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REVIEW

MicroRNAs: diagnostic, prognostic and therapeutic role in heart failure—a review

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Abstract

Heart failure is a leading cause of morbidity and mortality, with relevant social and economic burden on global healthcare system. Although the development of novel diagnostic tools and the advance in therapies have deeply influenced the diagnosis and treatment of this disease, improving both prognosis and life expectancy of patients, hospitalization is still high, and mortality remains considerable. MicroRNAs are small endogenous RNA molecules that post-transcriptionally regulate gene expression in both physiological and pathological processes. In recent years, microRNA have arisen as attractive therapeutic targets in the treatment of a wide spectrum of pathologies, including heart failure. In cardiac pathology, deregulation of microRNAs expression and function is associated to adverse outcome and heart failure progression. Circulating levels of specific microRNAs have emerged as useful biomarkers for the diagnosis of heart failure or as prognostic indicators. In the present review, we summarize the state of current research on the role of miRNAs as biomarkers for diagnosis and prognosis in patients with heart failure and their use as potential therapeutic targets for this condition.

Keywords Biomarkers; Heart failure; microRNA; Therapy

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide, with a relevant social impact and a heavy economic burden on global healthcare system.[1] HF is due to abnormality of cardiac structure and/or function that leads to reduced ability of the heart to deliver blood at a rate adequate to meet tissues requirements.[1] The mechanisms underlying the development and the progression of HF are still under investigation since several possible aetiologies, and specific risk factors and co-morbidities are involved.[2]

Recently, the development of novel diagnostic tools and drugs has deeply influenced the diagnosis and treatment of HF, improving both the prognosis and life expectancy of affected patients. However, despite the breakthroughs in evidence-based drugs and device therapies, hospitalization rates are still elevated, and mortality remains considerable, with almost 50% of people dying within 5 years of HF diagnosis.[3] Therefore, there is an urgent need to develop new diagnostic tools and therapies to provide improved patient care.

In recent years, emerging evidence has supported a pivotal role of microRNA (miRNA) in the pathogenesis and progression of several diseases, including HF. miRNAs are small endogenous RNA molecules, consisting of approximately 22 nucleotides that are involved in post-transcriptional regulation of genes expression in almost all physiological and pathological processes.[4] Each miRNA can influence the expression of several different target genes, thereby regulating key biological events, such as cellular differentiation, proliferation, homeostasis, survival, and death.[5] Therefore, it is not surprising that deregulation of miRNA function can lead to a variety of diseases. In the past years, numerous studies have supported the involvement of miRNAs in cardiac development

and disease.[6] Based on these findings, more research has been conducted aiming at evaluating the potential of circulating miRNAs as biomarkers and therapeutic agents for HF.

Herein, we summarize the current knowledge on miRNAs in HF, in order to better understand their role in the diagnostic flow chart and to determine their potential role as both biomarkers and therapeutic targets.

