Chapter 7

Physiology and Pathology of Infectious Diseases: The Autoimmune Hypothesis of Chagas Disease

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Abstract

Infectious pathologies are a group of diseases that contribute with great impact on public health worldwide. Among the various diseases, some have a higher epidemiological importance, since their morbidity and mortality are very significant. In addition to the usual immune response, mounted against noxious agents, there is still the concept of infection-induced autoimmunity. Autoimmune diseases are defined as illnesses in which the evolution from benign to pathogenic autoimmunity takes place. However, proving a disease to be of autoimmune etiology is not a simple task. It is well known that both genetic influences and environmental factors trigger autoimmune disorders. However, some theories are still under great discussion. One of the most intriguing self-induced disorders is the hypothesis of autoimmunity during Chagas disease. Since the mid-1970s, the Chagas autoimmunity hypothesis has been considered an important contributor to the complex immune response developed by the host and triggered by *Trypanosoma cruzi*. New ideas and findings have strengthened this hypothesis, which has been reported in a series of publications from different groups around the world. The aim of this chapter is to discuss the mechanisms involving autoimmunity development during Chagas disease.

Keywords: Chagas disease, autoimmunity, *T. cruzi*, autoantibodies, immunology, cardiomyopathy

1. Introduction

Autoimmune diseases are chronic disabling disorders described as immune responses against self-antigens that comprise cells, tissues, and organs, resulting in devastating consequences for patients [1]. For over decades, the concept of autoimmune disease has been studied, and the relationship between infectious diseases and autoimmunity has been established. Among all illnesses, Chagas disease has caught the attention of many researchers worldwide. Along with all the possible pathogenic mechanisms involved in *Trypanosoma cruzi* infection, the autoreactive hypothesis has been discussed over the years and plays an important role in the cardiac damage presented by Chagas patients. This chapter intends to explore the *T. cruzi*-induced autoimmunity hypothesis by discussing its pathogenic mechanisms and its potential role in the tissue aggravation during Chagas disease.

2. Autoimmunity: an obscure immunological path

In order to understand autoimmunity, it is essential to go back into the first steps of T- and B-cell development, differentiation, and maturation. During the process of generation of new lymphocytic clones derived from a stem cell, a novel lymphocyte carrying a specific pattern of B-cell receptor (BCR) or T-cell receptor (TCR) is formed as revised recently [2, 3]. While B-lymphocytes may undergo full maturation in the bone marrow, T lymphocytes need thymic education, as can be observed in **Figure 1**.

After egressing the bone marrow, T lymphocytes undergo differentiation and maturation in the thymus in which they pass through a process called negative and positive selection [4, 5].

Positive selection occurs during classical thymic differentiation, in which thymocytes may generate naive conventional T lymphocytes. These cells migrate to peripheral tissues and further differentiate in response to encounter with nonself-antigens. The negative selection is based on the elimination or inhibition of "self-reactive" cells. Nevertheless, some of these self-reactive T cells could escape negative selection and might become activated during the inflammatory process. On the other hand, a second or agonist-driven thymic selection, was proposed in which specialized T-cell subsets are generated from thymocytes that bind with high avidity to self-antigens. In this case, these cells leave the thymus as antigen-experienced activated T cells, such as double-negative TCR$\alpha\beta$+ intestinal T cells, CD8$\alpha\alpha$+, invariant iNKT, Foxp3+ nTreg cells, TH17 cells [6] and possibly mucosal associated invariant T cells (MAIT) [7]. Two barriers for self-reactive cells exist, which are the central and peripheral tolerance [5]. Failure in these processes may allow the proliferation of self-reactive clones, thus establishing an autoimmune pathogenic disease. Genetic disorders as well as environmental conditions can trigger the failure on central or peripheral tolerance, [8–12]. In addition, other pathways can lead to autoimmunity such as molecular similarity or mimicry, specific epitope spreading, indirect or bystander activation, B- and T-cell polyclonal activation, infections, and self-inflammatory activation that trigger innate immunity [8, 13].

