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Chapter 11

Novel Insights into the Pathophysiology of Chagas' Cardiomyopathy

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Abstract

The protozoan hemoflagellate *Trypanosoma cruzi* (*T. cruzi*) is the etiologic agent of the zoonotic Chagas' disease that affects approximately six to seven million people in Central and South America, causing dilated cardiomyopathy and megavisceral disease. Although Chagas' disease is the leading cause of heart failure in Latin America among people living in poverty and places an immense socioeconomic burden on society, it is still currently classified as a neglected tropical disease (NTD). The disease is typically transmitted by *reduviid* bugs or orally by contaminated food, while the transmission of parasitic organisms by other routes such as blood transfusion, organ transplantation, and transplacental infection is relatively rare. Given the wide cellular tropism infecting virtually all nucleated cells, the protozoan is able to persist asymptomatically for decades until ultimately causing organ-specific symptoms of chronic Chagas' disease such as chronic heart failure. The acute phase of the disease triggers an immune response that often does not restrict the dissemination of the parasite and may cause skin lesions, fever, enlarged lymph nodes, pallor, swelling, and abdominal and chest pain. Despite recent advances in our knowledge about the pathogenesis of this disease, the complex host-parasite interactions are not completely understood and, in particular, the persistence of parasites in host cells for such a long time remains largely undefined. In this book chapter, we focus on the pathophysiology of American trypanosomiasis and emphasize the role of host-specific transcription factors executing antiparasitic immune reactions.

Keywords: *Trypanosoma cruzi*, Chagas' disease, dilated cardiomyopathy, immune response, STAT transcription factors, apoptosis

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1. Introduction

The pathogenic protozoan *Trypanosoma cruzi* (*T. cruzi*) is the causative agent of Chagas' disease, and more than 150 species of mammals are affected by this unicellular parasite, including humans. The parasite was discovered in 1909 by the Brazilian physician Carlos Chagas, while dissecting assassin bugs (*Reduviidae*) from the subfamily *Triatominae* that act as vectors and hosts for the parasite, and was later named after Chagas' scientific mentor Oswaldo Cruz [1].

Chagas' disease, also termed American trypanosomiasis, causes the third largest disease burden of the tropics after malaria and schistosomiasis [2] and is responsible for higher morbidity and mortality than any other parasitic infection in America [3]. According to surveys of the World Health Organization (WHO) from 2014, six to seven million people worldwide are estimated to be infected with *T. cruzi*, while around 14,000 patients die annually as a result of the parasitosis. An overview of the geographic distribution of Chagas' disease is presented in **Figure 1**.

The link between poverty and dissemination of Chagas' disease is striking, as it particularly affects people living in simple huts made of mud and wood with roofs of straw or palm leaves in rural areas of Latin America, where the predatory bugs have easy access. In the most important endemic areas, vectors include *Panstrongylus megistus, Triatoma infestans, T. dimidiata, T. pallidipennis*, and *Rhodnius prolixus* [4] (**Figure 2**). Non-vectorial transmission, such as the ingestion of *T. cruzi*-contaminated food and congenital transmission from the mother to the fetus [5] as well as blood transfusion and organ transplantation, increase the number of people at risk, estimated at 100 million worldwide. Owing to international migration, isolated cases of Chagas' disease in nonendemic countries are increasingly being recognized.



Figure 1. Geographical distribution of Chagas' disease. Dark blue indicates endemic countries and light blue nonendemic countries.

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Figure 2. *Meccus pallidipennis* (syn. *Triatoma pallidipennis*, Hemiptera: *Reduviidae*) from the subfamily *Triatominae* as a vector for *T. cruzi*.

2. Biology and life cycle of *T. cruzi*

Assassin bugs infected with *T. cruzi* preferably sting sleeping victims and usually suck their blood unnoticed. After the blood meal, the pressure in the bug's gastrointestinal tract increases and the insect defecates on the skin near the wound. This behavior of *Triatominae* is crucial for their ability to act as a vector for *T. cruzi*, since infective stages of *T. cruzi* reach the stab wound only when the bugs defecate during food intake. The assassin bug transmits the parasites to the definitive host, by spreading excrement on the wound while escaping. When the pathogen-containing feces are rubbed into the fresh puncture wound by the victim or when the pathogen penetrates into uninjured mucosa, especially those of the eye, highly infectious and very motile metacyclic trypomastigotes of *T. cruzi* are transmitted into the blood flow of the host [6, 7] (**Figure 3**). The trypomastigotes are then disseminated successively into the organism of the host, and preferably infect cells of the reticuloendothelial and mononuclear phagocytic system [8]. A parasitophorous vacuole is formed only briefly during the life cycle of *T. cruzi*, while the intracellular parasites multiply in the cytoplasm of the host cell by binary division [9, 10].

