

Review Article

Trypanosoma cruzi Infection and Host Lipid Metabolism

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Trypanosoma cruzi is the causative agent of Chagas disease. Approximately 8 million people are thought to be affected worldwide. Several players in host lipid metabolism have been implicated in \(T.\) cruzi-host interactions in recent research, including macrophages, adipocytes, low density lipoprotein (LDL), low density lipoprotein receptor (LDLR), and high density lipoprotein (HDL). All of these factors are required to maintain host lipid homeostasis and are intricately connected via several metabolic pathways. We reviewed the interaction of \(T.\) cruzi with each of the relevant host components, in order to further understand the roles of host lipid metabolism in \(T.\) cruzi infection. This review sheds light on the potential impact of \(T.\) cruzi infection on the status of host lipid homeostasis.

1. Introduction

Trypanosoma cruzi (\(T.\) cruzi) is the etiological agent of Chagas disease (CD). It is estimated that 8 million people are infected worldwide [1]. In the endemic area of South and Central America, CD is transmitted through contact with the feces of the triatomine bug (the kissing bug). When taking a blood meal from a human, the bug defecates on the skin where \(T.\) cruzi can enter the wound or the mucosal membrane by scratching. Effective vector-control programs have greatly decreased disease transmission in these areas [2, 3]. However, CD was brought to North America, Europe, and Asia by infected individuals, through migration in recent years. In nonendemic area, CD is transmitted through blood transfusion, organ transplantation, and congenital transmission [4].

During the \(T.\) cruzi infection process, the parasite interacts with a wide range of host immunological and metabolic factors. In the past decade, special attention was given to the close relationship between \(T.\) cruzi infection and host lipid metabolism. Several research groups have uncovered the interaction between \(T.\) cruzi and players in the host cholesterol transport and storage system such as macrophage [5–7], adipocytes [8], low density lipoprotein (LDL), and high density lipoprotein (HDL) [9–11]. The molecular landscape and impact of these relationships in \(T.\) cruzi infection and pathogenesis, as well as host immunological responses and inflammatory reactions, will be reviewed in this paper.

There are three stages in CD progression: acute, indeterminate, and chronic. Although the majority of infected individuals are asymptomatic while carrying the life-long infection, some develop severe symptoms upon infection. During the acute stage, infected individuals may develop unspecific symptoms such as fever, nausea, diarrhea, and rash, as well as severe symptoms such as a raised inflammatory lesion at the site of parasite entry (chagoma), unilateral periorbital edema (Romana’s sign), lymphadenopathy, and hepatosplenomegaly [12]. The majority of patients survive the acute stage and enter the prolonged indeterminate stage without overt symptoms of disease, which lasts for life. However, thirty percent of patients develop chronic CD, which includes grave symptoms such as megasophagus, megacolon, and chronic heart disease [13].

\(T.\) cruzi has a complex life cycle and undergoes several transformations during the infection process. The parasite exists mainly in its epimastigote form in the triatomine vector. It transforms into metacyclic trypomastigote in the hind...
gut of the vector which is then defecated to infect human host. Once in the host, the metacyclic form infects a wide range of phagocytic (i.e., monocytes, neutrophils, mast cells, and macrophages) and nonphagocytic cells (i.e., epithelial cells, endothelial cells, fibroblasts, and mesenchymal cells). Upon infection, trypomastigotes transform into intracellular amastigotes and divide by binary fission. Once the division process is complete, amastigotes transform back into blood trypomastigotes which escape the cell to infect neighbouring cells or enter the blood circulation [14].

2. T. cruzi Infection and Macrophage Lipid Bodies

Lipid bodies (LB), also named lipid droplets or adiposomes, are lipid-rich organelles existing in almost all organisms. Unlike other organelles, lipid bodies are uniquely surrounded by a monolayer of phospholipids [15]. The core of the lipid body is rich in neutral lipids, mainly triacylglycerol and sterol esters, as well as other putative membranous structures [15]. Historically, lipid bodies were thought to function in neutral lipid storage and transport; however, recent research has uncovered their importance in regulation of host immune responses. Lipid bodies are involved in the formation of paracrine mediator eicosanoids in cells involved in inflammatory processes [16, 17]. The number of lipid bodies in leukocytes increases in response to a variety of inflammatory conditions, such as atherosclerosis and mycobacterial infections [18, 19].

