Current understanding of the Trypanosoma cruzi–cardiomyocyte interaction

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INTRODUCTION

Chagas disease, caused by Trypanosoma cruzi infection, has emerged as an important global public health problem due to the many Latin American T. cruzi–infected immigrants in non-endemic countries (Pérez-Molina et al., 2012). Although public health programs in the Southern Cone countries have reduced transmission by 70% (Moncayo and Silveira, 2009), blood and organ transplant transmissions in non-endemic countries (Rassi et al., 2009) and outbreaks of foodborne transmission (Pérez-Molina et al., 2012) have drawn attention to Chagas disease. An estimated 8–15 million individuals in 18 endemic countries in Central and South America are infected, with approximately 30 million people at risk (WHO, 2010; Rassi et al., 2012). Chronic chagasic cardiomyopathy, the most relevant clinical manifestation, is the leading cause of death from heart failure in endemic countries, and accounts for a significant burden of ischemic and inflammatory heart disease in the USA and Europe due to “globalization” of Chagas disease (Moncayo and Silveira, 2009; Mosolani et al., 2012). In this review, we summarize current knowledge of the biology of the T. cruzi–host cell interaction, high-lighting molecular aspects of T. cruzi–cardiomyocyte interplay, with a focus on early infection events and the effect of intracellular parasite development on the structure and function of the target cell.

CELL RECOGNITION AND INVASION PROCESS

T. cruzi–CARDIOMYOCYTE RECOGNITION

Interplay between parasite and host cell is essential for T. cruzi to successfully adjust to the different microenvironments it occupies in its vertebrate and invertebrate hosts. In the obligatory intracellular phase of its life cycle in the mammalian host, infection is driven by adhesion and internalization events involving a large variety of ligands and/or receptors on the surface of both the parasite and host cell interacting with one another to achieve recognition and invasion. Several different surface molecules in the cardiomyocyte have been implicated in adhesion and internalization by the parasite (Figure 1). Carbohydrate residues of membrane glycoconjugates in cardiomyocytes, including galactosyl, mannosyl, and sialyl residues, participate in T. cruzi cytoadherence (Barbosa and Meirelles, 1992, 1993), while mannose receptors at the surface of cardiomyocytes modulate parasite entry and are down-regulated by T. cruzi infection (Soeiro et al., 1999).

Extracellular matrix (ECM) components are also important in parasite–host cell recognition. Fibronectin, a high molecular weight glycoprotein present at the host cell surface, is recognized by fibronectin receptors of the parasite (Ouassif et al., 1984), which interact with the RGDS (Arg-Gly-Asp-Ser) sequence of fibronectin and mediate parasite entry (Calvet et al., 2004). Internalization with RGDS peptide induced protection in an experimental murine model of acute T. cruzi infection (Ouassif et al., 1986). Heparan sulfate proteoglycans (HSPG), another class of ECM component widely distributed in mammalian tissues, are also involved in T. cruzi attachment and invasion (Ortega-Barria and Pereira, 1991; Calvet et al., 2003). Treatment of trypanastigotes and amastigotes, the infective forms of T. cruzi, or cardiomyocytes with soluble heparan sulfate (HS) and heparinase II, respectively, efficiently inhibited parasite invasion (Calvet et al., 2003; Oliveira Jr. et al., 2008; Bambino-Medeiros et al., 2011). The binding of T. cruzi to HSPG involves the recognition of the N-acetylated/N-sulfated domain of the HS chain by heparin-binding proteins (HBPs) present at the surface of the parasite (Oliveira Jr. et al., 2008). Although T. cruzi HBPs are capable of binding HS and chondroitin sulfate (CS), only the HS–HBPs interaction triggers...
Calvet et al. T. cruzi–cardiomyocyte interaction

parasite invasion in cardiomyocytes (Calvet et al., 2003; Oliveira Jr. et al., 2008), while HS and CS are involved in vector–T. cruzi interactions (Oliveira Jr. et al., 2012).