T. cruzi can infect any nucleated cell but predominantly replicates in cardiac muscle cells as well as in cells of the nervous system, gonads, intestinal mucosa, and placenta [11]. After penetration into the cytoplasm of the host cell, the morphology of the metacyclic trypomastigotes



Figure 3. *Trypanosoma cruzi* metacyclic trypomastigotes on a peripheral blood smear shown by Giemsa staining.

changes to intracellular amastigotes with diameters of 3–5 μm, when they lose their undulating membrane which is a characteristic feature of mobile trypomastigotes [9, 12] (**Figure 4**). Intracellular amastigotes undergo several rounds of division and are then transformed into trypomastigotes, approximately 20-μm long, which leave the host cell and spread further into the organism to infect new host cells [13]. Unlike the African sleeping sickness caused by *T. brucei*, intracellular replication of *T. cruzi* in host cells is mandatory, since the pathogenic agent of American trypanosomiasis is not able to divide in the blood. For this reason, the intracellular amastigote form of *T. cruzi* is always present and can be histopathologically detected in tissue samples from spleen, liver, brain, and heart muscle. The life cycle of *T. cruzi* continues when the bug takes a blood meal from an infected host, and the parasites transform in the

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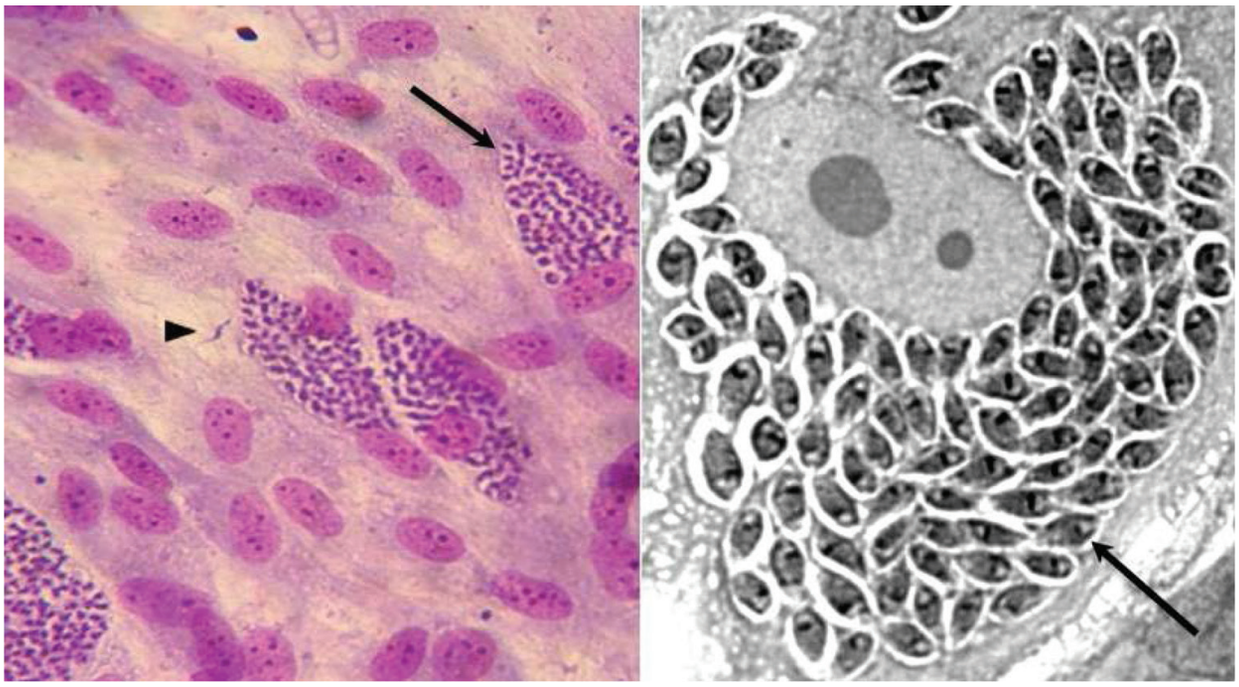


Figure 4. Intracytoplasmic localization of *T. cruzi* amastigotes in cultured fibroblasts stained with Giemsa at low (left) and high (right) magnification. Arrows mark intracellular amastigotes, and the arrow head (left) indicates an extracellular trypomastigote.

bug´s midgut to epimastigote forms and multiply by binary fission. Finally, the highly infectious metacyclic trypomastigotes develop in the rectum of the bug, and will be passed again with the feces during a subsequent second blood meal [14].

