Chapter

Trypanosoma cruzi Infection: Mechanisms of Evasion of Immune Response

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Abstract

Trypanosoma cruzi has a complex life cycle that involves a vertebrate as well as an invertebrate host. In this, last two stages are present: trypomastigotes, the flagellated and infective stage and the amastigote, which is the replicative stage. *T. cruzi* is considered one of the most successful intracellular parasites, because it cannot be eliminated by the immune system and has the capacity of invading, surviving, and replicating inside the host cells. The effects that the infection has over the immune system have been widely studied at the molecular and cellular level. However, understanding the mechanisms that the parasite uses to evade the immune system to persist in the infected individual is necessary for the effective development of drugs and/or vaccines. In this chapter, a compilation of the already described mechanisms will be carried out.

Keywords: *Trypanosoma cruzi*, immune system, *T. cruzi* immune evasion, immune modulation

1. Introduction

Chagas disease or American trypanosomiasis is a potentially life-threatening illness caused by the protozoan parasite, *Trypanosoma cruzi*. It is found mainly in 21 Latin American countries, where it is a mostly vector borne. An estimated 8 million people are infected worldwide, mostly in Latin America. Chagas disease has spread to the other continents over the last century mainly because of enhanced means of travel and global population movement to and from Latin America. It is estimated that over 10,000 people die every year from clinical manifestations of Chagas disease and more than 25 million people risk acquiring the disease [1].

Chagas disease is characterized by two stages, the initial phase is known as acute phase and lasts a few weeks and is characterized by an elevated parasitemia associated with fever, headache, nausea, that is rarely lethal and a severe hepatomegaly. The acute phase is followed by a chronic phase, which remains asymptomatic for many years. The parasites are then difficult to observe in the blood, and the other symptoms are also less severe. Most patients remain in this indeterminate stage for life (absence of any symptom), 5–10% of the people will develop anatomical and functional abnormalities at their esophagus and their colon, while 20–40% starts presenting a symptomatic chronic phase characterized by a progressive and debilitating Chagasic cardiomyopathy and sometimes mega syndromes. Arrhythmias increasing severely lead to congestive cardiac failure and death of the patients usually 10–30 years after the initial infection [2, 3].

The recognition of *T. cruzi* by the immune system relies on the activation of innate immunity and adaptative immunity. In this activation process, the recognition of pathogen-associated molecular patterns (PAMP) by Toll-like receptors of B and T cells is very important as a bridge between both types of immunity [4]. The innate and acquired immune responses are characterized by the recruitment of dendritic cells, macrophages, natural killer (NK), and B and T lymphocytes, as well as their secretion of soluble factors (cytokines and chemokines) [5]. IFN-γ plays a key role during *T. cruzi* infection, increasing the production of nitric oxide by macrophages, which inhibits the development of the intracellular from *T. cruzi* [6]. CD4+ Th1 lymphocyte that produces the cytokines interleukin-2 (IL-2) and IFN-γ can stimulate the expansion of cytotoxic CD8+ T lymphocytes, a central mechanism for systemic protection against *T. cruzi* infection [5, 7]. Recent studies have confirmed that CD8+ T cells act both indirectly by secreting IFN-γ to activate macrophages and directly through the production of perforin and their concomitant cytotoxic activity [8]. Thus, there is now a growing consensus that protective immune response against *T. cruzi* requires the activation of a Th1 immune profile, with the stimulation of CD8+ T cells, while antibodies may play a rather secondary role [9].

Although the immune response generated with *Trypanosoma cruzi* infection is potent and active, it fails to clear parasite infection, leading to the chronic phase of the Chagas disease. The parasite has developed sophisticated strategies to evade host immune responses. The *Trypanosoma cruzi* immune evasion is mainly based on altering the complement system and inhibitory effects on the mononuclear phagocyte system lifestyle [10–12], and therefore, this chapter summarizes the mechanism employed by *Trypanosoma cruzi* to escape the host's deleterious immune responses and enter into the host cells and establish persistent infection.