During acute T. cruzi infection, host macrophages are strongly activated and will inhibit parasite replication [20]. It has been demonstrated that activated murine macrophages are capable of killing the parasites in vitro [5–7]. The macrophage inhibition of parasite replication also correlated positively with increases in the oxidative burst activity [21], tumor necrosis factor-alpha production (TNF-α) [7], and nitric oxide secretion [22]. Macrophages from more resistant C57/BL6 mice strain also secreted higher TNF-α in the in vivo experiments compared to macrophages from the susceptible strains, such as C3H and BALB [23]. In macrophage-depleted T. cruzi infected rats, myocardial parasite load as well as blood parasitemia was significantly increased compared to control [24]. When irradiate rats, which have very low numbers of T and B lymphocytes, were treated with recombinant Interferon-γ (IFN-γ), which classically activates host macrophages, T. cruzi parasite load was significantly reduced [25]. These findings demonstrated the importance of macrophage in the clearance of parasites. However, the roles of macrophage in T. cruzi infection may not be as simple as previously thought. Certain features of macrophage activation may aid in parasite survival in the host. Melo showed that, during acute T. cruzi infection, there is a prominent increase in the number of lipid bodies in macrophages [26]. This increase in lipid body formation correlated with increased parasite load in vivo [27]. It was further demonstrated that the induction of lipid body formation during T. cruzi infection was Toll-like receptor (TLR-2) dependent and was enhanced by the uptake of apoptotic cells, which causes macrophage to interact with α, β3 integrin and activates TGF-β-dependent lipid body formation [27, 28]. Increased levels of TGF-β are known to cause phagocytic cells to become permissive to T. cruzi infection [29, 30] (Figure I(a)).

Increased lipid body formation also led to increased eicosanoid prostaglandin E2 (PGE2) production in inflammatory macrophages. Prostaglandins are known to inhibit TNF-α and IFN-γ production, while enhancing TGF-β secretion [31–33]. Release of prostaglandins reduces macrophage trypanocidal function [31, 34]. Although the impact of PGE2 release in T. cruzi infection is contradictory, the release of PGE2 was correlated in resistance against certain strains of T. cruzi infection [35]. In addition, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX) inhibitors was able to modulate lipid body formation and decrease PGE2 production, which led to decreased parasite growth in macrophages [27, 36].

Furthermore, these newly formed lipid bodies also varied significantly in size and light density, which indicated the structural participation of these organelles in immune responses to T. cruzi infection. The structural alterations of LB in macrophages may be related to the different lipid compositions in the organelle, stage of new LB formation, or fluctuation of the arachidonate production and concentration [37]. Ultrastructural investigation revealed that the newly formed lipid bodies are localized in close proximity to macrophage phagolysosomes or even within these structures. This suggests that lipid bodies may interact with the phagolysosomes during acute T. cruzi infection [38]. Lipid bodies are known to provide nutrients to intracellular parasites such as Leishmania chagasi, which are located in the phagolysosome [39]. The relationship between lipid body and phagolysosome can also be beneficial to the host. As reviewed by Melo et al., lipids recruited during lipid body formation, such as arachidonic acid (AA), are able to activate actin assembly, phagosome-lysosome fusion, and phagosome maturation [40, 41]. In addition, these lipids can activate phagosomal nicotinamide adenine dinucleotide phosphate (NADPH-) oxidase, which leads to pathogen elimination [42]. The implication of the close localization of lipid bodies and phagolysosome in T. cruzi infected macrophages needs to be further investigated.