3. Epidemiology

Following a decline in incidence in endemic countries of Latin America, recorded in the mid-1990s up to the beginning of this millennium due to vector-eradication campaigns, Chagas' disease is currently worldwide on the rise again even in Europe [15–21]. Alternative transmission modes of Chagas' disease, such as congenital infection and infection through contaminated blood and organ donations, now play a major role both in classical endemic areas and in countries outside Latin America due to an increase in worldwide migration. The disease is, therefore, increasingly being detected in Europe, since more than 14 million people have left the endemic areas of South America, four to five million for Europe [22]. In a statement from the WHO for Chagas' disease in Europe in 2010, the number of *T. cruzi*-infected individuals in Europe is estimated at 80,000–100,000. Switzerland is home to a group of people at risk, and it is estimated that of the approximately 40,000 legal immigrants from Latin America, 2000–4000 people may have become infected with this pathogen [23]. In Spain, the estimated number of people infected with *T. cruzi*, most of these being legal immigrants from South America, is 25,000–48,000 [17, 18].

Chagas' disease can also pose a threat to Germany. The data collection among the approximately 85,000 immigrants coming from endemic areas is, however, incomplete. It is estimated

that the prevalence of seropositive immigrants is 1.3–1.7% (1100–1450-infected individuals); however, it is assumed that the number of patients is significantly underdiagnosed with Chagas' disease [18, 24]. Epidemiological data from the United States of America estimated up to a million people infected with *T. cruzi*, and for the entire American continent including Mexico up to seven million [25]. In South America, Bolivia is the country with by far the highest infection rate, and serological screening in maternity hospitals detected up to 23.6% pregnant women infected with the parasite [26]. Recent data also underline the spread with increasing prevalence of Chagas' disease in Australia and New Zealand [27].

4. Symptomatology of Chagas' disease

Infection with *T. cruzi* can be divided into three distinct phases: the acute, indeterminate (latent), and chronic phase. The acute phase is characterized by the detection of circulating trypomastigotes in the blood. The majority of patients infected in adulthood are asymptomatic or show only mild and nonspecific symptoms. Children, however, are much more susceptible to a recognizable acute infection with *T. cruzi* and often have a higher parasitemia than adults. After an incubation period of 1–3 weeks, local inflammatory reactions develop at the entry point. In about half of all cases, the eye is the primary portal of entry. Parasites penetrate transconjunctivally into mesenchymal cells or are phagocytosed by macrophages and cause a local inflammatory reaction. Characteristic for acute Chagas' disease is a periorbital edema accompanied by conjunctivitis, which is termed Romãna's sign.

Inflammatory lesions or nodules on the puncture wound in the face are less frequently observed manifestations of the acute stage (Chagoma), indicating a local inflammatory response with tissue destruction. Invasion of neutrophils and activation of tissue macrophages result in the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). After a further 1–2 weeks, the stage of hematogenous and lymphatic spread is achieved, and further clinical symptoms of the acute phase may develop such as fever, anemia, muscle and bone pain, fatigue, diarrhea, lymphadenopathy, and hepatosplenomegaly. Whereas these symptoms typically disappear after 3–4 months, a small number of individuals, especially children, die from complications such as myocarditis or meningoencephalitis. The fatal course is highly dependent on the immune system and nutritional status of the host as well as the parasite load during transmission. The subsequent indeterminate phase is characterized by a very low parasitemia in the blood and can last for decades. Cellular immunity is at this stage an important endogenous strategy of the host to keep the parasites under control. Usually, 20–30% of seropositive patients develop the chronic phase of Chagas' disease [28]. In 40–50% of the affected patients, a progressive cardiomyopathy and less frequently neuronal dysfunction of the autonomic nerves of the gastrointestinal tract can develop [29]. These symptoms are often found clinically only at a later stage, as many patients are initially asymptomatic. During routine analysis, radiological signs of left heart failure and cardiomegaly can be found. Damage to the heart may result in atrioventricular (AV), His-bundle or intraventricular blocks with Adam-Stokes seizures and syncopes [30]. Cellular hypertrophy and subsequent chamber enlargement lead to systolic heart failure and