2. Immune evasion during the acute phase

2.1 Escape of the parasitophorous vacuole

Invading the host cell is a complex process that starts with parasite attachment to plasmatic membrane and then the compartment is formed called parasitophorous vacuole (VP), which fuses to lysosomes forming the phagolysosome (PLM). Acidification of the VP allows trypomastigotes escape from PLM to the cytoplasm, where it differentiates into amastigote forms. In the cytoplasm of infected cells, the amastigotes multiply by binary fission, they accumulate and transform to blood-form trypomastigotes, which are released in the bloodstream through the rupture of the host cell membrane to find new cells to invade [13–17].

Parasite escape from PLM occurs because the growth and development of *T. cruzi* cannot be maintained within it. Therefore, the trypomastigotes exit to the cytoplasm, and after a short period of time, they differentiate into amastigotes, and the rupture of this structure is activated by acidic pH generated by the fusion of the lysosomes [18].

To survive the acid medium into the phagolysosome, the trypomastigotes activate trans-sialidases/neuraminidase, and these enzymes transfer sialic acid from the sialyl-glycoconjugates in the membrane of the PLM to the β-galactoses of acceptor molecules (GPI-mucins) on the surface of the parasite [19, 20]. More specifically, the membrane of the phagolysosome is covered on the inner side with two important proteins known as lysosomes-associated membrane proteins (LAMP1 Y LAMP2), and these proteins are highly sialylated [21, 22]. The terminal sialylation of these proteins contributes to maintaining parasitophorous vacuole membrane integrity, whereby the removal of sialic acid residues sensitizes the membrane to the

action of a transmembrane protein forming pore secreted by the parasite (Tc-TOX) [23, 24]. When the phagolysosome is broken, the trypomastigotes are released into the cytoplasm.

2.2 Evasion of the oxidative response

Previously, it was mentioned that *T. cruzi* not only invades phagocytic cells via classic phagocytosis but also can actively invade mammalian nonprofessional phagocytic cells by induced phagocytosis [25]. The main host cells targeted by *T. cruzi* are resident macrophages at the site of infection and dendritic cells, both of which play a main role in the response of the immune system as they are specialized antigen presenting cells [11].

Macrophages have two roles; on the one hand, they are important effector cells for the control and killing of the intracellular form of the parasite by oxidative and nonoxidative mechanism. On the other hand, macrophages may also serve as long-term host cells that facilitate the replication and survival of the pathogens [26]. Macrophage membrane-associated NADPH oxidase is activated during phagocytosis of trypomastigotes, resulting in a stable superoxide radical anion ($O_2^{\cdot -}$) which can be transformed to H_2O_2 by superoxide dismutase (SOD) [6, 27, 28].

IFN-γ and TNF synthesized during *T. cruzi* acute infection stimulate infected macrophages to produce high amounts of nitric oxide ($^{\cdot}NO$) derived by the enzymatic activity of inducible nitric oxide synthase (iNOS). The nitric oxide generated reacts with $O_2^{\cdot -}$ and produces peroxynitrite ($ONOO^-$), a potent oxidant and cytotoxic effector molecule against *T. cruzi* [29–33]. *Trypanosoma cruzi* has five antioxidant enzymes such as peroxidases and four iron superoxide dismutases (FeSODs) that are located at different subcellular compartments of the parasite, which reduce equivalents from NADPH and defend the parasite against host oxidative stress of the host (**Tables 1** and **2**) [27, 34].

2.3 Complement evasion

Trypomastigotes after being released in the bloodstream become a targeted of the preexisting soluble factors that potentially recognize and destroy them by different effectors [11]. Serum components, such as the complement system, consist of 35 or more soluble protein and cell surface receptors/regulators that interact with pathogen structures and activate a cascade of proteases that eliminate invading parasites, and this system comprises the first line of defense [16, 43–45].

Peroxidase	Subcellular location	Function
Tryparedoxin peroxidase (TcCPX)	Cytosol	Detoxify $ONOO^-$, H_2O_2 and small-chain organic hydroperoxides [34–37]
Tryparedoxin peroxidase (TcMPX)	Mitochondria	
Glutathione peroxidase I (TcGPXI)	Cytosol glycosome	Hydroperoxidases [38, 39]
Glutathione peroxidase II (TcGPXII)	Endoplasmic reticulum	Lipid hydroperoxidases [34, 38, 39]
Ascorbate-dependent heme peroxidase (TcAPX)	Endoplasmic reticulum	Resistance H_2O_2 [34, 40]

Table 1.
Peroxidases of Trypanosoma cruzi.