Lipids also play an important role in T. cruzi–host cell interplay. Membrane rafts, enriched in cholesterol and sphingolipids, appear to participate in the invasion process (Barrias et al., 2007; Fernandes et al., 2007; Priotto et al., 2009). Recently, cholesterol has been demonstrated to modulate invasion of cardiomyocytes by T. cruzi (Hissa et al., 2012). Depletion of cholesterol from cardiac cell membrane induced an 85–90% reduction of parasite invasion by inhibiting parasites' association with lysosomes. Additionally, the low-density lipoprotein receptor, which is up-regulated in
myocardium of infected mice, also coordinates parasite entry and fusion of the parasitophorous vacuole (PV) with lysosomes (Nagajyothi et al., 2011). 

MECHANISMS OF T. cruzi INVASION

The large number of molecules involved in recognition of target cells by T. cruzi increases the parasite’s capacity to explore multiple strategies to ensure propagation in the mammalian host. A number of different mechanisms of T. cruzi invasion have been described, involving distinct host cell type, parasite genotype, and developmental stage. At least five models of invasion have been elucidated. (i) An actin-dependent mechanism leads to the rearrangement of microfilaments, inducing the host cell membrane to enclose the parasite (Barbosa and Meirelles, 1995; Procópio et al., 1999; Rosestolato et al., 2002; Ferreira et al., 2006). (ii) Lysosome-dependent mechanisms, involving an increase of transient cytosolic Ca2+ levels induced by the parasite, generate cortical actin depolymerization and lysosome recruitment to the parasite binding site (Rodriguez et al., 1999; Hissa et al., 2012). (iii) Activated signaling pathways also participate, including tyrosine kinase receptors (TαK and TβK), de Melo-Lougo and Pereira-Ferrin, 2007; Weinkauf et al., 2011) and phosphatidylinositol 3-kinase (PI3-K; Todorov et al., 2000; Chuenkova et al., 2001; Wolkowsky et al., 2001; Vietsra et al., 2002; Woolsley et al., 2003), bradykinin receptors (Scharfeinstein et al., 2000; Todorov et al., 2003), and transforming growth factor β (TGF-β; Ming et al., 1995; Waghabi et al., 2007). (iv) More recently, sphingomyelinasemediated plasma membrane repair has been proposed to participate in this process (Fernandes et al., 2011; Fernandes and Andrews, 2012), as has (v) the host cell autophagy pathway (Romano et al., 2009, 2012). Finally, the combination of different mechanisms has been described as coordinating the T. cruzi invasion process (Butler and Tyler, 2012).

Elevation of transient intracellular Ca2+ levels, an invasion-related effect provoked by T. cruzi binding to the host cell membrane (Figure 1), has also been demonstrated in cardiac cells (Barr et al., 1996; Garzoni et al., 2003). The increase of cytosolic Ca2+ has been reported to be brought about in two different ways: (i) by sarcoplasmic reticulum stores, which are sensitive to leupeptin, suggesting a cortical actin depolymerization and lysosome-dependent mechanism of invasion (Barr et al., 1996), and by (ii) extracellular Ca2+ influx through membrane Ca2+ channels, which are insensitive to leupeptin (Garzoni et al., 2003).

Recently, it has been suggested that Ca2+ influx may also occur as a result of lesions on the plasma membrane, suggesting that the membrane repair pathway frequently observed in muscle cells may also be involved in cardiac cell invasion by T. cruzi (Fernandes and Andrews, 2012).

Transforming growth factor β, a multifunctional family of proteins that controls a range of biological events in most cells, including proliferation and cellular differentiation (Moustakas et al., 2002), has also been shown to participate in T. cruzi invasion of cardiomyocytes (Waghabi et al., 2001). T. cruzi directly activates latent TGF-β and modulates TGF-β signaling (Waghabi et al., 2005). Inhibition of T. cruzi infection in cardiomyocytes was achieved by blockade of the TGF-β receptor type 1 (TGFβR1)/Smad2 signaling pathway by SB-431542, a TGF-β signaling inhibitor (Waghabi et al., 2007). Besides impairment of parasite invasion, the inhibitor treatment also reduced T. cruzi intracellular multiplication and differentiation. Recently, the therapeutic effectiveness of GW788388, an oral inhibitor of TGF-β signaling, has been demonstrated experimentally in acute phase T. cruzi infection, leading to a reduction of parasitemia and mortality, and also preventing cardiac fibrosis (de Oliveira et al., 2012).