may result in arrhythmias. Patients often die of sudden cardiac death induced by ventricular tachycardia and congestive heart failure [31]. Histopathologic examination of endomyocardial biopsies shows myocardial fibrosis, resulting from cell lysis by trypanosomes and/or immune-pathological mechanisms. Development of gastrointestinal mega-syndrome, particularly the esophagus and colon, are additional clinical manifestations of chronic Chagas' disease. The formation of mega-organs results from the destruction of the parasympathetic ganglia of the Meissner and Auerbach plexus in the gastrointestinal tract, which critically impairs peristalsis and leads to the ballooning of the organs. Clinically, these patients show symptoms of dysphagia, regurgitation, constipation, and secondary achalasia resulting from the dysfunction of the lower esophageal sphincter.

5. Diagnosis and treatment

Based on the aforementioned clinical signs of *T. cruzi* infection, chronic Chagas' disease is diagnosed using conventional methods in clinical cardiology. The electrocardiogram (ECG) is the diagnostic tool of choice in the question of Chagas' cardiomyopathy. Magnetic resonance imaging (MRI) allows noninvasive and accurate assessment of inflammatory infiltrates of the heart muscle and the identification of an apical ventricular aneurysm. To confirm the diagnosis, a series of laboratory tests should be employed. The classic laboratory diagnostic measure to confirm an acute infection is a blood smear, which is stained after fixation with Giemsa and typically shows motile trypanomastigotes. The serological diagnosis comprises detection of both immunoglobulin (Ig) M and IgG antibodies against *T. cruzi* using enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination assay (IHA) or indirect immunofluorescence assay (IFA). For suspected Chagas' disease, the WHO recommends two mutually independent tests [32]. The polymerase chain reaction (PCR) for the detection of nucleic acid sequences of parasites can be used to detect parasites in organ transplants, as well as to test the parasite load during and after chemotherapy. Finally, in unclear serological cases and when the blood smear is repeatedly negative, the xenodiagnosis developed by the French parasitologist Alexander Joseph Émile Brumpt may be applied using confirmed *T. cruzi*-negative assassin bugs, which take a blood meal on the patient´s skin. After 10–30 days, in the case of an infection of the patient with *T. cruzi*, even at low parasitemia, metacyclic trypomastigotes of *T. cruzi* can be demonstrated in the intestine of the bug and confirm the diagnosis [33].

In principle, two drugs for the treatment of acute Chagas' disease are available, nifurtimox and benznidazole, which require prolonged treatment and may cause significant side effects [34]. Nifurtimox, a nitrofuran with antiparasitic activity against both life cycle stages in the host, causes the accumulation of free radicals and superoxides and is generally genotoxic [35]. The nitroimidazole derivate benznidazole is an antiparasitic medication equally effective against the two life-cycle stages. This drug inhibits the synthesis of RNA and generates the accumulation of superoxides [35]. Although the parasite burden can be reduced below the detection limit in about 70% of all pharmacologically treated cases in acute Chagas' disease, there is still no evidence that antiparasitic treatment can cure the patient completely from *T. cruzi* [36–38]. Data for the treatment of patients with chronic Chagas' heart disease are not sufficiently

validated to recommend a basic chemotherapy for these patients due to the unfavorable side-effect profile. In nonrandomized clinical or animal studies, some authors conclude that treatment with benznidazole may also be of benefit during the chronic phase, since thus severe courses of Chagas' cardiomyopathy can be avoided [39, 40]. However, results from the multicenter, randomized Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial to assess the efficacy and safety of benznidazole treatment in patients with chronic Chagas' cardiomyopathy demonstrated that anti-trypanocidal therapy does not significantly reduce clinical deterioration through 5 years of follow-up as compared to placebo, despite reductions in the parasite load in serum samples [41]. These findings emphasize the urgent need for the development of new pharmacological agents against chronic Chagas' disease.

