NEW MICRORNA FOR THE DIAGNOSIS OF CARDIOMYOPATHIES

Summary:

Inflammation in the myocardium or myocarditis is a disease with heterogeneous aetiology, frequently caused by an infectious pathogen, toxins, drugs or by an autoimmune disorder. Its clinical variability and its nonspecific symptoms make the diagnosis of myocarditis a process that is not always easy. There is an urgent need for accurate, fast point-of-care tests that simultaneously provide diagnostic and prognostic information about a patient entering the hospital with symptoms of acute heart failure. CNIC researchers have identified the role of an specific miRNA in cardiomyopathies processes and have studied the differential expression in blood plasma of patients compared with healthy subjects. These miRNAs can be used as biomarker to improve the diagnosis of acute myocarditis.

Innovative aspects:

Inflammation of the myocardium or myocarditis is a disease caused by an infectious pathogen or by an autoimmune disorder. Myocarditis is characterized by inflammatory cell infiltration into the myocardium. Recent studies estimate the prevalence of myocarditis in about 22 of 100.000 patients annually (International Classification of Diseases, WHO), and the American Heart Association and American College of Cardiology rank myocarditis as the third leading cause of sudden cardiac death in professional athletes. Moreover, between 1-5% of patients with acute viral infection develop myocarditis.

Although differential diagnosis can be challenging in myocarditis patients, it can be well-established after coronary angiography to rule out obstructive coronary artery disease and cardiac magnetic resonance (CMR) imaging. However, CMR is not widely available in all centers and its use in patients with acute chest pain is controversial, as it may not be determinant of a final diagnosis. Endomyocardial biopsy (EMB) is still considered the gold standard diagnosis of myocarditis. However, EMB is not commonly performed due to safety reasons. In recent years, the use of more sensitive troponins has improved the detection of cardiomyocyte necrosis and myocardial damage, one of the consequences of myocarditis. However, its use for the diagnosis of myocarditis can lead to overdiagnosis due to lack of specificity, as well as to underdiagnosis in mild forms or in early stages in which necrosis does not yet exist.

Circulating miRNAs secreted to the human fluids into extracellular vesicles are altered during pathological events, offering a unique opportunity to develop non-invasive molecular diagnostic tools. Recent discoveries uncovering the role of miRNAs as modulators and markers of

cardiovascular disease (CVD) have offered unanticipated insights into pathogenic mechanisms, and have opened the way to fundamentally new therapeutic strategies.

In a recent project to identify specific biomarkers for myocarditis, CNIC researchers studied microRNAs derived from Th17 cells during experimental autoimmune myocarditis (EAM) and coxsackievirus (CVB3) infection mouse models. Th17 cells are necessary and sufficient for the development of myocarditis. Unlike the increase of troponin levels, which could only be detected 4 weeks after EAM induction, the change in the levels of a certain miRNA was measurable in plasma in only one week, before the acute phase of heart damage occurs.

The study also identified, cloned and validated the homolog human miRNA which is selectively synthesized by Th17 cells in patients with myocarditis. These results were validated in plasma and extracellular vesicles from plasma samples of three independent cohorts of acute myocarditis patients (n=113) compared to acute myocardial infarction (MI) (n= 101), MI with non-obstructive coronary arteries (MINOCA) patients (n=20) and healthy volunteers (n= 80). These results point out the role of this miRNA in the pathophysiology of myocarditis and dilated cardiomyopathy, being studied as biomarker for the disease.

This technology provides a novel strategy for a reliable, non-invasive diagnosis of acute myocarditis, allowing its differentiation from acute myocardial infarction, based on the determination of the human miRNA homolog in plasma samples. The identification of this biomarker in plasma provide an avenue for uncovering additional methods for the challenging diagnosis of myocarditis.

Competitive advantages:

- Expression of the biomarker in three different cohorts of patients with acute myocarditis showed that the homolog human miRNA yielded a robust area under the curve (AUC) of 0.9702 for myocarditis/MI group and AUC of 0.9888 for myocarditis/healthy control group. This biomarker yielded a sensitivity of 93.5% and a specificity of 95.0% for classifying the myocarditis versus acute MI showing a high diagnostic value.

- Both murine and human homologous of the miRNA are encapsulated in plasma extracellular vesicles (EVs) preserving their stability in this fluid and protecting them from the degradation by RNAses postulating it as an excellent biomarker candidate in clinical practice.

- This miRNA can be used to improve the diagnosis of acute myocarditis, allowing precisely supporting or ruling out its presence in the initial stages of clinical suspicion.

- The validation of this alternative method to EMB and CMR, when these technologies are not possible or available, or in a combined manner, could contribute an enormous

benefit in the early recognition of this disease, the handling of the patients and in the advance of the knowledge of its prevalence.

- The increase in the expression of this miRNA occurs earlier than that of myocardial damage markers, such as troponins, so it could contribute to an improvement in the knowledge of myocardial inflammatory disease in situations of low suspicion with no elevation of troponins.

Key words: cardiomyopathies, myocarditis, acute myocarditis, troponins, microRNA, Th17 cells, Regulatory T cells.

Technology type: cardiomyopathies, diagnostic, miRNAs.

Patent information: EP3384043B1 (granted) and US20180355427A1 (applied)

Stage of development: prospective and observational study in clinical practice to be started in 2020.

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