Iron superoxide dismutase (FeSODs)	Subcellular location	Specificity
TcSODB1	Cytosol	Detoxify $O_2^{\cdot -}$ and hence the formation of $ONOO^-$ [41, 42]
TcSODB1-2	Glycosome	
TcSODA	Mitochondria	
TcSODB	Mitochondria	

Table 2.
Iron superoxide dismutase of Trypanosoma cruzi.

Briefly, the action of the classical pathway is mediated by the antibodies binding to pathogen antigens, then the antibodies interact with the complement C1 protein, and it cleaves C2 and C4 to generate C2a and C4b, which join to the pathogen surface and form the C3 convertase C4b2a [16, 46]. Lectin complement pathway is the first to recognize *T. cruzi*; this is active by the binding of ficolins to the carbohydrates on the parasite surface and also mannan-binding lectins (MBLs) to the mannan on the surface of the parasite; then cysteine proteases bound to these molecules and cleave C2 and C4 and; this event also generates the C3 convertase C4b2a [47–49]. Finally, the alternative pathway is activated by the spontaneously hydrolyzed C3 or C3b originating from the other complement pathways; C3b interacts with factor B, and the latter in then cut into Bb by factor D, forming the C3 convertase C3bBb [50]. The three pathways differ in the initial steps of activation, but all three converge to produce a C3 convertase and then a C5 convertase, allowing the formation of the membrane attack complex (MAC) which is responsible for membrane lysis and subsequent pathogen elimination [16].

Trypanosoma cruzi trypomastigotes are normally resistant to the lytic effects of complement from vertebrate hosts susceptible to infection. This resistance of the trypomastigotes to direct lysis by the complement system facilitates parasite survival and infectivity but during the course of chronic infections; however, the vertebrate hosts produce antibodies that render the trypomastigotes sensitive to lysis, primarily via the alternative complement cascade and amplified by the classical pathway, and this resistance is a developmentally regulated phenomenon because the parasite is susceptible to complement lysis when it is in epimastigote form [51].

Complement activity present in normal human serum has been reported to lyse circulating forms of *T. cruzi* following activation by specific host antibodies bound to the surface of the parasites [52]. Incubation of trypomastigotes with human complement does not lead to lysis when the trypomastigotes do not have immunoglobulins on their surfaces. However, if such trypomastigotes are preincubates with sera obtained from chronically infected hosts, IgG immunoglobulins bind to their surface, and the parasites become sensitive to lysis by fresh human sera as a source of C5, thus lysis required antibodies and complement in mammals [53, 54], and on the other hand, birds, amphibians, and reptiles are naturally refractory to *T. cruzi* infection, due to complement-mediated lysis and macrophage-induced killing of the parasites [52, 55, 56]. Sera of the birds is capable of lysing infective forms of the parasite which as mentioned above are resistant to lysis by human serum, and this normal lytic activity of chicken serum seems to be independent of antibody, because it has been observed that the lytic activity of serum in vitro was not impaired in chickens that had been immunosuppressed by four different procedures, and the lysis occurs even in the absence of antibodies (e.g., bursectomized chickens are refractory to *T. cruzi* infections) in which chicken complement is probably activated through the alternative pathway [52, 57–59]. The details of the mechanisms of resistance of birds to *T. cruzi* infection need further investigation,

since it could improve our understanding of the host-parasite interactions and favor the establishment of the innate mechanism of resistance and/or susceptibility of vertebrate hosts to *T. cruzi*.

2.3.1 Molecules of Trypanosoma cruzi that interfere with complement pathways

T. cruzi relies a variety of molecules that block or disrupt different steps of the complement pathways to evade complement lysis [44, 60, 61]. Below are some molecules of *T. cruzi* that it uses to get rid the action of the complement pathways.

a. Calreticulin (TcCRT): This protein is expressed in trypomastigotes, and it is mainly located in the endoplasmic reticulum (RE), but it has also been found in the Golgi, reservosomes, flagellar pocket, cell surface, cytosol, nucleus, and kinetoplast. After the infection, calreticulin moves from RE to the emerging area of the flagellum on the plasma membrane surface [62–64]. Calreticulin is a 45 kDa calcium-binding protein that binds to host mannose-binding lectin collagenous tails, preventing their interaction with parasite mannan and also interacts directly with L-ficolin preventing C4 conversion to C4b. TcCRT also interacts with C1q collagen-like domain, and therefore TcCRT inhibits both the classical and lectin pathway activation [65–67].