Biogenesis and release of miRNA

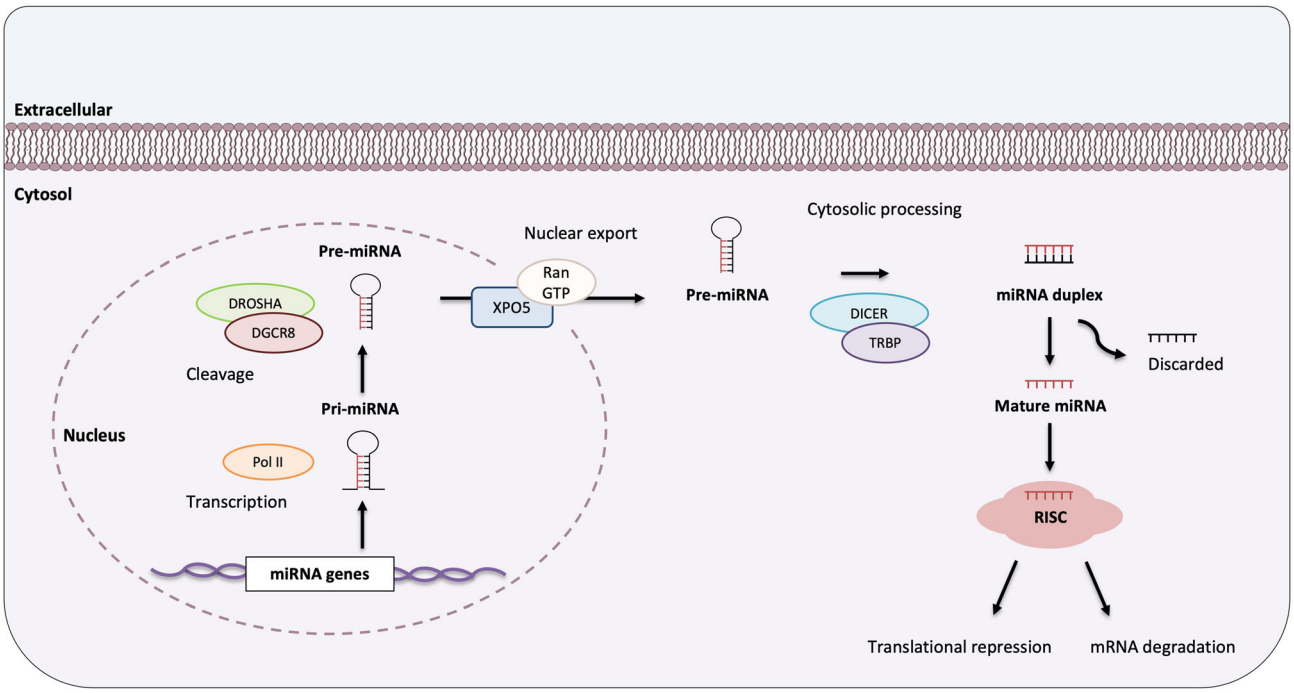
The first miRNA was identified in 1993 in *Caenorhabditis elegans* as a short RNA encoded by the gene *lin-4*, capable to post-transcriptionally regulate the expression of lin-14 mRNA.[7] Since then, the research frontiers in miRNAs biology have considerably expanded.

miRNAs are mainly transcribed by RNA polymerase II (Pol II) as long unstructured precursors (pri-miRNA) that undergo nuclear and cytosolic processing events to produce mature miRNAs. These primary transcripts are typically kilobases long and have a characteristic stem-loop structure.[8] Pri-miRNAs are then recognized and cleaved in the nucleus by the microprocessor complex that includes the enzyme double-stranded RNA-specific endoribonuclease (DROSHA) and its cofactor, DiGeorge syndrome critical region gene 8 (DGCR8). This cleavage leads to the formation of a precursor miRNA of approximately 70-nucleotides (pre-miRNA).[9] Pre-miRNAs are subsequently exported by Exportin-5 (XPO5) and Ran-GTP to the cytoplasm, where they are further cleaved by the endonuclease DICER and its cofactors, such as the protein activator of protein kinase R (PACT) or the trans-activation response RNA-binding protein (TRBP). This processing produces a mature miRNA duplex of approximately 22-nucleotides.[10]

One strand of the mature miRNA, also known as guide strand, binds to the Argonaute proteins (AGOs) to generate the RNA-induced silencing complex (RISC), whereas the other strand is discarded.[11] The RISC assembly containing the single-stranded miRNA binds to the 3′ untranslated regions (UTR) of the target mRNA transcript, leading to the degradation of the target mRNA or to the suppression of the translational machinery[11] (*Figure 1*). Although most miRNAs are known to regulate target mRNA production by interacting with the 3′-UTR, their interaction with other regions, including gene promoters, 5′-UTRs or coding sequences have also been described.[12] This different kind of interactions may result in distinct outcomes, such as activation of gene expression, in specific conditions.[12]

Besides their action in the cytoplasm, miRNAs can also be released into the extracellular space. Circulating miRNAs have been detected in serum and plasma for the first time in 2008.[13] While the specific mechanisms underlying the release of miRNAs into extracellular space are largely unknown,

Figure 1 Schematic representation of miRNA biogenesis. miRNAs are transcribed by RNA polymerase II (Pol II) as long unstructured precursors (pri-miRNA) that undergo nuclear processing by DROSHA-DGCR8 to produce a pre-miRNA. Pre-miRNAs are then exported to the cytoplasm, where they are further cleaved by the endonuclease DICER and its cofactors. This processing produces a mature miRNA duplex. One strand of the mature miRNA is then loaded onto the RISC assembly, leading to translational repression or target mRNA degradation.