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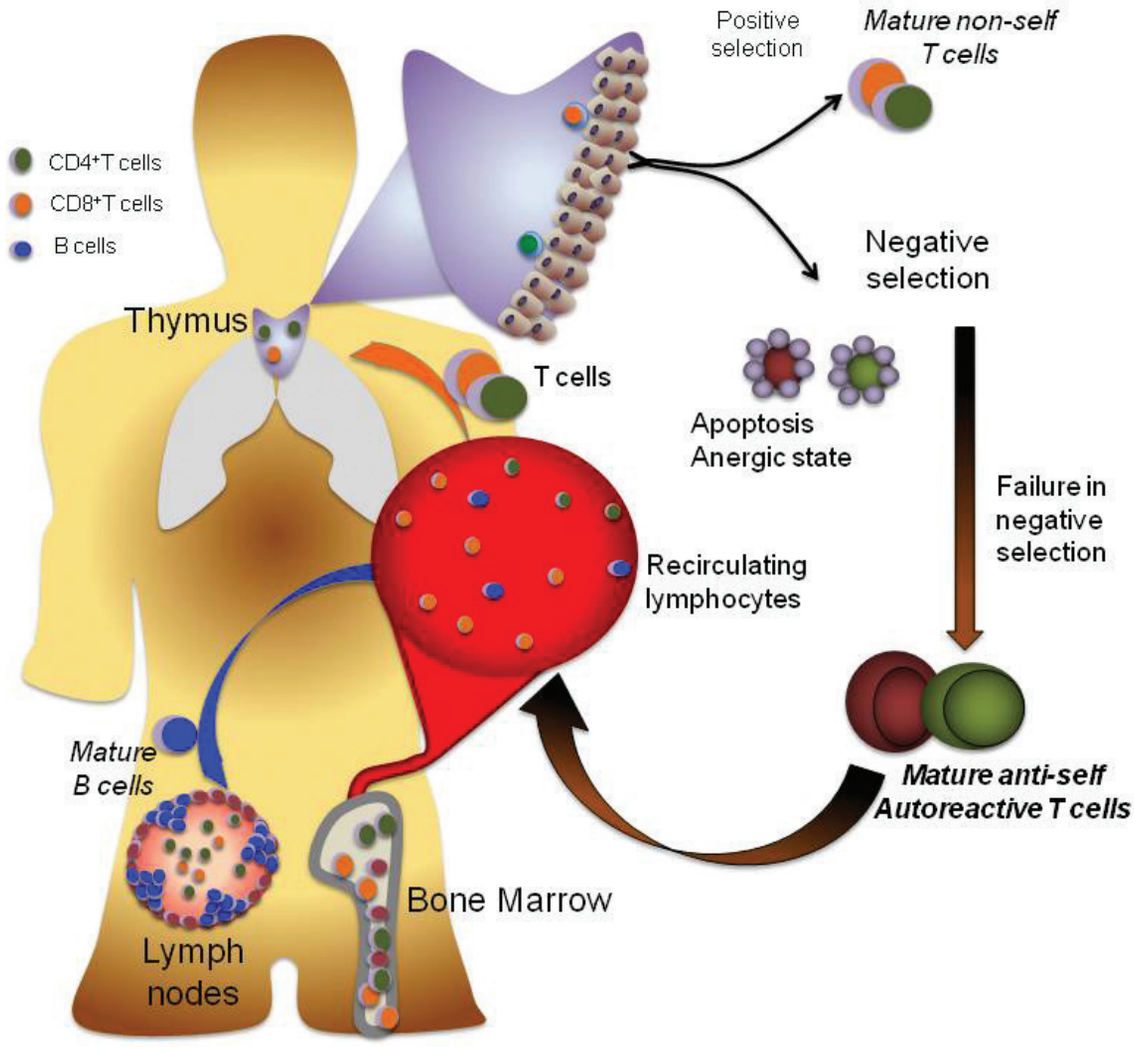

Figure 1. Dynamics of hematopoiesis, maturation and recirculation of newly generated lymphocytes as well as thymic selection of T-cell clones.