Bradykinin receptors (B1R/B2R) have also been reported to be involved in cardiomyocyte infection by T. cruzi (Todorov et al., 2003). This mechanism of invasion is regulated by cooperation between HSPG, kininogen, and cruzipain-1, the major cysteine protease isofrom of T. cruzi, resulting in the release of kinin. Invasion through the kinin transduction pathway, activated by G protein-coupled bradykinin receptors, induces intracellular Ca2+ mobilization from stores in the endoplasmic reticulum (Scharfeinstein et al., 2000). The B2R agonist captopril stimulates the invasion of T. cruzi while B1R and B2R antagonists, present inhibitory effects on cardiomyocytes, suggesting that these receptors interdependently drive invasion of the parasite (Todorov et al., 2003).

As evidenced in other non-professional phagocytic cells (Rosestolato et al., 2002; Ferreira et al., 2006), T. cruzi entry is also mediated by an endocytic process in cardiac muscle. A protrusion of cardiomyocyte plasma membrane, orchestrated by cytoskeleton rearrangement, is observed during T. cruzi–cardiomyocyte interaction. A dense actin-based membrane skeleton meshwork projects from the sarcoldemna and encloses the entering parasite (Barbosa and Meirelles, 1995). This event was drastically inhibited (75%) when cardiac cells were treated with cytochalasin D, an agent that depolymerizes actin filaments, prior to T. cruzi infection; no parasite invasion was observed in fixed cardiomyocytes (Barbosa and Meirelles, 1995). Once inside the cells, the parasite is located within a PV that lacks Ca2+-Mg2+-ATPase, adenylyl cyclase, and anionic sites (Meirelles et al., 1986) but has carbohydrate residues such as N-acetylgalactosamine and N-acetylgalactosamine (Barbosa and Meirelles, 1992, 1993). Ultrastructural cytochemistry for the lysosomal enzymes aryl sulfatase and acid phosphatase has revealed the fusion of the parasite-containing vacuole with lysosomes (Meirelles et al., 1987). The acidification of the PV by lysosomal fusion, leading to the activation of TC-TOX and disruption of the PV membrane (Andrews et al., 1990; Hall, 1993), is a prerequisite for the trypomastigote to exit the phagosome, also allowing the parasite to be retained intracellularly and complete its life cycle (An夺得ra and Andrews, 2004, 2005; Mott and Burleigh, 2008).

EFFECT OF T. cruzi INFECTION IN CARDIOMYOCYTE PHYSIOLOGY

During the T. cruzi–cardiomyocyte interaction the parasite gains control of overall host cell gene expression, including expression of genes related to immune response, inflammation, cytoskeletal organization, cell-cell and cell-matrix interactions, apoptosis, cell cycle, and oxidative stress (Goldenberg et al., 2009; Manque et al., 2011). The intense trypanocidal immune response generated in cardiomyocytes in response to infection by T. cruzi results in the production of cytokines, chemokines, and nitric oxide that, while essential elements of the defensive reaction in cardiac tissue...
(Machado et al., 2008, 2009; Manque et al., 2011), can also result in cardiaco hypertension (Petersen and Burleigh, 2003; Waghahi et al., 2009). Several studies report that *T. cruzi* infection stimulates production of nitric oxide synthase 2, matrix metalloproteinase-2 (MMP-2) and MMP-9 in cardiomyocytes, as well as interleukin-6 (IL-6), tumor necrosis factor-alpha and TGF-β (Petersen and Burleigh, 2003; Petersen et al., 2003; Waghahi et al., 2009; Gutierrez et al., 2008; Waghahi et al., 2009; Nogueira de Melo et al., 2010). Peroxisome proliferator-activated receptor γ is also implicated in regulating the inflammatory process (Havrassian et al., 2011). Moreover, IL-1β-mediated development of cardiomyocyte hypertrophy is orchestrated by Toll-like receptor 2 (Petersen et al., 2005). Proinflammatory cytokines also modulate production of mitochondrial reactive oxygen species, impairing the efficiency of the respiratory chain (Gupta et al., 2009). Mitochondrial disturbance has been identified as an important effect of chagasic cardiomyopathy (Gang et al., 2003; Baez et al., 2011). Inflammatory mediators have also been reported to regulate Rab expression (Stein et al., 2003) thereby interfering with host cell trafficking. Down-regulation of Rab GTPase proteins, including the effector molecule of Rab5 (REEA1), Rab6, and Rab11, has been demonstrated in *T. cruzi*-infected cardiomyocytes, and it has been proposed that a delayed endocytic pathway may favor microbical activity and increase antigen processing (Batista et al., 2006).