several pathways involving extracellular vesicles, such as exosomes and other microvesicles, have been identified. These vesicles can exit the cells via plasma membrane blebbing and then fuse with the target cell membrane, thus establishing intracellular communication and influencing protein synthesis in recipient cells.[14] In addition, miRNA can be carried in the bloodstream by other molecules, such as high-density lipoproteins (HDL) and apoptotic bodies, or as miRNA-protein complexes.[15]

Cardiac miRNA and their involvement in heart disease

Several studies have demonstrated the involvement of miRNAs in cardiac development and in pathological mechanisms leading to human heart diseases, including HF. For instance, miR-1, miR-133a, miR-208, and mir-499 are the most abundant miRNAs expressed in myocardial tissue and are involved in the regulation of early stages of heart development and differentiation of cardiomyocyte.[16] In adult heart, miR-1 and miR-133a control cardiac electrical conduction, while miR-208 and miR499 regulate expression of sarcomeric contractile proteins.[16] Therefore, activity and expression of these miRNAs must be strictly regulated to ensure proper cardiac function. In contrast, their dysregulation is associated with the occurrence and progression of cardiac disease, including HF and its associated deleterious processes, such as arrhythmias, apoptosis, hypertrophy, fibrosis, and reverse remodelling.[17]

In 2007, Ikeda and colleagues performed an extensive genome-wide profiling of miRNA expression in left ventricular (LV) myocardium of patients with different forms of heart disease, including ischaemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis.[5] They found a significant alteration in miRNA profiling expression in the diseased hearts, compared with non-failing controls, and this alteration differentially correlated with the underlying aetiology of the cardiac disease.[5] Subsequent studies were conducted to identify miRNAs that could be potentially dysregulated in coronary heart disease, including myocardial infarction (MI). In this context, Bostjancic *et al*. demonstrated dysregulation in miRNA expression profiling after MI in human autopsy samples of infarcted heart tissue.[18,19] The most important finding was the up-regulation of cardiac miR-208 and the down-regulation of miR-1 and miR-133a after MI. Interestingly, some patterns of miRNA expression observed in MI hearts were similar to those observed in fetal hearts.[19] Accordingly, Thum *et al*. demonstrated that miRNA expression pattern of the failing heart has similarities with the fetal cardiac tissue profiling, thus supporting the concept of the fetal gene reprogramming that is observed during HF.[20]

Circulating MiRNAs have been increasingly proposed as biomarkers for cardiac diseases. In patients with acute MI, plasma levels of miR-1, miR-133a, miR-499, and miR-208, which are highly expressed in the myocardium, have been reported to be up-regulated, indicating cardiomyocyte damage and massive release into the blood.[21] In particular, Gidlöf *et al*. studied the dynamics of these cardiac-specific miRNAs in patients with ST elevation MI and demonstrated that miR-1, miR- 133a, miR-499-5p, and miR-208b were increased in plasma, with a peak within 12 h from MI. Furthermore, peak values of miR-208b correlated with troponin T and cardiac function, thus indicating a possible role for these molecules as tools for the diagnosis of acute coronary syndrome as well as the prediction of the risk of long-term complications.[22] Widera *et al*. investigated the levels of six cardiac-enriched miRNAs in plasma samples of 444 patients with acute coronary syndrome, and they found increased levels of miR-1, miR-133a, and miR-208b in patients with myocardial infarction. Further to this, they demonstrated that, during 6 months of follow-up, miR-133a and miR-208b levels were significantly correlated to the risk of death, thus speculating on the diagnostic and prognostic impact of these miRNAs.[23]

A recent meta-analysis by Lee and coworkers confirmed that circulating miR-1, miR-133, miR-208, and miR-499 are most commonly explored in patients with MI, and these miRNAs have been shown to be reliable biomarkers for the diagnosis of acute MI. In addition, circulating miR-208 showed both a diagnostic and prognostic predictive value for acute MI.[24]

In addition to these well-characterized cardiac-specific miRNA, a growing number or promising candidates have emerged, although further validation is necessary for most of them. In 2014, Zhong *et al*. found increased level of circulating miR-19a in patients with acute myocardial infarction, compared with control group, thus suggesting a potential role of this miRNA as a blood biomarker for diagnosis of acute myocardial infarction.[25] In addition, Mansouri and colleagues confirmed a significant increase of circulating miR-19a levels in patient with acute myocardial infarction and this increase correlated with the severity of coronary artery stenosis in these patients. Therefore, circulating miR-19a could be a promising molecular target for diagnosis and prognosis of acute MI.[26] More recently, Rincón *et al*. demonstrated the strong prognostic value of several miRNAs (miR-210-3p, miR-221-3p, and miR-23a-3p) in predicting long-term hospitalizations for HF and cardiovascular mortality among patients with MI.[27]