6. Prevention

Hitherto, the only sure prevention of the disease is the exposure prophylaxis by aerial spraying of insecticides and by modernization of traditional huts in rural areas. *T. cruzi*-infected pets, especially dogs and cats, provide a large reservoir of pathogens. Some countries perform an obligatory blood bank screening for the pathogen of Chagas' disease. These include, for example, Brazil, Uruguay, Argentina, Colombia, and the United States, but also Spain and Portugal. A vaccination against *T. cruzi* does not yet exist. Surface components of the parasite, particularly glycolipids such as glycosylphosphatidylinositol (GPI) anchors, have been well studied for their role in infectivity [42]. Trypanosomal trans-sialidase, belonging to the family of GPI-anchored proteins which transfer sialic acids from the cell membrane of the host to glycoproteins on the parasite surface, is involved in the infection of the host cell, and trans-sialidase inhibitors have been successfully tested *in vitro* [43].

7. Innate immune response to infections with *T. cruzi*

The innate immune system is essential in order to control the spread of *T. cruzi* parasites in the body and to ensure the survival of the host [44]. Pattern recognition receptors (PRRs), particularly the transmembrane toll-like receptors (TLRs), recognize the so-called pathogen-associated molecular patterns (PAMPs) in microorganisms [45]. Binding of glycoinositol-phospholipids (GIPL), GPI anchors, DNA, and RNA fragments of *T. cruzi* to TLR2, TLR4, TLR7, and TLR9 initiates a signaling cascade that finally activates important pro-inflammatory processes [46–52]. In myocarditis, genes for the endogenous TLR-7 and TLR-9 receptors are upregulated and their gene products serve as potential biomarkers for inflammatory heart disease [53]. Through the adapter molecule myeloid differentiation factor 88 (MyD88), a signal pathway is activated that finally leads to the upregulation of pro-inflammatory genes, such as interleukin-(IL)-1β [54], IL-6 [55], IL-12 [56–60], TNF-α [57, 58, 61], IFN-β [62–64], and IFN-γ [54, 59–61, 65–67].

Activation of these pathways is critical for resistance to infection with *T. cruzi*. Mice functionally deficient in MyD88 expression are more susceptible to infection by this protozoan, which

is probably due to a defect in the production of pro-inflammatory cytokines [68]. In *T. cruzi*-infected macrophages, the expression of pro-inflammatory cytokines is mediated by two transcription factors: nuclear factor-κB (NF-κB) [69–71] and interferon-regulatory factor 3 (IRF3) [64]. NF-kB also activates inducible NO synthase (iNOS) which catalyzes the production of microbicidal nitric oxide (NO). Mice with a deficiency of iNOS or IFN-γ receptor are sensitive to infection with *T. cruzi*, showing a high rate of parasitemia, and, furthermore, macrophages from these mice have impaired trypanocidal activity due to lower amounts of NO [72].

8. Apoptosis of cardiac myocytes in Chagas' disease

The chronic stage of Chagas' disease usually leads to symptoms of dilated cardiomyopathy, which is characterized by an enlargement of the heart muscle with a steadily progressive loss of systolic function. The decrease in the biventricular ejection volume is presumably reflecting altered heart muscle remodeling and may include apoptotic cell death. Apoptosis is a form of programmed cell death which differs from necrosis by actively carrying out a cell-death program [73]. Apoptosis-regulating genes such as Bax and Apaf-1 are involved in the execution of apoptosis, whereas Bcl-2 is an antiapoptotic protein.

Proteolytic enzymes termed caspases play a central role in the execution of apoptotic cell death. The activation of the caspase cascade can be initiated by both intra- and extracellular stimuli. Extracellular stimuli induce the activation of caspases 8 and 10 through the Fas ligand and TNF receptors, whereas the intracellular pathway consists of the cytochrome C-regulated apoptosome which activates caspase 9. The JAK-STAT-signaling pathway regulates apoptosis via STAT3 (signal transducer and activator of transcription 3) by promoting the expression of antiapoptotic genes coding for the Bcl-2 protein family [74]. Cytotoxic T lymphocytes (CTLs, $CD8^+$ T-cells) activate caspases 3 and 7. These are key caspases in which caspases 8 and 9 converge and henceforth result in a common final pathway of the signaling cascade. Apoptosis of cardiomyocytes in the context of *T. cruzi* infection is a potential mechanism of the host to limit the spread of parasites.