Changes in cytoskeletal proteins have also been shown during parasite intracellular development (Figures 1 and 2). The complex cytoskeleton organization of cardiomyocytes involved in the contraction-relaxation process of the heart is affected by *T. cruzi* infection (Pereira et al., 1993; Tanwaki et al., 2006). Breakdown of myofilaments has been seen in areas of amastigote nests (Pereira et al., 1993; Tanwaki et al., 2006) and disturbance of intermediate filaments (desmin) and microtubules was also induced by parasite proliferation (Pereira et al., 1993). Interestingly, the actin isoform mRNA expression of heart-specific α-actin and β-actin mRNA is altered during the parasite intracellular cycle (Pereira et al., 2000). Down-regulation of α-actin and mRNA concomitant with up-regulation of β-actin mRNA suggested the reactivation of non-differentiated cell program. Also within the context of cytoskeletal changes, actin-binding proteins have been demonstrated to be altered in *T. cruzi*-infected cardiomyocytes. Alpha-actinin, an F-actin cross-linker protein that anchors actin to the Z line, and costanines, repeating adhesion structures consisting of vinculin involved in the lateral transmission of contractility force to the sarcolemma, are disrupted and down-regulated in *T. cruzi*-infected cells, reducing force and strength transduction (Melo et al., 2004, 2006). These cytoskeletal disorders are accompanied by deregulation of Ca2+ influx, affecting cardiac cell contractility (Tanwaki et al., 2006). One striking feature of trypanocidal drugs is their effect on the recovery of cardiomyocyte cytoskeleton (Garzoni et al., 2004; Simon et al., 2006; silica et al., 2011a; Adesse et al., 2011a). Posaconazole, an ergosterol biosynthesis inhibitor, and amiodarona, an anti-arrhythmic drug, also restored the recovery of myofilaments (Garzoni et al., 2004; Adesse et al., 2011a) and may represent interesting alternatives for Chagas therapy.

In addition to disruption of the cytoskeletal architecture by the parasite, cell-cell adhesion (adherens junctions) and intercellular communication (gap junctions), which play important physiological roles in cardiac tissue, are also been disrupted by *T. cruzi* infection (Adesse et al., 2008, 2011b; Melo et al., 2008). Alteration in spatial distribution and down-regulation of the adherence junction proteins N-cadherin and β-catenin in *T. cruzi*-infected cardiomyocytes (Melo et al., 2008) may interfere with tissue integrity and perturb the function of the cardiac conduction system, as has been proposed to be the case in arrhythmogenic cardiomyopathies (Mezzano and Sheikh, 2012). Additionally, electrical conduction disturbance, frequently seen in both acute and chronic phases of Chagas disease, seems to be related to altered gap junction (connexin-43) coupling of cardiomyocytes induced by *T. cruzi* (de Carvalho et al., 1992, 1994; Adesse et al., 2008, 2011b). Connexin-43 dysregulation has also been attributed to increased levels of TGF-β (Waghahi et al., 2009). Following treatment of *T. cruzi*-infected cardiomyocyte cultures with amiodarone and SB-431542 causes reversal of the disorganization of gap junctions and return to their normal distribution (Waghahi et al., 2009; Adesse et al., 2011a), making these compounds potential therapeutic candidates for treatment of Chagas disease.