Circulating miRNAs have also been proposed as useful biomarkers for the diagnosis of atrial fibrillation (AF) that is the most common form of arrhythmia among patients with cardiovascular diseases. The first data regarding the association between miRNAs and AF in the general population come from the Framingham Heart Study. McManus *et al*. demonstrated that circulating levels of miR-328, which is known to promote atrial electrical remodelling, were associated with

prevalent AF.[28] Subsequently, Vaze *et al*. identified four circulating miRNAs that were significantly associated with atrial remodelling and prevalent AF in the Framingham Offspring Cohort (miR-106b, miR-26a-5p, miR-484, and miR-20a-5p).[29] Data from the population-based Rotterdam Study expanded these previous findings; indeed, Geurts *et al*. demonstrated that plasma levels of miR-4798-3p were significantly associated with the odds of prevalent AF in man.[30]

Although our knowledge of miRNA transcriptome is still incomplete, these results suggest that alterations in miRNA expression might be an important clinical tool in the diagnosis and treatment of cardiovascular diseases.

Circulating miRNA as biomarkers for diagnosis and prognosis of heart failure

Circulating miRNAs are highly stable in the extracellular space, where they are protected from RNA-degrading enzymes because of their association with protein complexes or microvesicles.[12] The presence of cardiac miRNAs in the bloodstream is supported by previous studies in patients with acute coronary syndrome. A unique profiling of miRNA for HF has not been identified yet; however, research efforts have been made to show that circulating levels of specific miRNAs in patients with HF may be used as biomarkers for the diagnosis of HF or as prognostic indicators.

In 2010, Corsten and colleagues investigated plasma levels of selected miRNAs, including heart-enriched miRNAs in patients with acute myocardial infarction, viral myocarditis, diastolic dysfunction, and acute HF. They found out that only miR-499 was significantly elevated in patients with HF.[31] One of the first attempt to assess plasma miRNA profiles in patients with HF was conducted by Fukushima and coworkers.

This study led to the identification of up-regulated plasma levels of miR-126 that were negatively correlated with age and New York Heart Association class in patients with HF.[32]

Tijsen *et al*. identified several miRNAs that are elevated in patients with HF. Among others, miR423-5p was strongly related to the diagnosis of HF at hospital admission and appeared to be an attractive diagnostic predictor of HF.[33] Another study by Goren and colleagues, also detected elevated serum levels of miR-423-5p, along with miR-320a, miR-22, and miR-92b in patients with chronic systolic HF and the levels of these miRNAs were highly correlated to clinical prognostic parameters, such as elevated serum levels of B-type natriuretic peptide (BNP) and dilatation of the LV and atrium.[34] Although previous studies suggested miR-423-5p and miR-133a as biomarkers for HF, these results were obtained in small groups of patients and control subjects.[33,35] In a subsequent study by Bauters *et al*., circulating levels of miR-133a and miR-423-5p were not associated with the level of natriuretic peptides, and these miRNAs failed to be useful indicators of LV function and remodelling during a 1 year period after myocardial infarction.[36]

In addition, a recent meta-analysis, conducted by Yang and coworkers, including four relevant articles concerning circulating miRNAs in patients with HF, revealed that low levels of three miRNAs (miR-30, miR-423-5p, and miR-18), among others, were associated with worse overall survival of patients, thus demonstrating their significant prognostic value in HF.[37]

Elevated levels of miRNA-21 in human failing heart tissues have been previously reported.[5] In addition, a recent study by Zhang *et al*. investigated whether miR-21 could serve as an indicator for human HF. They demonstrated that circulating miRNA-21 could be not only a promising biomarker of HF but also an efficient predictor of severity, prognosis, and re-hospitalization rate.[38]

A recent study by Ding *et al*. led to the identification of miR-21-5p, miR-30a-3p, miR-30a-5p, miR-155-5p, miR-216a, and miR-217 as biomarkers for early screening of HF and related diseases.[39] Of note, the identification of a biomarker able to differentiate ischaemic heart disease from non-ischaemic cardiomyopathies would be useful in the diagnosis of HF. Several studies were conducted in this field, aiming at identifying specific miRNAs involved in myocardial failure.