In autopsy samples from Chagas' cardiomyopathy patients, signs of apoptotic cell death were detected post mortem in cardiac myocytes [75], confirming earlier results that *T. cruzi*-infected cardiomyocytes undergo fibrosis and apoptotic cell death [76, 77]. Zhang and colleagues detected apoptosis in a canine model of acute chagasic myocarditis characterized by the presence of amastigotes and trypomastigotes of *T. cruzi* within the cytoplasm of cardiac muscle cells [76]. In a gene expression study, Manque and colleagues showed that the infection of murine cardiomyocytes with *T. cruzi* resulted in the upregulation of the two classical pro-apoptotic genes *bid*, encoding BH3-interacting domain death agonist, and *fas* which encodes a member of the TNF receptor gene. In addition, the *gadd45b* gene engaged in cell cycle control, DNA repair, and apoptosis was upregulated upon infection [78].

However, there are conflicting results on the role of apoptosis in murine cardiomyocytes during infection with *T. cruzi* trypomastigotes. De Souza et al. reported that cardiomyocytes became apoptotic after infection with different strains of *T. cruzi* [79], whereas Aoki et al.

showed that the cysteine protease cruzipain on the surface of *T. cruzi* appears to have a protective effect on the host cell and serves as a survival factor supporting the propagation of the parasites [80]. Our group demonstrated apoptotic rat cardiomyocytes upon infection with either trypomastigote or amastigote stages of *T. cruzi* [81]. Petersen et al. showed that both *T. cruzi* infection and activation of NF-κB prevented apoptotic cell death in isolated neonatal rat cardiomyocytes [82]. Another study reported that amastigotes presented higher rates of apoptosis-like cell death as compared to trypomastigotes [83].

The JAK-STAT-signaling pathway has an important role in cardiomyopathy, myocarditis, and myocardial infarction [84]. Cardiomyocytes express various receptors for cytokines and growth factors (among others, TNFα and EGF) on their surface. Secreted cytokines or growth factors may be involved in the apoptotic cell death of cardiomyocytes and chronic cardiomyopathy. Specifically, the balance in the activation state of the two related transcription factors STAT1 and STAT3 may determine the outcome between cell death and survival of cardiac muscle cells during infection with *T. cruzi* [85].

In the context of chronic Chagas' disease, which can develop up to 25 years after parasitic infection, the question arises as to how the parasite can persist and replicate for such a long period of time in the host without causing an exacerbating immune response. The most obvious explanation is that the parasite has developed effective mechanisms to circumvent the immune response which affects the steady balance between parasite load and apoptosis-induced destruction of host cells. Various parasitological studies highlight the dogma that the replication of parasites in the cardiac myocytes is required to initiate the complete picture of Chagas' heart disease ranging from acute myocarditis to chronic cardiomyopathy [86].

9. The role of STAT proteins in Chagas' cardiomyopathy

There is growing evidence that not only NF-kB but also STAT transcription factors are engaged in *T. cruzi* infection. Recently, we have demonstrated that serine phosphorylation of STAT1 at position 727 is targeted by *T. cruzi*, suggesting that the parasite inhibits the antiparasitic effects of STAT1 [87] (**Figure 5**). Ponce and coworkers reported that the secretion of endogenous IL-6 or the addition of recombinant IL-6 protects cardiomyocytes from cell death by apoptosis during an infection with *T. cruzi* [88]. Furthermore, the authors showed the phosphorylation of STAT3 at tyrosine 705 by IL-6 in response to infection with *T. cruzi*. In cardiac tissues, the expression of the STAT3-regulated antiapoptotic factor Bcl-2 was increased, suggesting that, during the acute phase of infection with *T. cruzi*, tyrosine-phosphorylated STAT3 acts as a mediator of cell survival. In summary, the results of this important study suggest that STAT3 executes pro-survival effects in cardiac muscle cells evoked by the parasite.

In addition, Ponce et al. demonstrated that, in *T. cruzi*-infected cells, the release of IL-6 via a TLR2-dependent pathway is required to induce survival of cardiomyocytes [88]. The enzymatic activity of cruzipain, the main cysteine protease secreted by this parasite, critically interferes with IL-6-mediated STAT3 phosphorylation by means of cleavage of the ectodomain of glycoprotein gp130, which is the shared receptor of several IL-6-type cytokines [89]. The parasite cysteine protease inhibitor chagasin inhibits cruzipain-induced gp130 cleavage,