3. T. cruzi Infection and Host Adipose Tissue

Adipose tissue is one of the largest organs in the host. It is comprised of a wide range of cell types including adipocytes, pericytes, monocytes, macrophages, and endothelial cells [43]. The function of adipose tissue has long been considered to be energy storage. More than 95% of adipocyte cell mass is lipid droplets where triglycerides and cholesterol esters are stored [44]; however, it was recently uncovered that the functions of adipose tissue include not only energy storage, but also metabolic regulation, neuroendocrine, and immune regulations [45]. Adipose tissue is home to a variety of adipokines, such as adiponectin [46], leptin [47], and resistin
Figure 1: *Trypanosoma cruzi* interacting with various components of host lipid metabolism. (a) *T. cruzi* infects macrophage and activates TLR-2 signaling which causes the increased lipid bodies (LB) number and altered LB morphology. This effect is further enhanced by macrophage uptake of apoptotic cells. Increased LB number causes increased eicosanoid production, which leads to upregulation of TGF-β and increased cell susceptibility to *T. cruzi* infection. (b) *T. cruzi* uses adipocytes as a reservoir for chronic infection. *T. cruzi* infection causes adipocytes to display an inflammatory phenotype, upregulating cytokines such as IL-1β, IFN-γ, TNF-α, CCL2, CXCL10, and CCL5. TLR-2 and 9, which are essential to *T. cruzi* infection, are also upregulated. The infection also causes downregulation of adiponectin secretion via PPAR-γ expression. (c) Host LDL inhibits *T. cruzi* trans-sialidase and increases *T. cruzi* infection in vitro. LDL can be taken up by the liver and extrahepatic cells by LDLR. It is unknown whether LDL-LDLR interaction plays a role in *T. cruzi* infection. (d) *T. cruzi* enters host cell via LDLR. LDL-R activation leads to lysosomal recruitment to parasitophorous vacuole and parasite internalization. (e) HDL inhibits *T. cruzi* trans-sialidase activity and increases *T. cruzi* infection in vitro. HDL is uptaken by host cells via receptor mediated interaction with SR-BI. Whether this interaction can be utilized by *T. cruzi* cell entry process is not known. (f) Apo A-I in the HDL complex is cleaved by the major cysteine protease of *T. cruzi*, cruzipain. Cruzipain and trans-sialidase are similarly expressed and located during different life stages of *T. cruzi*. It is possible that HDL is bound to the surface of *T. cruzi* trypomastigotes by trans-sialidase and is cleaved by cruzipain in the acidic environment in the parasitophorous vacuole. Host cholesterol transport by VLDL, LDL, and HDL is indicated in red arrows. Host VLDL and lipid-poor nascent HDL particles are produced in the liver. By effluxing cholesterol, host VLDL transforms to become LDL and nascent HDL becomes mature HDL. LDL particles can be oxidized and uptaken by macrophage. Lipid-laden macrophages are termed foam cells and are major contributors in host atherosclerosis development. HDL effluxes cholesterol from peripheral tissue via the action of ABCA1 or ABCG1 and returns cholesterol to hepatic tissues for storage or excretion.

[48], which are prominent regulators of lipid homeostasis and immunological functions.

Recently, metabolic dysfunction was linked to CD pathogenesis by the observation that there are greater incidences of diabetes in *T. cruzi* infected individuals [49]. Later research showed decreased insulin level and dysregulated glucose responses among CD patients [50, 51], which further demonstrated the dysregulation of energy metabolism in these patients. It was also shown that chemically induced diabetic mice as well as genetically predisposed *db/db* diabetic mice with defective leptin receptors had higher parasitemia and mortality after *T. cruzi* infection, which suggests that the dysregulation of host metabolism may be beneficial to parasitic survival in the host [52].

Adipocytes are the key cell type in metabolic dysregulations such as diabetes [53]. The role of adipocytes in CD pathogenesis was therefore investigated. Mice infected with *T. cruzi* showed symptoms of hypoglycemia during the acute
stage of infection; however, insulin sensitivity was unaltered [54]. Levels of adiponectin and leptin were significantly reduced in T. cruzi infected mice, which further suggest the altered state of glucose regulation and possible adipocyte involvement in disease progression [54]. Adiponectin is the only adipokine secreted exclusively by adipocytes and is strongly associated with insulin resistance and hyperglycemia. High parasite load was detected in the adipose tissue at the chronic stage, 300 days postinfection, as measured by quantitative polymerase chain reaction (qPCR). Decreased levels of adiponectin in the plasma and adipose tissue of infected mice were also observed during the chronic stage. Microscopic investigation revealed the preferred localization of T. cruzi in the brown fat of adipose tissue, where lipid bodies are higher in number and smaller in size compared to white adipocytes. These findings suggest that adipose tissues may serve as the parasitic reservoir during chronic infection and adipokine synthesis was disrupted possibly due to the infection [54]. Observations that T. cruzi parasite is present in the adipose tissue biopsy of chronically infected human patients have further confirmed the finding that adipose tissue is the reservoir of chronic T. cruzi infection [55]. Several follow-up studies have also shown the susceptible nature of adipocytes to T. cruzi infection [8, 56].