Besides their involvement in the early steps of *T. cruzi* cardiomyocyte recognition, ECM components also present a striking role in chagasic cardiomyopathy pathogenesis since their accumulation leads to fibrosis, disposing patients to heart failure ventricular arrhythmias (Rassi et al., 2010, 2012). In experimental systems, ECM accumulation begins during the late acute phase of infection (Andrade et al., 1989; Calvet et al., 2004), concomitantly with the onset of inflammatory infiltrates, indicating that the process of fibrogenesis is triggered in the early stages of *T. cruzi* infection. A general increase in ECM transcripts and expression was detected by microarray analysis in acute infection (Garg et al., 2003). Cardiac hypertrophy and ECM remodeling were also seen in a *T. cruzi*-infected 3D cardiomyocyte model (Garzoni et al., 2008; Figure 2). Surprisingly, reduction of ECM in *T. cruzi*-infected cardiomyocytes was detected by silver staining in acute infection in mice (Factor et al., 1993). Additionally, *T. cruzi*-mediated down-regulated ECM gene expression in cardiomyocyte cultures (Goldenberg et al., 2009; Manque et al., 2011) and a reduction of ECM in the synthesis and spatial distribution of fibronectin were detected in heavily infected cardiomyocytes (Calvet et al., 2004; Figure 2) even after TGF-β stimulation (Calvet et al., 2009), suggesting that despite the general enhancement of ECM in the heart, the cells harboring the parasites display low ECM expression. The anti-fibrogenic effect of *T. cruzi* has also been seen in human dermal fibroblasts, with repression of transcription factors that regulate expression of fibroblast genes involved in wound repair and tissue remodeling, including ctf/gcn2 connective tissue growth factor gene, followed by down-regulation of ECM proteins such as fibronectin and collagen I, suggesting another route of parasite dissemination and infection (Unnikrishnan and Burleigh, 2004; Mott et al., 2011).

Frontiers in Immunology | Microbial Immunology October 2012 | Volume 3 | Article 327 | 4
Another point worth discussing relates to the ability of *T. cruzi* to modulate host cell apoptosis, or programmed cell death, a physiological process of cell replacement to maintain tissue homeostasis (Mondello and Scovassi, 2010). Pathogens can hijack the host cell apoptotic machinery as an offensive strategy to eliminate the host’s immune response (Lamkanfi and Dixit, 2010). Both anti- and pro-apoptotic gene expression are differentially modulated during *T. cruzi*-cardiomyocyte infection, leading to a balance between cell death and survival at different stages of infection (Manque et al., 2011). Induction of apoptosis by *T. cruzi* infection is controversial and seems to be dependent on host cell and parasite genotype (de Souza et al., 2003;
While our knowledge of T. cruzi-host cell interactions has greatly improved, many questions remain open. There are still gaps in our understanding of the molecular interactions involved in cellular recognition and/or signaling pathway in most of the mechanisms of invasion. What are the critical links between these processes? And little is still known about the cooperative role played by the host cell in parasite intracellular growth and differentiation. These questions demand deeper investigation.

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Furthermore, the intracellular parasites themselves also undergo apoptosis, hinting at a host attempt to control parasite burden (de Souza et al., 2003, 2010). Interestingly, it has been shown that α2-macroglobulin, a plasma protein inhibitor, regulates apoptosis in T. cruzi-infected cardiomyocytes and macrophages, impairing the cell death process (de Souza et al., 2008). In contrast, an anti-apoptotic effect has also been demonstrated in cardiac cells (Petersen et al., 2006). The prevention of apoptosis appears to be related to NF-κB activation by inhibiting the signaling of caspases, thus avoiding cell death. Thus, avoidance of apoptosis reduces cardiac damage and may be responsible for the persistence of T. cruzi infection.

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