b. *Trypanosoma cruzi* complement regulatory protein (TcCRP) Gp160: The protein TcCRP, also called Gp160, which is GPI-anchored on the surface of trypomastigotes, can bind to C3b and C4b, thus inhibiting the formation of the classical and alternative complement C3 convertase [10, 68, 69].

c. *Trypanosoma cruzi* complement C2 receptor inhibition trispanning (TcCRIT): TcCRIT is a 32 kDa transmembrane protein mainly expressed in trypomastigotes. TcCRIT has amino acid sequence homology with the C4 beta-chain, the binding site of C2. Thus, it blocks C2 cleavage by C1s or MASP-2 into C2a and prevents C3 convertase formation, thus regulating the activation of the lectin and classical complement pathway [70–72].

d. Trypomastigote decay-accelerating factor (T-DAF): T-DAF is an 87–93 kDa glycoprotein expressed on the surface of metacyclic, bloodstream, and tissue-culture-derived trypomastigotes of *T. cruzi*. T-DAF mimics the activity of the complement regulatory protein DAF and regulates the activation of the alternative, classical, and probably the lectins pathways of the complement. In summary, T-DAF activity either accelerates the dissociation or assembly efficiency of C3 convertases [73, 74].

e. Glycoprotein 58/68: Gp58/68 is a glycoprotein expressed on the surface or released by trypomastigotes. This protein is part of a fibronectin/collagen receptor of *T. cruzi*, and for this reason, it plays an important role in the interaction of *T. cruzi* with mammalian cells. Gp58/68 allows the parasite to evade alternative pathway complement activation because it is able to inhibit the formation of cell-bound C3 convertase (decay-accelerating activity) by preventing the initial association of FB to surface fixed C3b [44, 75, 76].

On the other hand, it has been reported that *T. cruzi* metacyclic trypomastigote induces the release of membrane-derived vesicles (microvesicles) from host cells, such as lymphocytes, monocytes, and macrophages, in a Ca^{2+} dependent process. These vesicles inhibit the classical and lectin pathways of

the complement by binding to C3 convertase C4b2a on the *T. cruzi* surface and inhibit its catalytic activity [44, 77].

3. Immunoregulatory effects by *Trypanosoma cruzi*

In the early stages of *T. cruzi* invasion, the host's resistance to the infection is mediated by innate immunity, which acts as the first immunological barrier. Macrophages, NK cells, and dendritic cells are the cells from the innate immune system and produce cytokines (IL-12, TNF-α, and IFN-γ) and effector molecules that control parasite replication. Dendritic cells are the connecting cells between the innate and acquired immunity, generating cytokines (IL-12) necessary for the differentiation and clonal expansion of T helper 1 (Th1) CD4+ as well as CD8+ T cells and plasma B cells. CD4+ Th1 or CD8+ T cells synthesize IFN-γ, which activates effector mechanisms in macrophages to eliminate both amastigotes and phagocytosed trypomastigotes, while cytotoxic activity by B cells lyse the extracellular trypomastigote form or facilitate the phagocytosis of parasites opsonized with IgG [3, 78, 79]. However, *T. cruzi* uses different mechanisms to modulate this action of the host immune response and then the parasite spreads to many tissues during the acute phase to finally reach the chronic stage of the Chagas disease [16]. In the acute phase, *T. cruzi* infection can induce immunosuppression [80], involving the decrease and clonal deletion of the T cells, together with strong polyclonal B cell stimulation, which ultimately restricts the development of antigen-specific lymphocytes [78, 81].

In the early steps of a primary *T. cruzi* infection, there is no activation of various host defense mechanisms, leading to silent entry [82]. There are three events that could contribute to this silent entry: the relatively slow kinetics of *T. cruzi* intracellular cycle, the parasite escape from the phagolysosome (which was previously explained), and the immunoregulatory response mediated by toll-like receptor (TLR) activation in dendritic cells [83]. A TLR-dependent activation of dendritic cells is required to induce their maturation and migration to regional lymph nodes and to activate naïve T cells [84].