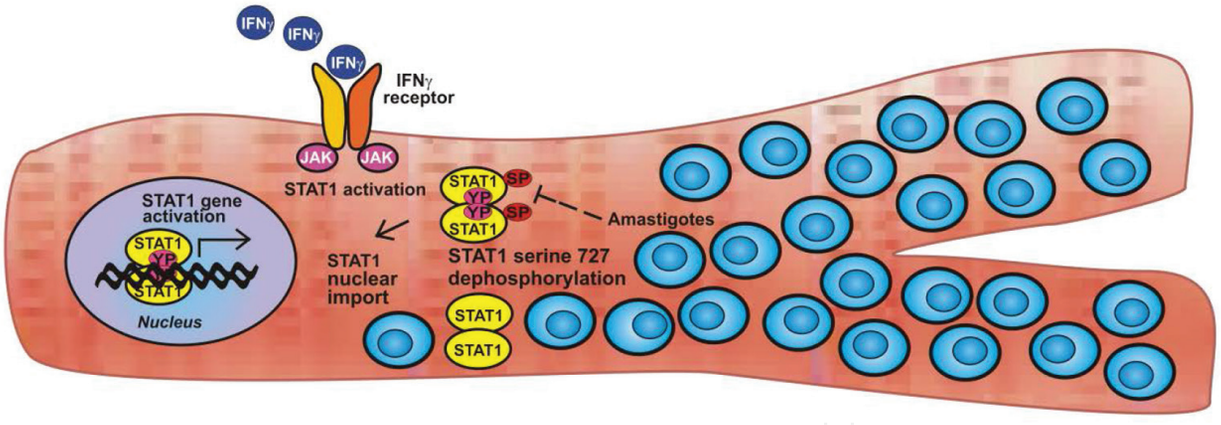


Figure 5. Illustration of a cardiac myocyte showing replicating intracellular *T. cruzi* parasites that evade the protective role of IFN-γ signaling by targeting essential components of the JAK-STAT pathway such as the dephosphorylation of STAT1 at serine 727. While phosphorylation of STAT1 serine 727 is required for full transcriptional activity, its dephosphorylation inhibits antiparasitic effects of STAT1.

suggesting that the pro-inflammatory IL-6 response in *T. cruzi*-infected cells is modified by cysteine protease activity. In addition, it has been well established that STAT transcription factors activate genes whose products have been identified as *s*uppressors *o*f *c*ytokine *s*ignaling (SOCS) which act as inhibitors of the JAK-STAT pathway in a negative feedback loop [90].

Previous studies have described how STAT3 is activated by the two cytokines IL-6 or IL-10 [91, 92] and how the expression of SOCS3 is upregulated by the anti-inflammatory IL-10 in *T. cruzi*-infected cardiomyocytes [71]. During chronic infection with *T. cruzi*, the expression of SOCS2 is upregulated and most probably plays a significant role in the etiopathogenesis of Chagas' heart disease by influencing heart muscle damage [93].

Another member of the STAT family, the transcription factor STAT4, is activated in response to the cytokine IL-12, which acts as a pro-inflammatory cytokine and drives Th cells along a Th1 lineage. STAT6 is activated by receptor binding of two cytokines with anti-inflammatory properties, IL-4 and IL-13, which provide an alternative signal for the development along a Th2 lineage. Tarleton and coworkers demonstrated that STAT4-deficient mice were highly susceptible to infection with *T. cruzi*, whereas STAT6-deficient mice showed enhanced resistance with lower parasitemia and little or no evidence of inflammatory processes in the heart muscle as compared to their wild-type littermates [94]. The apparent absence of disease in chronically infected STAT6-deficient mice is remarkable despite their inability to achieve entire parasite clearance. The findings in this investigation suggest that the severity of inflammation critically depends on STAT4- and STAT6-mediated cytokine-driven immune reactions which modulate tissue parasite load [94]. Finally, the authors infer that the clearance of intracellular parasites may not be required to prevent the progression of the disease to cardiomyopathy.

10. Concluding remarks

In summary, the pathogenic protozoan *T. cruzi* has evolved complex and still undefined mechanisms to circumvent an effective immune response in the human myocardium. The

bypassing of protective signaling pathways by the parasite such as the JAK-STAT pathway may account for the intracellular multiplication and long-lasting persistence of *T. cruzi* in the host. Amastigotes of *T. cruzi* proliferating in the cytoplasm of infected cardiomyocytes have developed effective strategies to counteract the attack executed by STAT proteins, which are crucial for an effective immune defense against the protozoan. Further research efforts are required to elucidate the role of cytokine-driven gene expression in the fight against the parasite.

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