In vitro infection of cultured adipocytes with T. cruzi revealed that a panel of proinflammatory cytokines was upregulated; these include IL-1β, IFN-γ, TNF-α, chemokine ligand (CCL2), CCL5, and C-X-C motif chemokine 10 (CXCL10). The expressions of TLR-2 and 9 are also upregulated [8]. Other pathways, such as notch, extracellular signaling-regulated kinases (ERK), and phosphoinositide-3-kinases (PI3K), were also activated. It was shown that both ERK and PI3K pathways were activated upon T. cruzi infection [57, 58]. Furthermore, PPAR-γ is highly expressed in adipose tissue and, along with adiponectin, exerts anti-inflammatory effect [59]. Levels of peroxisome proliferator-activated receptor (PPAR-γ) were decreased in the infected cells, which may have led to the decreased secretion of adiponectin and increased inflammatory reactions. These findings suggest that infection of adipocytes with T. cruzi may contribute to the systemic proinflammatory immune responses as well as metabolic dysregulation [8] (Figure I(b)).

In summary, recent research has revealed that adipose tissue may be the most important reservoir for T. cruzi chronic infection and these infected adipocytes display a proinflammatory phenotype. Altered activation profile of several kinase pathways in adipose tissues may also contribute to host metabolic dysregulation. However, questions remain unanswered. It is clear that chronic T. cruzi infection displays tissue tropism; however the evolutionary benefits of T. cruzi residing in adipocytes are unknown. T. cruzi may utilize the lipid stores within the adipocytes for its multiplication and survival. It is also possible that T. cruzi chooses adipocytes for its prolonged life-span. In addition, the specific mechanism of T. cruzi-adipocyte interaction is unknown. Further research is needed to unravel the biological processes behind the relationship between T. cruzi and adipocytes.

4. T. cruzi Infection and Host Cholesterol Transport Pathways

T. cruzi glycoprotein 85 (gp85)/trans-sialidase is similar to that of viral and bacterial neuraminidases. However, unlike other neuraminidases, upon hydrolysis of α-linked sialic acid from glycoconjugates on cell surfaces, T. cruzi trans-sialidase transfers the sialic acid onto parasitic receptors [60]. The expression and activity of trans-sialidase are developmentally regulated and are present at about the same extent in epimastigotes and trypomastigotes. Minimal trans-sialidase activity was detected in amastigotes [61]. Trans-Sialidase is known to be involved in trypomastigote cell adhesion and invasion process by interacting with a wide range of ligands, such as laminin, fibronectin, and collagen [62–65]. Inhibition of T. cruzi trans-sialidase by specific antibodies led to the increased rate of infection [66].

Cholesterol transport chains are the major components of maintaining host lipid homeostasis and lipoproteins are essential players in these pathways. Lipoproteins are categorized based on their density and protein content into high density lipoproteins (HDL, density 1.603–1.210), low density lipoproteins (LDL, density 1.019–1.603), intermediate density lipoproteins (IDL, density 1.006–1.019), very low density lipoproteins (VLDL, density 0.95–1.006), and chylomicrons (density < 0.95). All lipoproteins allow the transport of hydrophobic lipid contents, such as cholesterol, triglycerides, and phospholipids, within the hydrophilic blood circulation system.

LDL is characterized by the presence of a single copy of apolipoprotein B-100 (Apo B-100) molecule on its surface. It is generated from liver-derived VLDL by a process mediated by lipoprotein lipase and hepatic lipase as well as lipid exchange proteins [67, 68]. LDL has been shown to be a potent inhibitor of T. cruzi trans-sialidase and enhances the infection of human fibroblasts in vitro in a dose-dependent manner [10]. The enhanced infection rate seen upon the addition of LDL in vitro is comparable to that of the enhancement caused by trans-sialidase inhibition [10]. LDL particles were seen covering the parasite cellular surface of T. cruzi trypanostigotes, but not amastigotes [69]. The localization of LDL particles correlates with trans-sialidase localization on the parasite surface and suggests that LDL may directly inhibit T. cruzi surface trans-sialidase to enhance rate of infection (Figure I(c)). However, the exact molecular mechanism of this interaction has yet been demonstrated.