Toll-like receptors (TLRs), members of a family of pattern recognition receptors, are responsible for the recognition of pathogens because they can distinguish between host molecules and molecules of the pathogens referred to as pathogen-associated molecular patterns (PAMPs). These receptors are expressed on the cell surface or in the lumen of intracellular vesicles (endosomes or lysosomes) of the antigen presenting cells (macrophages and dendritic cells), cells of the adaptive immunity (T y B lymphocytes), and nonimmune cells (epithelial and endothelial cells and fibroblasts) [84–88]. Twelve TLRs family members have been identified in mice and 10 in humans. The TLRs 1–9 are conserved in both species, whereas TLRs 11–13 is only expressed in mice and TLR10 in humans [87, 89]. TLR4 and TLR9 are homodimers, whereas TLR2 and TLR6 form heterodimers [90, 91]. Activation of the TLRs induces production of proinflammatory cytokines (MyD88-dependent signaling cascade, except TLR3) and chemokines, and therefore, these receptors are important because that activate innate immunity and molding the subsequent acquired immune responses [3, 92–94].

Infection with *T. cruzi* activates the synthesis of several inflammatory genes by different TLR pathways [87]. The parasite has molecules that can activate TLRs such as the surface molecules, glycoinositolphospholipids (GIPLs), and anchor glycoproteins and polysaccharides that contain identical GPI structures [95]. Glycosylphosphatidylinositol anchors derived from mucin-like glycoproteins (GPI-mucin) are TLR2/6 activators in dendritic cells and macrophages, and this leads to the production of the TNF-α, IL-12, and NO. On the other hand, GIPLs activate TLR4 of

macrophages to increase IL-2 production. The IL-2 increase activates NK cells and B cells to secrete immunoglobulins during infection [3, 96]. *T. cruzi* genomic DNA (CpG DNA motifs) active TLR9 and TLR7 is involved in parasite RNA recognition, and this activation results in the production of IL-12 [97, 98]. CpG DNA motifs are concentrated in genomic regions encoding large gene families of surface proteins, such as mucins, trans-sialidases, and mucin-associated surface proteins (MASPs) [98]. These genes are involved in parasite immune evasion mechanisms [4].

TLR7 and TLR9 are expressed in the membrane of phagolysosome, and they are active when the parasite is lysed, but as mentioned above, parasite escapes from the lysosome, thus the activation of these receptors is reduced. On the other hand, TLR2 appeared to act as immunoregulator in the early stage of infection [99].

T. cruzi in addition to evade its destruction also has the capacity to modulate the pattern of secreted cytokines, and examples of this are *T. cruzi* membrane GPI-anchored mucin (AgC10), which can bind to the macrophage surface and induce the secretion of IL-1B but not of IL-12 or TNF-α, which are essential in a protective response. Inhibition of TNF-α and IL-12 by *T. cruzi* could be involved in the evasion of the immune response by this parasite [12, 100]. The parasite also promotes the production of IL-10 and TGF-β in infected macrophages, which inhibit the induction and effects of IL-12. A cysteine protease (cruzain) prevents macrophage activation by blocking the NF-κB P65 pathway and downregulated the expression of the proinflammatory cytokine, IL-12. Therefore, the infection of the macrophages favors the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β that affect the development of protective immune response and favors the spread of infection [101, 102].

Trypanosoma cruzi induces the production of both Th1 and Th2 cytokines in infected individuals, and high expression levels have been reported for Th1 cytokines IFN-γ and IL-2, as well as for Th2 cytokines IL-4 and IL-10 [103]. The ability of *T. cruzi* to infect a host and to survive and develop and cause Chagas´ disease depends on a complex balance Th1 and Th2 cytokine production, as the display antagonistic effects, the former being protective for the host and the latter for the parasite [11].

In addition to the TLR's roles in the modulation of innate immunity, TLRs participate in the induction of the adaptive immune response [89]. This happens mainly by their action on antigen-presenting cells (APCs), either by promoting cross-presentation for CD8+ T-cell activation or by increasing the levels of costimulatory molecules and by stimulating the secretion of lineage-specific cytokines such as IL-12, IL-16, IL-1β, IL-18, and IL-23 by APCs and thus promoting Th1 and Th17 differentiation [86].

