

New microRNAs for the diagnosis of cardiomyopathies.

Summary:

The present invention provides an in vitro method for obtaining data useful for diagnosing a cardiomyopathy, measuring the expression levels of two microRNAs in the blood plasma of patients.

Inflammation of the myocardium or myocarditis is a disease with heterogeneous etiology, apart from genetic susceptibility, is frequently caused by an infectious pathogen (bacteria, virus, fungi or protozoa) or by an autoimmune disorder. Myocarditis is characterized by inflammatory cell infiltration into the myocardium. After the acute process, the loss of cardiomyocytes and the development of fibrosis and necrosis in the myocardium take place, ventricle remodeling, permanent dysfunction of the ventricular wall, dilated cardiomyopathy, heart failure and arrhythmias being able to arise.

CNIC researchers have identified the role of two specific miRNAs in cardiomyopathies processes and have studied the differential expression in blood plasma of patients compared with healthy subjects. The invention illustrates the amounts of sample used in the present experiments to detect those miRNAs in the serum of mice with peripheral ischemia, myocarditis or in patients with myocarditis, and the comparison of the fold induction between these samples.

The invention provides the sequence of these miRNAs and claims the in vitro use of a kit with the necessary elements to obtain data useful for diagnosing a cardiomyopathy in a human subject.

Innovative aspects:

Several cells have been detected as necessary and sufficient for the development of myocarditis, such as Th17 cells and Regulatory T cells. In addition, several molecules such as ROR γ t, IL-23, IL-17 and IL-6 have been identified as being critical for the development of the pathology and have been found to be expressed in a different proportion of patients with dilated cardiomyopathy compared with healthy subjects.

However, little research has been conducted concerning specific biomarkers circulating in the blood of patients with myocarditis. In addition, there is a substantial discrepancy with respect to the predictive value of the proportion of some of these cells and molecules circulating in blood in patients with acute and chronic heart pathologies.

Based on all this information, it can be concluded that given the absence of diagnostic methods capable of assuring a degree of acceptable specificity and sensitivity, the diagnosis of myocarditis, particularly during an acute episode, can be complicated. The present invention solves this problem by providing a specific and sensitive assay for diagnosing myocarditis, during an acute episode, by using blood samples, particularly plasma samples.

Competitive advantages:

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. Also, between 1-5% of patients with acute viral infection develop myocarditis.

The diagnosis of myocarditis made based on clinical, laboratory, ECG, and Echo findings is not always easy. Moreover, a safe and sensitive non-invasive diagnostic test to confirm the diagnosis of acute myocarditis, compared to other pathologies with myocardial injury like acute coronary disease, is not available nowadays. Endomyocardial biopsy (EMB) is still considered the gold standard diagnosis of myocarditis. However, EMB is not commonly performed due to safety reasons; 6% of wide range complications and 0,4 incidence of death due to perforation.

Acute myocarditis resolves in about 50% of cases in the first weeks, however 25% develop persistent heart failure that can progress to end-stage dilated cardiomyopathy and heart transplantation. Therefore, early diagnosis of the disease is vital for the specific treatment of the patient (antiviral, immunosuppressive, heart failure therapies, etc) and subsequent development of the disease.

In the present invention, it has been determined for the first time an extraordinary increase in two specific miRNAs expression in the plasma of patients with acute myocarditis compared to healthy subjects. Patients in the chronic phase of the disease also presented expression levels of these miRNAs that were much higher than those of healthy volunteers, but not as high as during the acute phase.

Ref: OT-46

These results point out the role of these miRNAs in the pathophysiology of myocarditis and dilated cardiomyopathy, being susceptible to being studied as biomarkers and/or therapeutic targets of these diseases.

Key words: cardiomyopathies, myocarditis, Takotsubo cardiomyopathy, microRNA, Th17 cells, Regulatory T cells.

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