For instance, dilated cardiomyopathy (DCM), a condition characterized by depressed LV function and LV dilatation, is an important cause of HF.[40] Characterization of a miRNA signature would represent an attractive tool in the differential diagnosis of DCM. In this context, a recent study by Wang *et al*. identified three miRNAs (miR-3135b, miR-3908, and miR-5571-5p) that were significantly up-regulated in DCM patients, compared with healthy controls.[41] In addition, miR-5571-5p was correlated with severe New York Heart Association (NYHA) classification.[41] A subsequent study identified a miRNA profile that, associated with clinical variables, was able to highly discriminate DCM aetiology and stratify the risk, based on LV dysfunction.[42] In particular, miR-130b-3p, miR-150-5p, and miR210-3p were found to be differentially expressed in patients with idiopathic DCM, thus defining idiopathic from ischaemic origin.[42] Conversely, 12 circulating miRNAs were found to be significantly increased in patients with hypertrophic cardiomyopathy. Among these, only three miRNAs (mir-199a-5p, miR-27a, and miR-29a) were correlated with cardiac hypertrophy, whereas only miR-29a was also correlated with myocardial fibrosis evaluated with cardiac magnetic resonance.[43]

Detailed characteristics of circulating miRNAs in patients with HF of different aetiologies are listed in *Table 1*.

Circulating miRNA as biomarkers for differentiation of heart failure phenotypes

Evaluation of circulating levels of miRNAs could also be a useful diagnostic tool in the differentiation of HF with reduced

Table 1 Circulating miRNA associated to HF of different aetiology

miRNA	Sample	Study cohort	Results	Ref.
miR-499	Plasma	33 patients with acute HF and 34 control subjects	Increased in HF	31
miR-126	Plasma	33 patients with ischaemic heart diseases and 17 asymptomatic controls	Negatively correlated with age and NYHA class in patients with HF	32
miR423-5p	Plasma	12 HF patients and 12 healthy controls	Up-regulated in HF patients and strongly related to the clinical diagnosis of HF	33
miR-423-5p miR-320a miR-22 miR-92b	Serum	30 stable chronic systolic heart failure patients and 30 controls	Elevated in HF patients and correlated with important clinical prognostic parameters (serum levels of BNP and dilatation of the left ventricle and atrium)	34
miR-133a miR-423-5p	Plasma	246 patients with a first anterior wall Q-wave MI	Not associated with the level of BNP, left ventricular function and remodelling	36
miR-21	Serum	80 patients with HF and 40 control individuals	Higher in HF patients and correlated with ejection fraction and BNP; correlated with prognosis and efficient in predicting re-hospitalization	38
miR-21-5p miR-30a-3p miR-30a-5p miR-155-5p miR-216a miR-217	Plasma	62 patients with HF and 62 healthy controls	Up-regulated in HF patients	39
miR-3135b, miR-3908 miR-5571-5p	Plasma	19 DCM patients and 20 controls	Up-regulated in DCM patients; miR-5571-5p also correlated with NYHA classification	41
miR-130b-3p, miR-150-5p miR210-3p	Plasma	60 patients with ischaemic DCM, 55 patients with idiopathic DCM and 44 healthy controls	miR-150-5p and miR210-3p had a positive value while miR-130b-3p had a negative value for idiopathic DCM diagnosis	42
miR-199a-5p miR-27a miR-29a	Plasma	41 patients with hypertrophic cardiomyopathy and 41 controls	Increased in patients with hypertrophic cardiomyopathy and correlated with cardiac hypertrophy; only miR-29a was also correlated with myocardial fibrosis	43

(HFrEF) or preserved ejection fraction (HFpEF). Watson *et al*. analysed the plasma RNA pool of 270 patients (90 with HFrEF, 90 with HFpEF, and 90 with risk factors for HF development). In this study, five miRNAs were found to be reduced in HF (miR-30c, miR-146a, miR-221, miR-328, and miR-375), with miR-375 only reduced in HFrEF. Therefore, these miRNAs were considered as potential useful tool to differentiate HFpEF from HFrEF.[44] In another report by Wong and colleagues, the authors compared circulating miRNAs profiles between control subjects and patients with HFpEF or HFrEF recruited in the SHOP study. They identified a group of circulating miRNAs able to distinguish HF from non-HF patients, and HFpEF from HFrEF.[45] In a subsequent study, the authors identified a panel of eight circulating miRNAs that, in conjunction with NT-proBNP are highly discriminatory in detecting non-acute HF and categorizing different HF subtypes.[46] In conclusion, all these studies suggest that combining analysis of miRNAs profiling with existing gold standards could be a useful tool to differentiate HFpEF from HFrEF.

