MicroRNA and cardiac pathologies

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TO DATE, a handful of reports have been published connecting microRNAs (miRNAs) to specific cardiac processes and phenotypes. The miRNA expression profile (or miRNome) of these phenotypes is, at the moment, only partial. Linking individual miRNAs to specific aspects of the pathogenesis of human pathologies may aid the development of needed innovative therapies, whereas characterization of miRNomes might provide novel diagnostic and prognostic tools.

Hypertrophic Phenotypes

miRNA in the pathological setting. Many diseases generate abnormal hemodynamic loads on the heart; in response, the heart increases its mass. Cardiac hypertrophy is thus the phenotypic end point that has been the most studied in relation to miRNAs of the heart to date. In animal models of hypertrophy, whole arrays of miRNAs have been reported to be upregulated, downregulated, or unchanged with respect to normal heart (4, 5, 8, 13, 15, 16, 18). In these studies, the overlap between the sets of miRNAs reported to be involved is partial, which may reflect in part the differences in the techniques and models used. However, some miRNAs have been more frequently reported as dysregulated in the same direction than others, indicating the possibility that these miRNAs might have common roles in hypertrophy pathogenesis. For example, miR-1, miR-133, miR-29, miR-30, and miR-150 have often been found to be downregulated whereas miR-21, miR-23a, miR-125, miR-195, and miR-199 have often been found to be upregulated with hypertrophy. Interestingly, in cultured cardiomyocytes, the forced expression of individual miRNAs found to be upregulated with the stimulation of cardiomyocyte growth was sometimes sufficient to induce hypertrophy, whereas inhibition of miRNAs found to be downregulated during hypertrophy could blunt increases in cardiomyocyte size. For a few miRNAs, these results have been replicated in vivo. For example, miR-195, found to upregulated in a model of stress-induced hypertrophy, was sufficient to provoke pathological cardiac growth when overexpressed in transgenic mice (18); similarly, knockdown of miR-133, a miRNA found to be downregulated in enlarged hearts, was sufficient to induce hypertrophy in wild-type mice (2).

Importantly, results obtained from clinical samples have evidenced the relevance of some of these findings also for human disease: for example, mature miR-1/miR-133 (2) and the precursor of miR-208 (19) have been reported to be downregulated in forms of heart disease. Together, these facts argue for some miRNAs having a fundamental role in the development of disease in the heart and being potential targets and/or agents of novel therapies (Fig. 1).

Apart from the induction of hypertrophy of cardiomyocytes, however, the role of miRNAs in other fundamental aspects of cardiac function—such as chamber morphogenesis, conduction, and contraction—and between microRNA expression signatures and pathological cardiac phenotypes—such as hypertrophy, ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis. Congenital anomalies of the heart may also be associated with the dysregulation of specific microRNAs. Here we report on the latest findings.
Heart Failure and Heart Diseases

Heart failure, i.e., the inability of the heart to pump sufficient blood to the organism, is a frequent and fatal outcome of hypertrophy developed under pathological circumstances. Qualitative alterations—such as reexpression of a fetal gene program—inexorably progress from the hypertrophic stage and characterize this syndrome. Indeed, a transcriptome analysis revealed a similarity in the gene expression of failing and fetal human heart in that 353 mRNAs were found to be more than twofold regulated in common in these two situations with respect to normal adult heart tissue (16). Thus a shift toward a fetal miRNome seems to be the basis of part of the modification of the cardiac transcriptome occurring with hypertrophy and failure.

