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Molecular mechanisms of cardiac electromechanical remodeling during Chagas disease: Role of TNF and TGF-β

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ABSTRACT

Chagas disease is caused by the trypanosomatid *Trypanosoma cruzi*, which chronically causes heart problems in up to 30% of infected patients. Chagas disease was initially restricted to Latin America. However, due to migratory events, this disease may become a serious worldwide health problem. During Chagas disease, many patients die of cardiac arrhythmia despite the apparent benefits of anti-arrhythmic therapy (e.g., amiodarone). Here, we assimilate the cardiac form of Chagas disease to an inflammatory cardiac disease. Evidence from the literature, mostly provided using experimental models, supports this view and argues in favor of new strategies for treating cardiac arrhythmias in Chagas disease by modulating cytokine production and/or action. But the complex nature of myocardial inflammation underlies the need to better understand the molecular mechanisms of the inflammatory response during Chagas disease. Here, particular attention has been paid to tumor necrosis factor alpha (TNF) and transforming growth factor beta (TGF-β) although other cytokines may be involved in the chagasic cardiomyopathy.

Key words: Chagas disease, Cardiac electrophysiology, Action potential, Cytokine, Tumor necrosis factor, *Trypanosoma cruzi*.

Clinical aspects of Chagas disease

Chagas disease is one of the most important neglected diseases in Latin America. This disease was first discovered and described by the Brazilian physician Carlos Chagas in the early 20th century. Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*, and insect members of the sub-family *Triatominae* are intermediate host. They are known in the folk culture as "barbeiro." According to the World Health Organization, 6–7 million people worldwide, mostly in Latin America, are infected with *T. cruzi* and 7000 deaths are reported every year. Additionally, 25 million people are at risk for *T. cruzi* infection [1]. However, migration of infected people leads to a distribution that includes not only endemic areas but also North America and Europe and it may turn Chagas disease into a worldwide health problem in the near future [1].

T. cruzi has a complex life cycle and, usually, involves an intermediate invertebrate and final vertebrate host.

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For additional details, please refer to [2]. A small percentage of acutely infected patients, particularly children, die of acute myocarditis or meningoencephalitis. In the acute phase, the parasites are present in the blood circulation and patients may exhibit more general clinical signs of *T. cruzi* infection, such as fever, increased liver and spleen size, and Romanã signal, observed as swelling of the eyes, which is one of the most common points of *T. cruzi* infection. Only a small number of patients present signs of cardiac malfunction during this stage of the disease, making cardiac symptoms ineffective as an early diagnostic test. However, in most patients, as specific cellular and humoral immune responses develop, parasitaemia wanes and symptoms resolve completely, typically occurring in 2–4 months. The transition from acute to chronic phase is accompanied by a marked decrease in parasitaemia, due to a relatively effective immune response, which keeps parasite numbers below the detectable levels in the host. For more details about the subject, please refer to [3–5].

These individuals, then, enter into the indeterminate phase of *T. Cruzi* infection, which is characterized by detectable levels of specific antibodies and the absence of clinical manifestations. The indeterminate phase may last from months to an entire lifetime. In some patients, the evolution to the chronic phase of Chagas disease is synonymous with severe heart failure accompanied by cardiac arrhythmias [3]. No clear correlation has been established between the severity of acute Chagas disease and development of chronic cardiac and/or gastrointestinal manifestations years later. Two main hypotheses have been advanced to explain the pathogenesis of Chagas disease in humans, based on the relationship between parasite and host. The first hypothesis argues in favor of the pivotal role of the parasite's persistence in the host as a major cause of this disease [6,7]; while the second postulates that an immune response against self-antigens is responsible for the tissue damage observed in affected organs of chagasic individuals [8,9]. The treatment of Chagas disease involves both parasite-specific [10] and adjunctive therapies for the management of heart failure and arrhythmias [11]. Anti-parasitic therapy is clinically indicated for patients, mainly children, during the acute phase, recently infected persons, in those with congenital form of the Chagas disease, and in cases of reactivation due to immunosuppression [12,13].

The therapeutic approaches for management of chagasic cardiomyopathy are very similar to that already instituted for similar cardiomyopathies caused by other etiologies. However, most treatments are based on data from large clinical trials that did not focus specifically on heart failure and arrhythmias during Chagas disease [11]. Here, we will focus on heart dysfunction that is observed during the development of chagasic cardiomyopathy, the role of some key cytokines, such as TNF and TGF-β, in the cardiac pathophysiology and we will discuss the new possible therapeutic targets.

Macroscopic aspects of heart changes during acute and chronic phases of Chagas disease

The mortality rate during the acute phase of Chagas disease is low (i.e., approximately 5%). At this stage, there is an increase in parasite number in the blood stream. The parasitaemia is controlled by humoral and cellular immune responses as extensively reviewed [14–17]. The intense inflammatory process during the initial infection is essential to confine the etiologic agent in the intracellular environment and prevent tissue damage. The tissue lesions in the acute phase are characterized by the presence of localized inflammatory reactions, with predominance of mononuclear cells, occasionally with the formation of granulomas located mainly in skeletal muscle and cardiac tissue [18,19]. Denervation of the autonomic nervous system in the heart is frequently observed during the acute phase of Chagas disease due to the destruction of parasympathetic and sympathetic neurons. However, a recovery of heart innervation is observed during the chronic phase [4,20,21]. Nevertheless, the effect of heart denervation on the pathophysiology of Chagas disease remains unclear and deserves more attention. Previous reviews have covered this topic [22,23].

The clinical signs during the acute phase of Chagas disease include tachycardia, small ventricular hypertrophy, P-wave alternans, repolarization disturbances, ST abnormalities, and other electrical alterations [21,24,25]. These changes are found in humans as well as in experimental models of Chagas disease. Massive cardiac remodeling that is detected in the chronic phase of Chagas disease is by far the major problem after *T. cruzi* infection, and this is observed in 30–40% of patients [1,3,4]. The near absence of parasites in the myocardium also has led to several assumptions as to the etiology of chronic chagasic cardiomyopathy including a severe microvascular compromise, autoimmunity, and neurogenic mechanisms. Importantly, in most studies, the presence of the parasite is detected when DNA amplification method is used [26,27].

The most common heart alteration detected during the chronic phase, in humans and experimental models of *T. cruzi* infection, is a dilated heart with eventual cardiac hypertrophy and altered/disrupted morphology of cardiac cells [25,28–31]. The leading cause of mortality during the chronic phase of Chagas disease is sudden death, which occurs as a consequence of polymorphic cardiac arrhythmias and heart failure [3,4,32]. A chronic diffuse mononuclear inflammatory infiltrate is observed, with increasing fibrosis between ventricular muscle and conducting system cells and diastolic and/or systolic dysfunction [33–35]. The alterations that are observed in the electrical conducting system are thought to be important factors in reentry phenomena and sudden death that are observed during the chronic phase of chagasic cardiomyopathy [28,33,36–38]. Additionally, the prevalent forms of arrhythmia during the chronic phase are ventricular extrasystoles, right bundle branch block, ventricular repolarization disorders, and ventricular arrhythmias. The worst prognosis is related to the presence of monomorphic sustained ventricular tachycardia [32,39]. In addition, a pronounced reduction in heart function is also observed, contributing to the establishment of heart failure [34,40–42]. The basic cellular and molecular events involved in electromechanical remodeling of chagasic cardiomyopathy will be discussed in the next sections.