miRNA as therapeutic target in heart failure

As previously mentioned, miRNAs regulate gene expression by targeting mRNA, thus influencing several physiological processes. Therefore, it is not surprising that deregulation of miRNAs has been linked to a variety of disease conditions and miRNA-based therapeutic strategies have started to emerge. Innovative therapeutic approaches to modulate miRNAs expression and activity include miRNA replacement therapy using miRNA mimics, as well as inhibition of miRNAs through 'antagomiRs' or 'antimiRs'.[47] In recent years, numerous preclinical studies have investigated the use of miRNA-based therapeutics, setting the stage for clinical testing. Specifically, in the cardiovascular field, miRNAs provide promising therapeutic targets to reverse the pathological changes typical of the failing heart.[47,48]

After MI, circulating levels of cardiac miRNAs (miR-1, miR133a, miR-208, and miR-499) are significantly increased, thus suggesting their role as promising diagnostic marker. To date, results from several studies have been controversial on whether these cardiac miRNAs are beneficial or detrimental to cardiac function. In some studies, down-regulation of miR-1 and miR-133 has been reported to be associated to cardiac hypertrophy and adverse remodelling, whereas suppression of miR-1 has been shown to be beneficial after MI.[16,49,50] In contrast, elevated levels of miR-499 and miR-208 can contribute to cardiac pathology and HF.[16,51] Therefore, the effects of inhibiting these cardiac miRNAs in HF are still under investigation, and further studies are required before translation in clinical practice.

However, therapeutic strategies based on miRNAs inhibition have been recently tested in patients with HF. A first study in human patients has been conducted by providing an antisense oligonucleotide that targets miR-92a-3p (MRG-110).[52] Inhibition of miR-92a was shown to have several beneficial effects on cardiovascular disease and wound healing in preclinical models.[53] In this study, healthy subjects were randomly assigned to receive MRG-110 or placebo intravenously. It was demonstrated that MRG-110 therapy was able to reduce mir-92a levels and to induce de-repression of miR-92a targets in peripheral blood cells.[52]

Another randomized, double-blind, placebo-controlled study was conducted by Taubel *et al*. to assess the safety, pharmacokinetics, and pharmacodynamic effects of miR-132 inhibitor (CDR132L) in patients with HF of ischaemic origin.[54] Preclinical investigations identified miR-132 as a promising target, capable to influence the pathological cardiac remodelling in HF.[55] In accordance, treatment with CDR132L has shown therapeutic efficacy in a pig model of post-ischaemic HF, with improvement of cardiac function and relevant antifibrotic and antihypertrophic effects.[56] The relevance of miR-132 in human HF was reported by Masson and co-workers. In this study, the authors demonstrated that circulating miR-132 levels rise according to the severity of the disease, thus improving risk prediction for HF hospitalization.[57] The study by Taubel and colleagues was the first clinical trial of an antisense drug in patients with HF. The results of this study demonstrated that CDR132L was safe and well tolerated; moreover, this drug was able to provide improvements in cardiac function, as well as a simultaneous reduction in NT-proBNP values. Although this study was conducted on small sample sizes, the results are encouraging.[54] Detailed characteristics of miRNA-based therapeutics in human HF are listed in *Table 2*.

Therefore, larger studies are required to further assess the role of CDR132L in the treatment of HF. In this context, a subsequent study by Hinkel *et al*. investigated the effects of intracoronary antimiR-132 administration in a novel preclinical model of non-ischaemic HF. In this study, the authors demonstrated that, in a porcine model of percutaneous aortic constriction, injection of antimiR-132 at the time of stent implantation and 4 weeks later was able to improve cardiac function and capillary density, thus attenuating cardiac hypertrophy, interstitial fibrosis, and adverse remodelling. Interestingly, these results might pave the way for development of novel clinical trials aiming at evaluating the effects of antimiR-132 in patients with hypertrophic cardiomyopathy.[58]

Discussion

In the last decades, our understanding of miRNAs expression and function has significantly grown, and their role in cardiovascular diseases, including HF, has been extensively studied.

