

## EDITORIAL

## Achievements, Challenges and Opportunities in MicroRNAs and Chagas Disease

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MicroRNAs (miRNAs) were discovered in 1993 in studies of the nematode *Caenorhabditis elegans* and since then, these molecules have been of considerable importance in clinical practice for their use as potential biomarkers of different health and disease conditions.<sup>1</sup>

In cell biology, the miRNAs play an important role in the physiological and pathological regulation of various biological processes and act as post-transcriptional regulators by binding to messenger RNA and preventing its translation or promoting molecular cleavage.<sup>2-4</sup> miRNAs regulate different degenerative processes, cancer and immunological diseases. The increase and extracellular circulation reinforce the importance of these molecules as molecular biomarkers for prognosis, diagnosis, evolution, monitoring and therapy.<sup>5-9</sup>

In the healthy adult heart, miRNAs are normally expressed in cardiac tissue and therefore play a fundamental role in the morphofunctional maintenance of the organ.<sup>10</sup> In fact, the literature shows changes in miRNA levels in different biological fluids in several cardiovascular diseases, including ischemic heart disease, arrhythmias, arteriosclerosis, coronary artery disease, heart failure and acute myocardial infarction. This makes miRNAs, along with proteins, potential diagnostic targets for cardiovascular diseases.<sup>11-14</sup>

Chagas disease may have a unique clinical course known as chronic form and some of the infected individuals may develop chronic Chagas cardiomyopathy (CCC).<sup>15</sup> CCC results from the invasion of *T. cruzi* into the metallic structures and electrical conduction tissue of the heart, causing their destruction and replacement by

fibrous tissue. Thus, heart failure is the main cause of deaths related to the cardiac form of Chagas disease.<sup>16</sup>

This issue of the International Journal of Cardiovascular Sciences presents an extended and comprehensive review on miRNAs in Chagas disease pathogenesis. The paper focuses on the understanding of miRNA production and regulation in relation to the modulation of *T. cruzi* in the immune system, and its potential role as biomarkers for the diagnosis of Chagas cardiomyopathy.

By observations from *in vitro* experiments, the authors also point out the association of *T. cruzi* infection with the deregulation of several miRNAs, and its relationship with hypertrophy and fibrosis. They also highlight the need for clinical studies in humans and brings up the discussion about this critical topic, adding relevant and detailed information about the discovery of specific miRNAs as potential biomarkers in Chagas cardiomyopathy, including processes such as inhibition of TGF-Beta (miRNA-15 family), fibrosis and cardiac dysfunction (miRNA-208a), cardiomyocyte hypertrophy (miRNA-29b-3p) and myocarditis (miRNA-146a, miRNA-155 and miRNA-21). These could also be used to identify morphofunctional changes and monitor the disease.

Despite these great discoveries, many challenges still remain, since many miRNAs described for Chagas cardiomyopathy diagnosis are not specific, and are also produced in minimal quantities in normal physiological processes. A good example is miRNA-155, which is a typical multifunctional miRNA with differentiated expression in various physiological and pathological processes, such as differentiation of hematopoietic lineages, immunity, inflammation, cancer, and cardiovascular diseases.<sup>17</sup> These and other factors open up great opportunities for scientific investigation, focusing on morphophysiological changes and the expression of miRNAs in specific pathophysiological processes.

## Keywords

microRNA, Chagas disease, chagasic cardiomyopathy, biomarker, diagnosis

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In addition, a major challenge and opportunity for study is the difficulty in classifying individuals with CCC and a detailed elucidation of the involvement of miRNAs. The literature has suggested different classifications for individuals with the cardiac form of Chagas disease – individuals with structural heart disease, evidenced by electrocardiographic changes, but presenting normal global ventricular function, without current or previous signs and symptoms of CCC; individuals with structural heart disease characterized by global ventricular dysfunction, but without previous or current signs and symptoms of CCC; individuals with ventricular dysfunction and previous or current symptoms of CCC and individuals with refractory symptoms of CCC at rest, despite optimized clinical treatment, requiring specialized interventions – highlighting the complexity of clinical classification of patients with left ventricular dysfunction.<sup>18</sup> This reinforces the difficulty in understanding the pathogenesis of the disease and its predominant clinical manifestations, as well as the molecular and immunoregulatory processes involved, including the key role of miRNAs in these processes.

Opportunities for scientific research also involve the evaluation of the expression and production of miRNAs and the new class of RNA molecule LncRNA (long non-coding RNAs) specific to different phases and forms of the disease (indeterminate, digestive, cardiac and mixed), and clinical studies that can reveal the expression of these molecules during periods of both disease progression and treatment.

Finally, there are still many gaps to be filled in developing and improving diagnostic approaches. For example, the PCR technology, microarrays, biosensor nanotechnology and mass spectrometry open new perspectives for monitoring molecules on a laboratory scale.<sup>19,20</sup> Future research should focus on identifying and quantifying non-coding RNAs on large scale, as well as combining the monitoring of these molecules with other types of non-nucleic biomarkers in multiplex format diagnostic platforms, thus enabling greater speed, cost-benefit improvement and application in diagnostic medicine laboratories.

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