3. Chagas disease: an outburst of inflammatory events that may lead to autoimmunity

T. cruzi is a haemoflagellate parasite transmitted by several species of triatomine bugs. The best known mood of transmission is the vetorial via, which consists of vector insects ingesting contaminated blood meal containing bloodstream trypomastigotes. Later on, inside the insect's gut, the parasite differentiates into epimastigotes and replicates. The cycle is complete once the insect defecates, and releases metacyclic trypomastigotes forms which invade the host through the bite wound or mucosal membranes. Chagas disease progresses from a somewhat asymptomatic short acute phase to a chronic phase. Most individuals that progress to chronic phase remain asymptomatic, and the disease is detected by serological tests, but no clinical, radiologic, electrocardiographic, or echocardiographic evidenced. Overall, 20–40% of asymptomatic individuals develop clinically relevant Chagas heart disease, while approximately 10%

of the cases progress to digestive problems [14, 15]. In fact, the disease outcome toward differential clinical forms is related to many factors including the host-parasite interaction. Several studies have been proposed that the host immunological response plays a major role in the pathogenesis of Chagas disease [16]. Indeed, the *T. cruzi* can trigger an immune response, since parasite antigen has been consistently found in heart tissue infiltrated from cardiac patients [17, 18]. Nevertheless, the divergence between low parasite load in the tissue and severity of the lesions observed during the chronic phase reinforces the hypothesis that other factors than the immune response developed against the parasite might be involved in the development of Chagas pathology [19]. In this context, humoral and cellular autoimmune mechanisms are developed during Chagas disease [20–23]. Autoimmune mechanisms triggered during infection by *T. cruzi* may occur after bystander activation, parasite-cardiomyocyte harm, or molecular mimicry [24]. The mechanisms discussed in this chapter are schematically summarized in **Figure 2**.