Apart from these alterations in miRNA expression, a decreased level of Dicer is a newly reported feature of heart failure in patients with dilated cardiomyopathy (4). Dicer is the only known enzyme involved in the maturation of miRNAs from their precursors, so reduced Dicer expression reduces the expression of all mature miRNAs as shown by microarray data (4). However, how a global decrease in miRNA maturation can be reconciled with increased expression of those miRNAs found to be upregulated with disease needs to be addressed. One explanation might be that decreased Dicer expression occurs as progression of disease nears failure and is, therefore, a late phenomenon. In support of this, Dicer-knockout mice pups, which presented with dilated hearts, died rapidly by postnatal day 4; hearts from patients presenting with aortic stenosis, which presumably were hypertrophic, had higher levels of Dicer with respect to failing hearts; and Dicer reverted to significantly higher levels in failing hearts after a left ventricular assist device was installed for mechanical support in anticipation of transplantation (4). This might be an important finding that could shed light on why the heart starts failing when it does. In addition, the miRNome has been reported to undergo temporal changes during the development of experimentally induced hypertrophy in mice (5, 13); it cannot be ruled out, therefore, that there may also be some changes in the miRNome that predispose to heart failure progression.

The contribution of miRNAs to disease stage- and/or etiology-specific pathogenesis has been clearly highlighted by a recent genomewide miRNA expression profiling study that evidenced distinct miRNomes for three human heart pathologies, i.e., ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis. Forty-three out of eighty-seven tested miRNAs were differentially expressed in at least one of these disease groups (8). Interestingly, the greatest differences were seen between the aortic stenosis group (which had a largely compensated function) and the dilated cardiomyopathy group, whereas the two cardiomyopathic groups were the most similar. This fact opens the door to the development of biomarkers for determining prognosis and response to therapy for a variety of heart disorders. It also demonstrates the importance of more accurate detailing of pathological characteristics when reporting human miRNA data.

Congenital Heart Defects and Idiopathic Disease

miRNA was initially described as being fundamental for developmental biology first in nematode worms and then in phylogenically more advanced organisms. Not surprisingly, many defects of the miRNA machinery are incompatible with correct and/or continued development. The heart is susceptible to congenital defects more than any other organ, but whether miRNAs contribute actively to these is still unknown. However, a number of reports describing the importance of miRNAs for cardiogenesis in mice (1) have shown that misexpression can produce defects. For example, miR-1-2 was shown to be
important for correct chamber morphogenesis, its knockout producing thickened walls due to persistent proliferation; in this mouse model, septal defects were common and often fatal (21). Deletion of the miR-19–92 cluster has also been reported to produce septal defects in mice (20). Therefore, it may be argued that dysregulation of developmentally important miRNAs might result in congenital heart diseases. On this point, dysregulation of miRNAs has been reported recently to occur with trisomy 21 (Down syndrome), the most common genetic cause of congenital heart defects (9). In fact, five miRNAs (miR-99a, let-7c, miR-125b, miR-155, and miR-802), identified by bioinformatics to be present on human chromosome 21 (Hsa21), were found to be overexpressed in the heart of afflicted subjects because of transcription of the extra Hsa21 chromosome. However, neither bona fide targets nor the type of effect that these miRNAs could cause in cardiac experimental models was reported. Revealingly, however, a couple of these miRNAs (let-7c, miR-125b) have been reported elsewhere as being upregulated in acquired heart diseases (13, 15, 16). The extent to which miRNAs contribute to this pathology remains unknown.

Furthermore, analysis of 10 major primary skeletal muscular disorders has revealed a striking complexity in the alteration of the miRNome occurring with the pathologies studied: subsets of commonly dysregulated miRNAs, differentially dysregulated miRNAs, and specific miRNAs dysregulated in individual pathologies were found (7). This fact allowed the authors to assign distinctive signatures to each congenital condition. The report evidenced that miRNAs are potentially involved in the underlying pathophysiology of inherited muscular diseases and have a probable role in secondary pathological pathways. Work on the heart might reveal a similar state of affairs for cardiac congenital diseases.