Previous reports have also shown that LDL can be endocytosed by T. cruzi epimastigotes [69]. Gold-labelled LDL particles were found within flagellar pockets. Immunelectron microscopy showed that trans-sialidase expression is most concentrated in the flagellar pocket region, which suggested that despite LDL inhibition of T. cruzi trans-sialidase, trans-sialidase may also facilitate LDL endocytosis by the parasite [70]. Reservosomes are the site of accumulated endocytosed proteins and lipids in T. cruzi. This organelle in the parasite provides support for metacyclogenesis from epimastigotes to trypomastigotes [71, 72]. LDL particles were also found in the T. cruzi membrane enclosed vesicles and reservosome within the parasite. LDL may be stored and
processed in the reservosome for usage during this transfor-
mation and infection process [73]. Similar process of LDL
uptake was also demonstrated in *Leishmania amazonensis*, a
parasite closely related to *T. cruzi* in the Trypanosomatidae
family [74].

Another important molecule in the LDL metabolic cycle
is the LDL receptor (LDLR). LDLR plays an essential role
in the internalization of circulating LDL in the host liver
and peripheral cells. A significant amount of cholesterol is
delivered to these organs via the interaction of LDL-LDLR
[75]. Approximately 50% of LDL is removed at the liver
[76]. LDLR also facilitates the endocytosis of a variety of
other ligands, such as proteinases and proteinase-inhibitor
complexes, as well as interacting with cytoplasmic adaptor
proteins which have signaling transduction functions [77].
The expression of LDLR by the host cell is regulated by a wide
range of lipid metabolic and immune regulatory stimuli, such
as intracellular cholesterol level, oxysterols, various growth
factors, and cytokines [78, 79]. Ruan et al. demonstrated that,
in human mesangial cells, increased levels of TNF-\(\alpha\), TGF-
\(\beta\), and IL1-\(\beta\) caused increased transcription of LDLR [80].
LDLR was previously shown to be a potential host receptor
for Hepatitis C virus (HCV) and other flaviviridae viruses
[81, 82]. However, this direct interaction was not documented
in parasitic infections until recently.

The *T. cruzi* parasite specifically binds to LDLR during
the infection process [83]. Activation of LDLR facilitates the
recruitment of lysosomes to the parasitophorous vacuole,
which leads to the internalization of *T. cruzi* into the cyto-
plasm. Disruption of LDLR by genetic knockout resulted in
62% reduction in *T. cruzi* infection, which suggests LDLR
is essential for *T. cruzi* cell invasion process (Figure 1(c)).
Furthermore, upregulation of LDLR expression was also seen
in the heart of *T. cruzi* infected CD1 mice [83]. Moreover,
in *Toxoplasma gondii* infection, LDLR functions to uptake
LDL particles and support intracellular parasite growth [84].
It is recently demonstrated that *T. cruzi* interaction with
LDL receptor leads to the increased accumulation of LDL-
cholesterol in host tissue in both acute and chronic CD [85].

Alterations in the micro- and macrovascular circulations
and atherosclerosis-like symptoms are commonly seen in
cardiomyopathic patients [86, 87]. Bestetti et al. reported that
*T. cruzi* infection in combination with a high cholesterol diet
can induce early symptoms of atherosclerosis in mice [88, 89].
LDL and LDLR were implicated extensively in atherosclerosis
pathology and progression. It is known that LDL particles are
transported across the endothelium and become trapped in
the matrix of arterial wall cells, which leads to the production
of highly cytotoxic oxidized LDL and subsequently activates
inflammatory pathways, such as NF\(\kappa\)B [90]. The interaction
of *T. cruzi* with LDLR may increase host susceptibility to
atherosclerosis and arterial pathology.

In addition to the parasite interaction with LDL and
LDLR, *T. cruzi* also interacts with HDL (originally named
cruzin in *T. cruzi* research [91]), the major component of
the reverse cholesterol transport pathway. HDL is a com-
plex, multistructured particle consisting of two layers of
phospholipids that are held together by two molecules of
apolipoprotein A-I (Apo A-I). The main function of HDL is to
remove excess cholesterol from peripheral tissues and return
it to the liver for storage and excretion [92]. Other functions
of HDL also include inhibiting LDL oxidation, platelet
aggregation and coagulations, and endothelial inflammation,
and as well as promoting endothelial nitric oxide production
and prostacyclin bioavailability [93, 94].