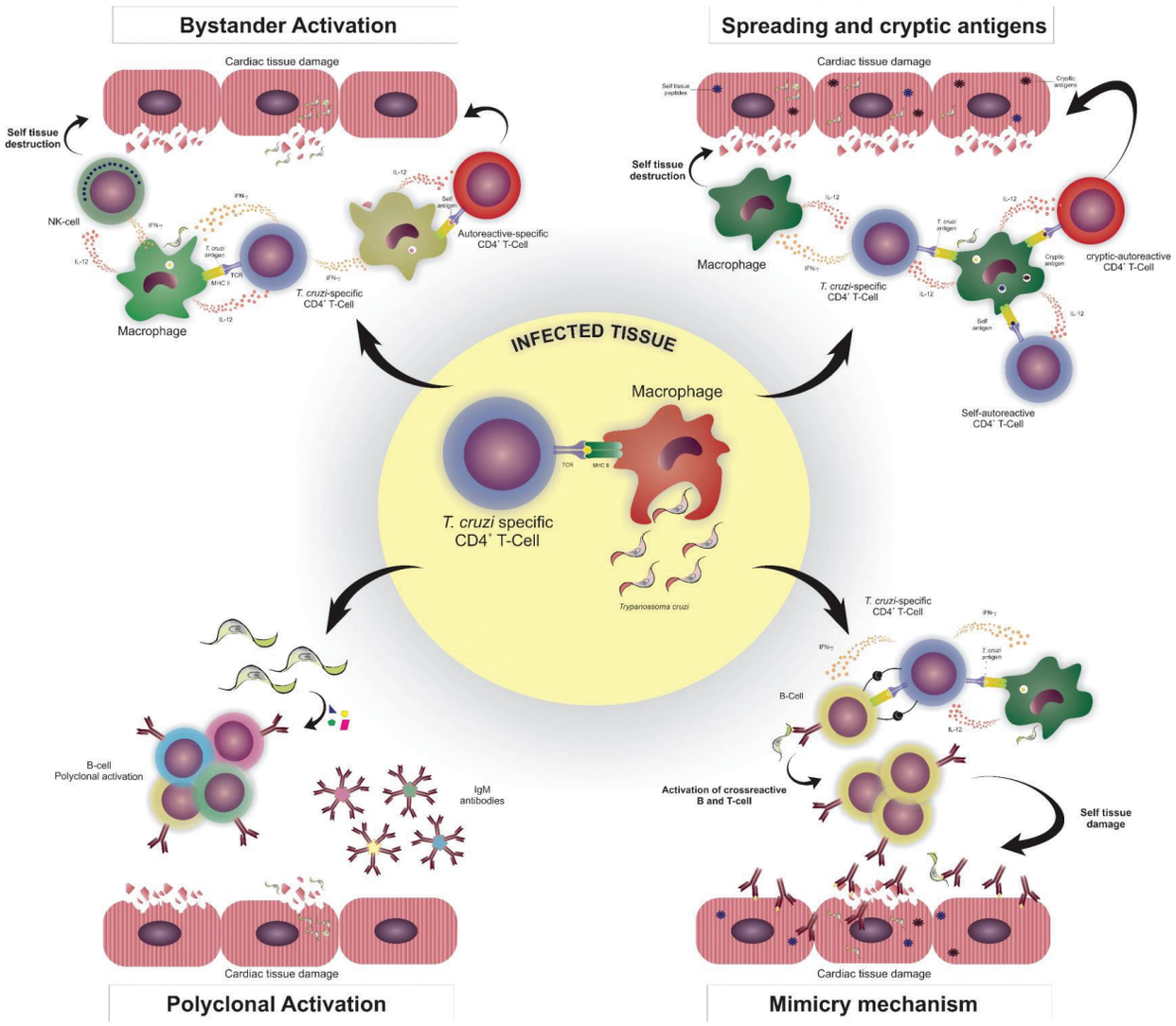

Figure 2. Scheme of the probable mechanisms involved in the autoimmune pathogenesis of Chagas disease.

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Since *T. cruzi* presents a high variability of surface antigens, it is possible that the parasite causes polyclonal activation, which involves the T-independent stimulation of self-reactive B lymphocytes [25]. The lipopolysaccharide has been described as polyclonal activator, which induces the hypergammaglobulinemia phenomenon with higher secretion of autoantibodies, mainly IgM isotype [26]. Furthermore, *T. cruzi*-derived antigens can activate B1 lymphocytes before the development of T-cell-mediated immune response during the early stages of Chagas disease. [27, 28]. High percentage of B1 cells are found in the peripheral blood of chronic Chagas patients, as well as a significant decrease in the percentage of $CD3^+$ T cells [27, 28]. Additional studies have demonstrated that auto-anti-idiotypic antibodies (Ids) from chagasic cardiac disease patients preferentially stimulate B1 cells and $CD8^+$ T cells in magnified proportion as compared to indeterminate patients [29, 30]. The lower levels of T cells in the peripheral blood of chagasic cardiac patients suggest that T-cell-mediated immunity should be restricted to inflammatory foci, considering previous reports of the presence of T cells, mainly $CD8^+$ T lymphocytes, in the inflammatory infiltrate of cardiac tissue from individuals infected by *T. cruzi* [16]. A study using murine experimental model based on infection by *T. cruzi* demonstrated that the onset of cytokine production by T cells in the cardiac tissue is correlated with the local increase in the expression of cell adhesion molecules that is consistent with the T-lymphocyte migration to the inflammatory milieu [31]. In this study, the authors propose that chronic inflammation in the cardiac tissue from Chagas disease patients is highly active and is related to a permanent proinflammatory immune pattern that extends from the recent acute phase to the late stages of the chronic phase. Indeed, it is well accepted that the absence of pathology in individuals infected by *T. cruzi* is associated with the individual's ability to regulate the anti-*T. cruzi* response, which is responsible for the control of persistent parasitemia and tissue inflammatory damage, characteristic of Chagas disease [16, 32–34]. Certainly, the tissue inflammatory damage should be more severe in the absence of regulatory mechanisms involving both innate and adaptive immune responses. Indeed, our group has reported that in the indeterminate clinical form of Chagas disease, there is a higher frequency of $CD4^+CD25^{High}$ T cells and NKT lymphocytes than individuals with cardiac disease [35, 36]. As $CD4^+CD25^{High}$ T cells and NKT lymphocytes showed an important role in modulating the activation of $CD8^+$ T cells via apoptosis, as well as throughout the secretion of regulatory cytokines, it is possible that these cells during indeterminate clinical state further contribute to the control of the cytotoxic activity and deleterious events mediated by $CD8^+$ T cells [37, 38]. It is worth to mention that a fine equilibrium between inflammatory and regulatory cytokines represents a crucial element in the establishment of distinct clinical forms of chronic Chagas disease [33, 38]. It has been demonstrated that in the severe cardiac clinical status, leucocytes produce more IFN-gamma, while IL-10 is predominantly produced by PBMCs from indeterminate [38, 39].

