found to be conserved indicating there may be a common regulatory pattern. Expression profiles of lncRNAs indicate that they are cell type, tissue, and developmental stage specific although less abundant (64,65). Compared to mRNAs, lncRNAs are found to be enriched in the nucleus than the cytoplasm (66). They are transcribed by RNA pol II, and nascent RNA transcripts undergo 5' capping, polyadenylation and chemical base modification (67). Mass spectrometry-based analysis suggest that most of these lncRNAs do not translate into protein although ribosomes are attached to the lncRNAs. LncRNAs and mRNAs have a comparable stability (68). To date few lncRNAs that are functionally characterized are known to increase or suppress transcription activation, act as protein or RNA decoys, enforce stable repressive chromatin state activity and assist in formation of higher order nuclear architecture such as chromatin remodeling (69,70) Overexpression, under-expression and mutation of lncRNAs have been implicated in numerous diseases (7). In this review some of the known lncRNAs that contribute to cardiovascular diseases are discussed below.

LncRNAs and ischemic heart disease (IHD)

IHD is one of the most common causes of HF worldwide. In case of IHD, cardiomyocytes are lost either through necrosis or apoptosis. Therefore, reducing cardiomyocyte death may be an efficient way to prevent the progression to HF. LncRNA Carl inhibits mitochondrial fission and affects cardiomyocyte apoptosis through its interaction with miR-539 and PHB2 as demonstrated in a mouse model of ischemia/reperfusion (I/R) injury (71). Another lncRNA APF regulates autophagic cell death along with the involvement of miR-188-3p and ATG7 in the heart (72). NRF lncRNAs act as sponges of miR-873 and miR-873 in turn suppresses RIPK-1/RIPK-3, a known necrosis regulator thereby reducing myocardial infarct damage. This study illustrates that NRF and miR-873 are involved in the cardiomyocyte apoptosis (73). These above-mentioned lncRNAs identified in mouse models provide a new therapeutic target to reduce cardiac ischemic injury which was previously unknown. An initial study reported that following MI, 5 lncRNAs have been shown to be increased in the plasma in humans (74). These circulating levels of the lncRNAs can act as a predictor of MI in patients. Further studies involving large number of patients are required in the future to understand if these lncRNAs can be successfully used as biomarkers.

LncRNAs and CF

CF results in excessive ECM accumulation that can progress to HF. H19 lncRNA can reduce the proliferation of cardiac fibroblasts by inhibiting DUSP5/ERK1/2 and plays a key role in the pro-proliferative and profibrotic pathway (75). Augmented expression of lncRNA NR024118 in rat cardiac fibroblasts led to alteration of cell cycle inhibitor CdKn1c (76). TGF-β/Smad3 pathway is a known regulator of the fibrotic pathway. High throughput RNA sequencing from SMAD3 KO mice kidneys reveal 21 novel lncRNAs (77) that need further investigation regarding their role in CF. LncRNA NFAT has been shown to modulate transcription factor NFAT. Experiments performed using 3T3 fibroblasts when NFAT is knocked down leads to different subcellular localization (78). Interestingly, the role of maternally expressed gene 3 (Meg3) lncRNA to inhibit hepatic stellate cell activation and liver fibrogenesis is known but whether it is also important for the process of CF is currently unknown.

LncRNAs and cardiac hypertrophy

Cardiac hypertrophy can be due to various pathological stimuli and maladaptive hypertrophy can eventually lead to HF. Mhrt binds to the Brg1 chromatin remodeling protein complex. This complex then prevents binding to its genomic DNA targets such as Myh6 and Myh7 thereby blocking fetal gene activation (79). The conserved H19 lncRNA targets CAMKIIδ thereby acting as a negative regulator of cardiac hypertrophy (80). miR-675 is a known target of H19 lncRNA. This lncRNA also acts as in CF. CHRF lncRNA regulates Myd88 via miR-489 (81). Chast lncRNA, is a pro-hypertrophic RNA, a GapmeR silencing this lncRNA suppresses transverse aortic constriction (TAC)-induced pathological cardiac hypertrophy (82). Chast lncRNA has been shown to negatively regulate pleckstrin homology domain containing protein family M member 1 disrupting cardiomyocyte autophagy and promoting hypertrophy. ROR lncRNA is a key player in the pathogenesis of cardiac hypertrophy. In hypertrophic mouse hearts, ROR expression is increased, and on the other hand a decrease in ROR expression attenuates cardiac hypertrophy. ROR negatively correlates with miR-133 (83). The role of lncRNAs in pathological cardiac hypertrophy has been studied so far but has not been studied extensively in physiological cardiac hypertrophy.