In this review, we have summarized the current knowledge on the regulatory effects of miRNAs in HF, focusing on the role of circulating miRNAs in the diagnosis, prognosis, and treatment of this disease. The first findings about the involvement of miRNAs in cardiac dysfunction have been reported in studies conducted on patients with acute coronary syndrome. An increasing number of promising candidates has been identified, including miR-1, miR-133a, miR-499, and miR-208, that are highly expressed in the heart and released into the bloodstream after MI, thus indicating cardiomyocyte damage and necrosis.[21,31] Therefore, circulating miRNAs are gaining interest because as potential biomarkers.

Although a growing number of miRNAs have been investigated in HF models, allowing us to get a better understanding of its pathogenesis, a unique miRNA profiling has not been identified for HF. Early studies have been conducted on small sample numbers and collected massive amounts of data regarding altered circulating levels of miRNAs in patients with HF. Among these, miR-122, miR-210, miR-423-5p, miR-499, and miR-622 have emerged as potential candidates in more than one study.[50] In this context, miR-423-5p and miR-133a have been reported to be up-regulated in human HF and correlated to prognostic parameters, such as elevated levels of BNP and NYHA classification.[33–35] In contrast, a subsequent study performed by Bauters *et al*. in a larger population of post-MI patients demonstrated that miR-133a and miR-423-5p were not associated with the levels of BNP and failed to be useful indicators of LV function and remodelling.[36]

Although all these studies confirmed an increase in plasma concentration levels of these miRNAs, the results appear to be controversial. These differences might exist because, in the study by Bauters *et al*., all patients received maximal treatment regardless of the level of remodelling, whereas in other studies, there were major imbalances in baseline med-

Table 2 miRNA-based therapeutics in human HF

Inhibitors	miRNA	Delivery	Study Cohort	Results	Ref.
MRG-110 (locked nucleic acid-based antisense oligonucleotide)	miR-92a-3p	Intravenous	Healthy adults	Reduced mir-92a levels and derepression of miR-92a targets in peripheral blood cells	52
CDR132L (locked nucleic acid-based antisense oligonucleotide)	miR-132	Intravenous	Patients with HF of ischaemic origin	Safe and well tolerated; Improved cardiac function, and reduced NT-proBNP values	54

ications. In addition, these results were obtained in selected patients with a first anterior MI, thus excluding patients with MI in another location or patients with recurrent events.[36] Therefore, further studies are needed to identify novel circulating miRNAs that could be useful as diagnostic and prognostic biomarkers for HF.

miRNA-based drugs represent one of the most revolutionary advances in recent years, and offer enormous potential for future clinical applications in HF. To date, several methods have been described to specifically target miRNA pathways, such as miRNAs replacement by miRmimics or inhibition of overexpressed miRNAs via antagomiRs. Nevertheless, there are significant barriers that still need to be solved before this technology may be safely and effectively implemented in HF patients. For instance, there are still pharmacological challenges to overcome, like degradation in the bloodstream as well as the poor systemic or local delivery to the target site.[47] To achieve target tissue selectivity, the pharmacokinetics, biodistribution, and tissue penetration of miRNA-based therapeutics must be enhanced. In this context, catheter-based delivery strategies such as intramyocardial injection or transcoronary infusion may be used instead of intravenous administration to prevent off-target repercussions in HF patients.

Despite all these difficulties, results of a first Phase 1b study in humans with HF have been recently published.[54] In this study CDR132L, a specific miR-132 inhibitor, was safe and well tolerated, with positive improvements of cardiac function. However, additional studies, using larger HF cohorts, is needed to confirm the positive role of CDR132L and to further explore RNA-based therapeutics for cardiovascular diseases.

Conclusions

In recent years, miRNAs are emerging as possible therapeutic options in heart disorders, in addition to their role in numerous cellular processes and pathophysiologic settings. Despite the urgence of novel findings, the first clinical studies, supporting specific delivery of microRNA-based treatments, have been demonstrated to be safe and effective. Further research, aiming at expanding knowledge in miRNA physiopathology, is necessary to establish miRNA-based therapeutics as the most successful therapeutic methods for several human disease, including HF.

Conflict of interest

None declared.

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