In this regard, the functional role of peripheral blood leukocytes in patients infected by *T. cruzi*, after antigen stimulation has demonstrated that the main source of IFN-γ in cardiac patients is $CD4^+$ T lymphocytes, while monocytes are responsible for the production of high levels of IL-10 in patients with indeterminate status, favoring the regulation of the immune response and the control of disease morbidity [40]. It is possible that regulatory T cells are involved in this process, since they can inhibit the synthesis of IFN-γ, which could explain the low levels of

this cytokine produced by T cells from indeterminate Chagas disease patients. In this context, it is important to reinforce that the inflammatory environment and cell destruction induced by *T. cruzi* infection could alter and induce antigen processing/presentation in such a way that novel self-epitopes are generated and recognized by the immune system, namely, cryptic epitope [41]. In steady state, the cryptic epitope displays low affinity for MHC molecules and is rarely presented by somatic cells, while dominant peptides show a high affinity for MHC molecules and are frequently presented by somatic cells. Furthermore, $CD8^+$ T cells specific for cryptic epitope could escape from the negative selection process in central tolerance [42]. Despite the fact that this process during *T. cruzi* infection is not yet clearly understood, this mechanism has been demonstrated to be involved in the pathogenesis of other autoimmune diseases [43]. Moreover, it has been shown that antigen processing and presentation were altered after the in vitro IFN-γ treatment, strengthening the hypothesis that the higher levels of IFN-γ in cardiac patients may favor the establishment of autoimmune mechanisms during Chagas disease. Indeed, the bystander activation mechanism caused by massive host antigens released in a proinflammatory environment may stimulate autoimmunity during *T. cruzi* infection.

4. The autoimmunity during Chagas disease: theories, concepts, and mechanisms triggered by *Trypanosoma cruzi*

Starting from the innate response, the human organism defends itself in a variety of ways. Physical barriers, phagocytic cells, (such as macrophages and dentritic cells), natural killer cells, neutrophils and the complement system are just a few examples of how precise and efficient our body reacts. Besides the innate response, the immune system is comprised of the adaptive response, a complex compartment of defense. Leucocytes (T and B lymphocytes), antibodies, and many other molecules are constantly working in order to keep the homeostasis. Furthermore, another important mechanism that is part of the immunological system is the autoimmunity concept. The autoimmunity concept started when researchers proposed that *T. cruzi* infection promoted rejection of allogeneic heart cell transplants and that T lymphocytes from *T. cruzi*-infected animals rapidly destroyed embryonic cardiomyocytes in culture [44]. However, reports that protective *T. cruzi*-specific T-cell-mediated immunity could be induced without eliciting pathogenic autoimmunity were soon published.

The debate about a role for autoimmunity in Chagas disease continued. Autoreactive T cells and antibodies were identified in individuals with chronic Chagas disease, and several specific antigens abundant in the myocardium were identified as targets of autoreactive responses [22, 45, 46]. Inflammatory factors present in the local environment, such as cytokines and nitric oxide, were also found to promote the activation of potentially autoreactive T cells encountering major histocompatibility complex-bound cognate antigen [21, 47, 48]. In this context, the autoimmune hypothesis plays a crucial role in the pathogenesis of many infectious diseases, including Chagas. The mechanisms proposed in this section for the generation of autoimmunity during Chagas disease are mimicry, indirect or bystander activation, and epitope spreading.

Mimicry is defined by the development of immune responses against foreign antigens that share sequence or structural similarities with self-antigens. This is due to the fact that immune responses can be directed against peptides with similar charge distribution and shape [8].