lncRNAs as biomarkers

LncRNAs can directly bind to miRNA and indirectly interact with mRNAs through competing endogenous RNA (ceRNA) interactions. These interactions can be predicted by computer algorithms. Based on computer algorithms, lncRNAs (SLC26A4-AS1, RP11-344E13.3 and MAGI1-IT1) were predicted to be associated with cardiac hypertrophy but has not been experimentally verified. Malat-1 lncRNA that acts as a ceRNA for miRNA-133, an anti-cardiac hypertrophic miRNA (84). Of note, the absence of Malat-1 did not affect pressure overload induced cardiac remodeling in mice. To investigate the potential of lncRNAs to serve as biomarker of cardiovascular diseases, Kumarswamy *et al.* reported a decrease in the mitochondrial lncRNA LIPCAR after MI (85). Interestingly the levels were found to be upregulated during the later stages of the disease. In patients with MI progressing to HF plasma LIPCAR levels can be used to independently to predict survival (85). Patients suffering from hypertrophic obstructive cardiomyopathy (HOCM), the lncRNAs uc004cov.4 and uc022bqu.1 were upregulated but not in hypertrophic non-obstructive cardiomyopathy (HNCM), suggesting their predictive value in distinguishing these conditions (86). A study conducted by Greco *et al.* (87) demonstrated that 14 lncRNAs were dysregulated in ischemic HF patients. In addition, this study suggests that lncRNAs can be used as potential biomarkers for these patients in the future. The successful use of lncRNA to therapeutically treat HF patients have not been performed yet due to several limitations. These include lack of sequence conservation among rodent models and humans, predominantly nuclear localization of lncRNAs makes it harder to target, also lncRNAs regulate various pathways and there may be possible off-target effects.

circRNAs in cardiac remodeling

Noncoding RNAs constitute 95% of total gene regulation in the eukaryotic transcription. Covalently closed circRNAs are generated by back-splicing of either exon [exonic circular RNA (ecircRNA)], intron [circular intronic RNA (ciRNA)] or both to form exonic or intronic circRNAs (ElciRNA) (88). CircRNAs are usually catalyzed by spliceosomal machinery or group I and group II enzymes. The formation of closed loop provides an advantage in preventing degradation by RNA exonucleases. It is believed that circRNA expression is regulated by other factors and exhibit cell type and tissue specific patterns. The size of circRNA varies from 100 nt to several kilobases. The function of circRNAs are beginning to be elucidated. Few of the functions which are known to date include sequestration of miRNAs, proteins, changes in transcriptional, splicing and even translational activity.

circRNAs and cardiac hypertrophy

Evidence that circRNA plays an essential role in initiation and development of cardiovascular diseases comes from several studies. A previous study demonstrated that miR-223, present in myeloid cells and bone marrow is a regulator of cardiac hypertrophy and HF (89). Heart-related circRNA (HRCR) can bind directly to miR-223 and act as an inhibitor. In cardiomyocytes, miR-223 is known to act as downstream target of ARC (apoptosis repressor with CARD domain). Due to binding of circRNA HRCR to miR-223 there is an increase in ARC expression (90). These studies indicate that overexpression of HRCR could attenuate cardiomyocyte hypertrophy as well as HF *in vivo*.