Interestingly, results from skeletal muscle studies have also highlighted that altered muscle phenotype could be brought about directly by an alteration in the normal relationship between target and miRNA: in fact, a mutation of the myostatin gene of Texel sheep produces a binding site for miR-1/miR-206 on its messenger, which is absent in other genetic backgrounds (6). This produces a consequent gain-of-function polymorphism due to inappropriate targeting of myostatin mRNA that is responsible for a hypertrophic phenotype similar to the myostatin-null mouse. Whether mutations on miRNAs or their binding sites on mRNA might be responsible for forms of heart pathologies or altered susceptibility and progression to heart failure remains to be determined.

Concluding Remarks

From the reports published to date, it can be hypothesized that specific miRNAs have key roles in determining pathological phenotype and sets of miRNAs might distinguish between them. An important aspect, nonetheless, is the description of the connections between these gene products and the phenotypes or processes in which they are involved. Currently, this is more difficult to achieve for animal miRNAs than for their plant counterparts, mainly because of the increased difficulties experienced by bioinformaticists in accurately predicting targets of animal miRNAs because of their inherent characteristics, i.e., small size and tolerance for mismatches. Consequently, very few animal targets have been unequivocally identified to date. Studies on heart pathologies have, however, revealed a few validated targets: cell division cycle 42 (Cdc42), Ras homolog gene family member A (Rho-A), and Wolf-Hirschhorn syndrome complex 2 (WHSC2/NELF-A) for miR-133 (2); Ras GTase-activating protein (RasGAP), cyclin-dependent kinase 9 (CdK9), Ras homolog enriched in brain (Rheb), and fibronectin for miR-1 (13); and thyroid hormone receptor (THR)-associated protein 1 (THRAP1), the THR coregulator, for miR-208 (19). Unfortunately, there are few direct data on how these miRNA-target interactions actually modify the workings of the heart and what pathways induce miRNA dysregulation in the first place. To date, the thrap1/miR-208 interaction is the best characterized: miR-208 is encoded in an intron of the α-myosin heavy chain (α-MHC) gene and has been shown to control regulation of β-MHC in conditions of stress in mice. In fact, stress stimuli, usually responsible for the reduction of α-MHC transcription, consequentially also reduce the level of miR-208, which, in turn, relieves transcriptional repression on its target mRNA, thrap1. The resulting increase in THRAP1 protein influences the THR-regulated expression of α- and β-MHCs, which are inversely affected through a positive and a negative thyroid hormone response element, respectively. In this way, one of the hallmarks of pathological adaptation to stress, i.e., isoform switch from a fast adult contracting myosin to a slow embryonic myosin, can be explained mechanistically, at least in mice. In humans, where the β-MHC is dominant and isoform switching is less apparent, miR-208b, contained in the β-MHC gene, has been speculated to play a greater role (17).

Despite the improvements made in prevention and therapy over the past few decades, many forms of acquired cardiovascular disease have not only remained a major cause of morbidity and mortality but are also increasing in prevalence: in the West this has been due to improved disease management and the expansion of an elderly population, whereas increasingly dysregulated lifestyles associated with improving standards of living have contributed to the epidemiology in some developing countries. For example, heart failure, the syndrome consequential to many diseases of the cardiovascular system, is estimated in the West to have a prevalence of 1–2% and an annual incidence of 5–10 per 1,000 and is the leading cause of hospitalization in those over 50 years of age (12). These facts translate into enormous socioeconomic costs and an increasing burden on the family and state (10) that are further exacerbated by the increasing prevalence of congenital heart disease patients surviving early interventions and thus requiring management into adulthood (14). Breakthroughs in the knowledge of heart pathophysiology that can then be translated to the clinical setting through the innovation of novel diagnostics or therapeutics are urgently needed. miRNA is the newest piece of the puzzle and may introduce new prospects for the management of heart failure and some cardiovascular diseases. An enormous amount of work awaits the scientific community to establish the links between these gene products and pathophysiological mechanisms, and to identify miRNAs having a direct role in pathogenesis, which might be targeted therapeutically, and those becoming dysregulated secondarily to disease.

REFERENCES