Similar to LDL-*T. cruzi* interaction, HDL was shown to
bind to and inhibit *T. cruzi* trypomastigotes trans-sialidase
activity [11, 95]. Interestingly, this interaction is specific for
*T. cruzi* and was not found in *Trypanosoma rangeli*, an infectious
agent nonpathogenic to human hosts. *T. cruzi* and *T. rangeli*
overlap geographically, share antigenic protein, and are able
to infect the same triatomine vector and vertebrate hosts.
HDL inhibition of *T. cruzi* trans-sialidase functions in a dose-
dependent manner through a reversible noncompetitive
mechanism [95]. Maximum association between HDL and *T. cruzi*
trans-sialidase occurs in less than 5 min and lasts more
than 120 min [11]. More importantly, HDL inhibition of
*T. cruzi* trans-sialidase enhances parasite infection in vitro [10].
Recently, Weizong et al. have discovered similar interaction
between Apo A-I and Dengue virus. The research group
showed that Apo A-I is associated with the virus particles
and preincubation of dengue virus with HDL enhances viral
infection through a scavenger receptor-BI-(SR-BI-) mediated
mechanism [96]. These findings may also provide a possible
mechanism for the enhancement of *T. cruzi* infection by HDL
(Figure 1(c)). Furthermore, our research has shown that,
during the intracellular amastigote stage of infection,
groups infected in the presence of HDL had lower number
of intracellular parasites than groups without HDL (Q. Miao
& M. Ndao, personal communication). It is possible that
HDL inhibition of *T. cruzi* trans-sialidase led to the decreased
rate of trypomastigotes escaping from the parasitophorous
vacuole and delaying the process of trypomastigote transforma-
tion [97].

In the *T. cruzi* epimastigote form, HDL may also be
endocytosed and function as nutritional supply [10]. HDL
endocytosis was first observed in *Trypanosoma brucei brucei
(T. b. brucei)*, *T. brucei* (African trypanosome) is closely
related to *T. cruzi* (American trypanosome) in evolutionary
lineage and shares a high level of biological resemblance.
In the interaction of HDL with *T. brucei*, HDL is named
tryptolytic factor (TLF), because endocytosis of certain
HDL subspecies, which contain haptoglobin-related protein
(Hpr, TLF-1 [98]) and apolipoprotein L-I (Apo L-I, TLF-2
[99]), causes lysis of *T. b. brucei* and protects mammalian
hosts from infection [100]. However, *T. cruzi* has developed
resistance to TLFs. The exact mechanism of this resistance is
currently unknown.

The interaction between HDL and *T. cruzi* was recently
reinforced by the discovery that the major structural com-
ponent of HDL, apolipoprotein A-I (Apo A-I, full-length
28.1kDa), is truncated into fragments (24.7, 13.6, 10.3, and
9.3kDa) in sera of *T. cruzi* infected patients [101]. Apo A-I
(243 amino acids) accounts for \(\sim\)75% of HDL protein content
[102]. Both the N- and the C-termini of Apo A-I are involved
in lipid binding functions [103–105]. The central domain of
the Apo A-I protein is involved in the activation of lecithin-
cholesterol acyltransferase (LCAT), which is responsible for
the esterification and storage of cholesterol within HDL particles [106]. Minor changes in the Apo A-I amino acid sequence or structure could seriously affect HDL function [107]. Therefore, Apo A-I truncation seen in *T. cruzi* infection may contribute to the dysregulation of host lipid metabolism. The effect of this dysregulation needs to be further investigated. However, the unique truncation pattern seen in these patients has high discriminatory power between infected and uninfected patients and can be used as *T. cruzi* diagnostic biomarkers [101, 108, 109].

Our research has revealed that the series of Apo A-I truncations was facilitated by the major cysteine protease of *T. cruzi*, cruzipain [56], which is also known as GP 57/51 or cruzain. This protease which belongs to the mammalian papain superfamily is known to cleave immunoglobulin class G proteins [110, 111]. Cruzipain has an essential function in the invasion and survival processes of *T. cruzi* and is expressed in all developmental stages of the parasite life cycle [110]. At each stage, cruzipain is differentially located within the parasite to carry out stage specific functions [112, 113]. In the *T. cruzi* trypomastigote form, cruzipain is located on the parasite surface, flagellar pocket, and lysosome-like structure [114, 115].