More specifically, the activation of dendritic cells by *T. cruzi* PAMPs (DNA and RNA) will lead to their maturation and production of IL-12, favoring the differentiation of Th cell precursors toward the Th1 phenotype and IFN-γ production [98, 104].

4. Polyclonal activation of B cells

During early stages of the *T. cruzi* infection, B cells are fundamental to trigger T-cell functions related to the Th1 pathway that favors the control of parasite growth [105]. B cells are known to play a key role in the humoral adaptive immune response by producing and secreting antibodies [106]. The majority B cells activated by *T. cruzi* infection are not specific for parasite antigens [107]. The infection with *T. cruzi* induces polyclonal B cell activation and hypergammaglobulinemia based on parasite-derived B cell mitogen. These antibodies are parasite-specific and bind to the trypomastigote surface interfering with the binding of IgG inhibitory antibodies and consequently preventing the elimination of the parasite [12, 108].

4.1 Factors causing antibody deficiency

4.1.1 Antigenic variability

T. cruzi expresses a variety of antigens on its surface such as mucins, trans-sialidases, and MASPs, all of them are encoded by highly polymorphic multigene families. This high variety of molecules with coordinate expression delays the activation of specific B cells and also consequently delays the production and maturation of high-affinity antibodies with neutralizing capacity and the priming of effective T-CD8+ cells, and this mechanism is known as a smoke screen [16, 19, 109, 110]. Another important point to mention is that the presence of a broad range of antigenic motifs may also be a mechanism to drive the antibody response away from catalytic sites of key parasite surface proteins which causes a weak antibody response [111].

4.1.2 Reduction of immature B cells in the bone marrow

Immature B cells are reduced because of an increase in the rate of apoptosis. Apoptosis is a common process caused by pathogens on host cells, and it probably happens as a consequence of the host immune response or by a direct effect of the pathogen [112]. Apoptosis of lymphocytes is necessary to preserve a healthy and balanced immune system, but if this occurs prior to pathogen elimination, it could reduce the effectiveness of the effector mechanisms [113, 114]. This effect may be more important if apoptosis happens in the early stages of lymphocyte development [115]. Thus, the effect of the infection with *T. cruzi* is the induction of a marked loss of immature B cells in the bone marrow and also compromises recently emigrated B cells in the periphery [116]. It has been shown that the apoptosis caused by *T. cruzi* infection occurs in addition to Fas/FasL pathway by the participation of CD11b+ myeloid cells that secrete a product of the cyclooxygenase pathway, and this event depletes immature B cells in the bone marrow [116, 117]. It is possible that the parasite takes advantage of the host cell apoptosis; moreover, it has been shown that cell apoptosis may have an additional negative effect because the elimination of apoptotic bodies by *T. cruzi* infected macrophages promotes parasite replication, favoring the chronic establishment of the parasite in the host [118], so the induction of the host cell apoptosis is another mechanisms to evade the immune response.

4.1.3 Polyclonal activation of non-specific B cells

Polyclonal activation of B cells that normally contributes to the generation of specific antibodies for conserved structures presents in pathogens but in the case of *T. cruzi* infection can be a mechanism by which parasite-specific antibodies are reduced and irrelevant antibody are increased [115]. Presentation of multiple-related sequences on the surface of the trypomastigotes or extracellular amastigotes could alter the B-cell response by inducing anergy in specific CD4+ lymphocytes and/or reduction of affinity of antibodies [109, 119]. Another consequence of polyclonal activation can be the generation of antibodies specific of the self-and/or non-related antigens [107]. Some parasite molecules such as glycoinositol-phospholipids (GIPLs) generate hypergammaglobulinemia [16, 108, 120]. In the acute infection, expansion of total antibodies is slow and starts with IgM and IgA, followed by IgG (IgG1, IgG2a, IgG2b, and IgG3) with specificities not related to *T. cruzi* antigens, while the humoral response in the chronic stage shows preferential IgG2a production [121–123]. In addition to the high variability of parasite surface antigens, parasite-derived B cell mitogens also cause polyclonal B cell activation

and hypergammaglobulinemia which results in a delayed parasite-specific antibody response [108, 124, 125]. Glutamate dehydrogenase (TcGDH) [126], proline racemase [127], and trans-sialidase (TcTS) [128] are among the parasitic proteins identifying as polyclonal B cell mitogens [129].