circRNAs and CF

In two different mouse models, such as diabetic mouse myocardium and in Ang II-induced mouse, cardiac fibroblasts circRNA_000203 was reported to be upregulated (91). CircRNA_000203 binds to miR-26b-5p which in turn interact with the 3'-UTRs of CTGF and Col1a2. Overexpression of circRNA_000203 also caused an increase in expression of fibrosis-associated genes such as Col1a2, Col3a1, α-SMA, and CTGF. CircRNA_000203 could inhibit the anti-fibrotic effect of miR-26b in mouse cardiac fibroblasts. Zhou *et al.* also illustrated that another circRNA, namely circRNA_010567, promotes myocardial fibrosis by downregulating miR-141 function (92).

circRNAs and MI

Prolonged myocardial ischemia during MI leads to apoptosis. A detailed study on CDR1AS, a circRNA has been shown to be upregulated in MI mice with increased cardiac infarct size or in cardiomyocytes under hypoxia treatment. CDR1AS which is first identified as a miR-7a/b sponge promotes MI by regulating miR-7a target genes such as *PARP* and *SP1* (93). This study indicates the key role of Cdr1as/miR-7a axis in MI-induced myocardial apoptosis. Quaking gene are known to regulate specific set of circRNAs. Quaking gene is also downregulated in murine myocardium treated with doxorubicin. Quaking gene deletion by using a CRISPR/Cas9 mediated silencing increases cardiomyocyte sensitivity however, overexpression blocks doxorubicin induced apoptosis (94). Additional studies are needed in humans in the future to determine the role of other circRNAs in MI.

circRNAs as biomarkers

Importantly, recent studies on circRNAs suggest that they can serve as a non-invasive biomarker for detection of different cardiovascular diseases (95). They have an advantage because they are stable (lack of exposed terminal ends makes them less susceptible to RNases). Deep sequencing efforts have led to identification of large number of these circRNAs and they are present in whole blood, plasma and extracellular vesicles. In addition, the fact that circRNA expression is regulated during cardiac development and in failing hearts makes them ideal candidates to serve as biomarkers.

RNA microarray of circRNAs from peripheral blood samples of patients with coronary heart disease (CAD) detected increased expression of hsa_circ_0124644 with the largest area under the curve (96). Vausort *et al.* identified MI-associated circRNAs (MICRA), in the peripheral blood of patients with MI and left ventricular dysfunction which can predict left ventricular dysfunction in a few months following reperfusion (97). Another study demonstrated that circRNA_081881 act as a competitive endogenous RNA molecule of miR-549, via regulating PPARγ expression (98). Because circRNA_081881 can be detected in plasma and therefore circRNA may serve either as a biomarker or could be targeted for therapeutics for acute MI. High throughput RNA sequencing studies using adult human heart tissue allowed identification of 80 circRNAs from key cardiac genes including *Titin* (TTN), a gene with complex alternative splicing sites. It has been reported that only a small number of these circRNAs contribute to dilated cardiomyopathy. RBM20-KO mice lack circRNAs from I band of titin (99).

Collectively, these results indicate that circRNAs can serve as a biomarker for diagnosis of cardiovascular diseases. However, interpreting these data needs caution as circRNA expression can increase/decrease in the tissues but not the peripheral blood/plasma fluids, etc. Ongoing research on circRNAs also suggest that these RNAs also act as potential protein coding genes due to the presence of internal ribosome entry site (IRES), appropriate open reading frame (ORF). However, there has been no studies that has been conducted to suggest that these translatable circRNAs play a role in cardiovascular disease. As we gather new information about these circRNAs and their targets it would interesting to see if they can serve as a reliable biomarker for cardiovascular disease in the future.

miRNA therapeutic application

It is established that an individual miRNA may target thousands of different mRNAs; thus, it may be worth to develop miRNA-based strategies targeting the gene or pathway networks responsible for cardiac remodeling. The miRNA mimic and inhibitor are used for therapeutic intervention with a modification as gain-of-function or loss-of-function fashion. The modifications are primarily used for *in vivo* stability, specificity, and high binding affinity to the miRNA of interest or target. The modifications include 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'-MOE), 2'-fluoro (2'-F), or LNA (100,101). Another chemical modification applied is phosphodiester (PO) and phosphorothioate (PS) linkages between the nucleotides.