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This mechanism suggests that *T. cruzi*-induced cardiac damage and/or molecular mimicry between parasite and host antigens leads to a breakdown in self-tolerance, resulting in eventual tissue damage [49]. Two cardiac molecules that have been related to the induction of Chagas autoimmune responses are myosin and troponin I [50, 51]. Troponin I have been recently described in *T. cruzi*-naturally infected macaques, which present high titers of troponin I autoantibodies in their circulatory system. In regards to myosin, it is the most abundant protein in the heart and may represent a significant cardiac antigen. Several studies have demonstrated the presence of autoantibodies against this protein circulating in the sera of Chagas disease experimental models [41, 52, 53]. Its potential to become an antigen mimicry candidate has been under discussion for over decades, especially considering several studies, which have linked it to the autoimmune hypothesis. Furthermore, a robust myosin-specific autoimmunity as well as immune tolerization to myosin suppresses parasite-specific immunity [41, 53]. However, it seems that myosin-specific autoimmunity itself is not essential to establish an inflammation [54].

In addition, other host antigens have been studied and proved to cross-react with *T. cruzi* proteins, such as B1 and B2 adrenoreceptors, lymphocyte, neuronal tissues, muscle antigens, m2 muscarinic acetylcholine receptors, small nuclear ribonucleoprotein, and Cha, a novel autoantigen [22, 55]. Moreover, some *T. cruzi* proteins have also been identified as potential antigen mimicry candidates, like epitopes of B13, 24-kDa, 36-kDa, 38-kDa, ribosomal P1 and P2 proteins, the shed acute-phase antigen (SAPA), and the *T. cruzi* cysteine protease cruzipain [22, 51, 55–59]. Worthy of mentioning was the identification of three regions of homologous linear sequence among cruzipain and myosin as well as the partial homology displayed in ribosomal P protein internal peptide sequence between *T. cruzi* and humans. These findings provide more evidence that the molecular mimicry mechanism may stimulate autoimmunity and strengths the hypothesis.

An additional concept of great discussion is the bystander activation. During microbial infection, toll-like receptors (TLRs) and pattern recognition receptors present on antigen-presenting cells (APCs) are stimulated leading to the synthesis and release of proinflammatory mediators. Together with self-antigens, coming from tissue destruction and creating a milieu of proinflammatory factors, all of these mediators may defeat self-tolerance by decreasing the threshold of activation enough to activate potentially autoreactive T cells and trigger autoimmunity. Furthermore, $CD8^+$ T cells may also initiate bystander activation by proliferating in response to self-antigen presented by APCs [21, 49, 60]. Hyland et al. [61] have shown that a reduction in parasitemia via treatment with Benznidazole, decreased or eliminated myosin-specific autoimmunity. They hypothesized that reduction of parasitemia consequently reduces release of host antigens and also dampens the inflammatory environment lessening bystander activation. Altogether, these data bring great perspectives to elucidate the autoimmune hypothesis of Chagas disease.

Subsequent to bystander activation, there is the development of autoimmune responses to endogenous epitopes secondary to the release of self-antigens, the so-called epitope spreading. It results from a change in protein structure, for example, changing of an amino acid from arginine to citrulline, which may succumb in an immune reaction against either the original protein or the citrullinated protein. Some of the mechanisms involved in epitope spreading are endocytic processing, antigen presentation, and somatic hypermutation, all culminating

in broadening the immune response in autoimmune pathologies. Several authors have demonstrated the epitope spreading against many cardiac proteins, such as myosin, Cha protein, desmin, actin, myoglobin, tubulin, and B1 adrenergic receptor [49, 55, 62]. Still, more studies must be conducted in order to prove that this mechanism fully contributes to the propagation of autoimmunity in Chagas disease.

5. Final remarks

Chagas disease afflicts millions of people each year worldwide. Some individuals present mild to moderate symptoms during the chronic phase, while others develop severe and life-threatening cardiac and digestive conditions. There have been great advances in understanding the physiopathology of Chagas heart disease, which may contribute to the evolution in the field of drug development and therapy approaches. Apparently the auto-reactive cells are great responsible for destruction of the cardiac tissue leading to cardiac failure, the most severe consequence of the disease. Although the data describing the existence of *T. cruzi*-induced autoimmunity continues to grow, there is still lack of direct evidencere ported in the literature. Elucidating the autoimmune hypothesis of Chagas disease may help to solve potential complications for Chagas disease treatments involving autoimmunity, as well as to better understand many questions that remain unanswered about Chagas disease pathogenesis. Moreover, this hypothesis may serve as a model for studying infection-induced autoimmunity, which may be applicable to proposing and investigating new immune therapies for autoimmune diseases.

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