5. Immunomodulation of T cell

Expression of identical antigenic variants on the surface of the majority of parasite population is the characteristic of the antigenic variation, with only a small subgroup expressing different variants [130, 131].

Trypanosoma cruzi releases antigen in the intracellular host cell environment, and they are accessible for presentation by the major histocompatibility complex class I [3]. The presentation of the antigens promotes the priming of a robust but delayes *T. cruzi*-specific CD8+ T-cell responses. This event is evident 5–6 days postinfection, after the first round of intracellular replication of the parasite [110]. The early immunosuppression of the CD8+ T-cell response may be associated with the density of parasites in the cytosol, because during the initial infection, previous to the first cycle of replication, low concentration of antigens is produced by amastigotes, and on the other hand, because a large repertoire of highly polymorphic and immunogenic surface protein that are coexpressed by the parasite [110, 132–134].

The parasite has developed strategies to interfere with antigen presentation, and this strategy is related with hyperpolarization of the presented antigen repertoire, which means that the repertory of CD8+ T-cells is dramatically restricted, and this phenomenon is known as immunodominance and prevents complete pathogen elimination by host cells by antigen-specific cytotoxic T-cell response [135, 136].

GPI-anchored surface proteins particularly trans-sialidase proteins are among the major known CD8+ T cell immunodominant targets in *T. cruzi* infection [110, 137], due to high expression in the infective forms and repetitive/antigenic content [137, 138].

Trans-sialidases are a polymorphic protein subfamily of the GPI-mucin superfamily and are expressed on the parasite surface and released into the extracellular medium. These proteins are coded by a multi-copy gene family, comprised by more than 1400 genes [19, 139, 140]. These enzymes remove and efficiently transfer sialic acid from host-derived glycoconjugates to parasite mucin-like glycoproteins, which are the most abundant surface components of infective forms [141]. TcTS has several potential immunogenic candidates that can generate an unfocused response. The trans-sialidase immune response is focused on a relatively small number of epitopes encoded by multiple genes, and this protein is a prominent target of *T. cruzi*-specific CD8+ T cells [19, 110, 142].

Immunodominance may occur by different mechanisms including the formation of stable MHC-I peptide complexes on the surface of APCs, higher amounts or higher affinity T cell precursors or competition of T cells for APCs [135]. CD8+ T cells that recognize TS-derived epitopes remain highly competent throughout the chronic infection, despite persistent antigen exposure [137, 143, 144].

The immunodominance of TS-derived epitopes predictably results in the outcompetition of other epitope-specific CD8+ T cell populations. However, the significance of the tight focusing of the CD8+ T cell response on only a few vast arrays of possible parasite-derived epitopes is not known [138]. The immune response targets the parasites expressing the common TcTS variants, whereas failing to identify parasites that express rare variants of the antigen [145]; thus the immunodominance seems to be an important way by which the parasite escapes from the effector mechanisms of the CD8+ T cells and persists until the chronic stage.

6. Conclusions

Trypanosoma cruzi is a parasite that has a complex life cycle that goes from the passage through an invertebrate host to different mammals displaying different developmental stages during its life cycle. Furthermore, *T. cruzi* includes several lineages that have distinct morphology, infectivity, virulence, and pathogenicity [146]. The disease reaches the symptomatic chronic stage in only 30% of patients who acquire the infection, whereas 70% shown no clinical symptoms [147]. The above characteristics suggest that during infection may occur a complex interaction between the host and the parasite, and although for more than 100 years, since the Chagas disease was described, the immunological mechanisms of resistance or susceptibility to the parasite have been studied, and it has not been possible to determine exactly which are those that effectively can eliminate the parasite. Recently, there is a growing consensus that the protective immune response against *T. cruzi* requires the activation of a Th1 immune profile, with the stimulation of CD8+ T cells, but as it is detailed in the present review, the mechanisms of evasion to the immune response by *T. cruzi* are diverse and quite effective. So not withstanding this large amount of information available, it still impossible to predict what will happen in an individual infected with this pathogen. Considering the importance of Chagas disease in the world in which there are an estimated to be around 8–10 million of infected people and that currently there are no vaccines which prevent the parasite infection, it is necessary to look for a better and complete understanding of the mechanisms of immune evasion of *Trypanosoma cruzi*.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication on this chapter.

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