The bonding may provide stability and easy uptake (102). Krutzfeld *et al.* reported the first miRNA knockdown in mammals using cholesterol conjugated, 2'-O-methyl modified, so called "antagomiRs", to inhibit a liver specific miRNA, the miR-122 (103). There are some disadvantages of using anti-miRs which apparently arises from the chemistry itself. PS oligonucleotides, for example, can inhibit the tenase complex in the intrinsic clotting cascade (104) and activate innate immunity. The LNA-mediated anti-miRs apparently works better but hepatotoxicity was reported in some cases. Furthermore, LNAs are resistant to degradation and have long tissue half-life. To date there is only one miRNA drug in clinical trials (SPC3649: inhibitor of miR-122, Santaris Pharma, Denmark, ClinicalTrials.gov identifier: NCT01200420) (101,105). It has completed two phase I trials and are now in phase II trial with their miR-122 targeting Miravirsen. Treatment of chronic hepatitis C-infected chimpanzees with miravirsen led to suppression of HCV without any obvious side-effects (106,107). These results are encouraging and highlight miravirsen as a potential future replacement therapy for patients with chronic HCV infection. Other pharma like Miragen Therapeutics is currently testing miR-155, miR-29b and miR-92 for treatment of blood cancer, fibrosis and IHD (108). Regulus Therapeutics is testing miR-33a/b at preclinical non-human level (primates) (109).

Finally, the toxicity studies of chemically-modified miRNA inhibitors will be required to establish safety parameters for different anti-miR chemistries. Studies however suggest the safe use of anti-miR (LNA) technology to reduce miRNA expression, but there are many unknown situations may exist like the mode of action, degree of blocking, long-term effect and the chemistries behind them. Importantly, the dosage of anti-miRs are likely in the higher range and may not therapeutically applicable. An appropriate guideline for therapeutic dosage needs to be established to avoid unwarranted side-effects after the delivery.

The application of miRNA mimic is so far very limited because of unmodified state and application of high doses. The mimic primarily acts as a double stranded oligonucleotide comprised of mature miRNA sequence (guide strand), as well as a complementary passenger strand, that is required for the efficient recognition and loading of the guide strand into the RISC. A recent report showed that the export of miR-132 via mesenchymal stem cells-derived exosomes represents a novel strategy to enhance angiogenesis in ischemic diseases (110).

Conclusions

A significant number of differentially regulated miRNAs are observed in cardiac remodeling indicating their potential role in the development of the cardiac diseases. Our understanding of miRNA biology in cardiac remodeling is rapidly progressing and, the current literature suggest that miRNAs contributed to (adverse) pathological remodeling by regulating the critical events like myocyte growth, (cardiac) cell fate and ECM remodeling. The most fascinating part of miRNA modulation is that it influences proteome remodeling which may alter the contractile function and mechanics in the heart. Therefore, miRNAs are suggested for therapeutic tools and considered as promising approach for cardiac remodeling. Treatments are currently focused on systemic anti-miRNA delivery which made significant progress in alleviating adverse cardiac remodeling and showed promise for therapeutic intervention in rodent model. However, it raises concerns for off-target effects, efficacy and sustainability of anti-miRNA are the major challenges. Future efforts should be aimed at evaluating either cell-type-specific strategies or local delivery. Other ncRNAs like lncRNAs and circRNAs are more complex than miRNAs. Primarily, they function by binding with transcription factors or chromatin complex and act as molecular scaffolds to modulate gene expression or epigenetic regulation. The role of both lncRNAs and circRNAs in cardiac remodeling are still at immature phase and more investigation is required to gain in-depth mechanism of action. Despite having a multitude of obstacles, there is a possibility that ncRNA-based therapeutics that have the potential to become important for future clinical diagnostics and treatment modality.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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