Editorial

Are microRNA useful to predict prognosis in acute heart failure?

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Introduction

Acute heart failure (AHF) is a major cause of hospital admission in patients over 65 years of age (1). Despite improvements in the pharmacologic therapy, clinical outcome remain poor with 1-year mortality rates that reach 20–30% (2). The progression of HF is linked to numerous genetic and epigenetic factors (3), including small regions of highly conserved non-coding RNAs, called microRNAs (miRNAs), that are important regulators of gene expression and modulate numerous processes implied in the pathophysiology of HF (4,5).

miRNA discovery and function

In 1993 the first miRNA, lin-4 was discovered, in Caenorhabditis elegans (C. elegans) and the interaction between lin-4 and the complementary sequence in the 3' untranslated region (3'UTR) of lin-14mRNA was shown (6). miRNAs are a class of non-coding RNAs with a length of 19–25 nucleotides that are involved in the regulation of gene expression at the post-transcriptional level (7,8). They have a tissue-dependent expression and concentration-dependent effects in pathologically affected organs (9,10).

miRNAs in heart failure

Functional studies have shown that miRNAs have a leading role in the onset and progression of HF (11), contributing to hypertrophy, fibrosis and therefore to the remodeling of the left ventricle (12). They also seems useful indicators for diagnosis and prognosis of both acute and chronic HF (13).

miRNAs and hypertrophy

Many miRNAs are implicated in the pathogenesis of cardiac hypertrophy, however among these the main one is miR-1 (14). In an experimental model of aortic coarctation Sayed *et al.* has shown that miR-1 is down regulated before the onset of cardiomyocyte hypertrophy (15). Furthermore, Elia and coworkers have shown that miR-1 interacts with insulin-like growth factor 1 (IGF-1), IGF-1 receptor and twinfilin-1, favoring cardiac hypertrophy (16).

Finally, suppression by an adeno-associated virus (AAV) of miR-1 determinate a regression of cardiac hypertrophy (17). These results suggest that miR-1 it plays a role in the development of left ventricular hypertrophy and may represent a molecular target for its regression.

miRNAs and fibrosis

miR-21 and miR-29 were identified as those most implicated in cardiac fibrosis. miR-21 determines the activation of the MAPK signal in cardiac fibroblasts through the inhibition of the extracellular inhibitor of the sprout regulated kinase 1 (Spry1) (18). On the other hand, miR-29 interacts with the genes encoding the extracellular matrix (ECM) such as fibrillin, elastin and collagen, determining their inhibition. In fact, models *in vitro* have shown that a reduction of miR-29 is associated with an ECM alma, while its overexpression causes a reduction in cardiac fibrosis. These data have also been confirmed in vivo, since the

overexpression of miR-29b attenuates the progression of cardiac fibrosis (19).

miRNAs and diagnosis of HF

Several studies have assessed the role of circulating miRNAs in the diagnosis of heart failure. For example, in some studies, miRNAs have been able to discriminate between patients with cardiac dyspnea and those with other causes of dyspnea (20). Other studies have also described a miRNAs pattern in patients with AHF, with reduced plasma levels of some miRNAs (e.g., miR-103, miR-142-3p, miR-30b and miR-342-3p), and the increase of others (e.g., miR-499) (21).

miRNAs and prognosis in HF

Some studies have evaluated the prognostic value of circulating miRNAs in patients with acute and chronic heart failure. Qiang *et al.* have shown that elevated plasma levels of miR-508a-5p were associated with increased mortality in patients with chronic HF due to non-ischemic dilated cardiomyopathy (22). Furthermore, Ovchinnikova *et al.* have recently shown that an early reduction of some miRNAs (such as miR-18a-5p, miR-26b-5p, miR-27a-3p) were predictive of prognosis in patients with AHF (23). Therefore, miRNAs can be used as circulating biomarkers for prognosis, alone or in association with other well known markers, such as natriuretic peptides.

In a recent study (24) the plasma levels of circulating miRNAs were serially evaluated in patients hospitalized for AHF. The primary endpoint of this study was a composite endpoint of all-cause mortality and hospital readmission for HF. The study enrolled 476 patients and all the various miRNAs involved in HF were measured. miR-1306-5p was found to be positively and independently associated with all-cause mortality and hospitalization. This association was independent of NT-proBNP levels. Furthermore, repeated measurements of miR-320a, miR-378a-3p, miR-423-5p and miR-1254 were associated with the primary endpoint after adjustment for sex and age, but not after further multivariable adjustment for clinical characteristics.

The strength of this study is the serial evaluation of the miRNA, and the finding that they were associated with clinical outcome, suggesting a role for serial miRNAs evaluation in the management of patient with AHF. We postulate that patients with a lower reduction of miRNAs plasma levels after the start of HF therapy may be considered at greater risk requiring a more aggressive management, while patients with normalization of miRNAs plasma levels may be considered at lower risk and therefore require standard care therapy.

Moreover, miR-1306-5p plasma levels was associated with the primary endpoint independently of the natriuretic peptides, suggesting an independent role for the miRNAs especially in patients with overlapping causes of natriuretic peptides increase (e.g., comorbidities, such as hepatic cirrhosis with ascites, renal insufficiency, hypothyroidism).

Conclusions

miRNAs are emerging as responsible for a wide range of physiological and pathological processes.

In the cardiovascular arena, miRNAs are primarily implicated in the progression of HF through cardiac hypertrophy and fibrosis. Further research is needed, to confirm the promise regarding these small molecules, to translate the excitement from bench to bedside, and to confirm the role of biomarkers for a tailored management of patients with HF.

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