It was also shown that cruzipain was only able to cleave Apo A-I at an acidic pH, which suggests that the cleavage may take place within acidic environments. Furthermore, cruzipain from parasite surface (Figure 2(a)) and cruzipain within the lysosome-like structure (Figure 2(b)) are both required in order to produce the truncation pattern [56]. It is interesting to note that the localization of cruzipain highly resembles that of *trans*-sialidase. Therefore, it is possible that HDL is both endocytosed by trypomastigotes and bound to the surface of the parasite via *trans*-sialidase. During the infection process, the parasite bound HDL is cleaved by cruzipain in the acidic parasitophorous vacuole.

With the emerging evidence, it is becoming obvious that *T. cruzi* exploits the complex cholesterol transport system via a variety of molecules such as LDL, LDL-R, and HDL. The results of these interactions seem to all lead to the establishment of *T. cruzi* infection and Chagas disease chronicity. The impact of these relationships on host lipid metabolism is yet to be investigated.

5. Conclusion

Host lipid metabolism is an intricate system involving a wide range of factors. It interacts with other energy metabolic systems as well as the immune system. The role of host lipid metabolism in response to infectious agents is drawing increasing attention. This review may aid in deeper understanding of *T. cruzi* interacting with host lipid metabolism with a more systematic approach, as well as the role of lipids in *T. cruzi* pathogenesis. We have clearly illustrated that *T. cruzi* interacts with several specific factors in host lipid metabolism. Further research in these interactions and the role of lipids in *T. cruzi* pathogenesis will be highly useful in the future.

Conflict of Interests

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

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References

[1] L. V. Kirchhoff, “Epidemiology of American Trypanosomiasis (Chagas Disease),” Advances in Parasitology, vol. 75, pp. 1–18, 2011.

[2] J. C. P. Dias, A. C. SILVEIRA, and C. J. Schofield, “The impact of Chagas disease control in Latin America: a review,” Memorias do Instituto Oswaldo Cruz, vol. 97, no. 5, pp. 603–612, 2002.

[3] G. A. Schmunis and J. R. Cruz, “Safety of the blood supply in Latin America,” Clinical Microbiology Reviews, vol. 18, no. 1, pp. 12–29, 2005.

[4] J. A. Perez-Molina, F. Norman, and R. Lopez-Velez, “Chagas disease in non-endemic countries: epidemiology, clinical presentation and treatment,” Current Infectious Disease Reports, vol. 14, no. 3, pp. 263–274, 2012.

[5] N. Nogueira and Z. A. Cohn, “Trypanosoma cruzi: in vitro infection of macrophage microbicidal activity,” Journal of Experimental Medicine, vol. 148, no. 1, pp. 288–300, 1978.

[6] S. G. Reed, “In vivo administration of recombinant IFN-γ induces macrophage activation, and prevents acute disease, immune suppression, and death in experimental Trypanosoma cruzi infections,” Journal of Immunology, vol. 140, no. 12, pp. 4342–4347, 1988.

[7] J. S. Silva, G. N. R. Vespa, M. A. G. Cardoso, J. C. S. Aliberti, and F. Q. Cunha, “Tumor necrosis factor alpha mediates resistance to Trypanosoma cruzi infection in mice by inducing nitric oxide production in infected gamma interferon-activated macrophages,” Infection and Immunity, vol. 63, no. 12, pp. 4862–4867, 1995.

[8] F. Nagajyothi, M. S. Desruisseaux, N. Thiruvur et al., “Trypanosoma cruzi infection of cultured adipocytes results in an inflammatory phenotype,” Obesity, vol. 16, no. 9, pp. 1992–1997, 2008.

[9] Q. Miao, C. Santamaria, D. Bailey et al., “Apolipoprotein A-I truncations in Chagas disease are caused by cruzipain, the major cysteine protease of Trypanosoma cruzi,” American Journal of Pathology, vol. 184, no. 4, pp. 976–984, 2014.

[10] R. P. Prioli, I. Rosenberg, and M. E. A. Pereira, “High- and low-density lipoproteins enhance infection of Trypanosoma cruzi in vitro,” Molecular and Biochemical Parasitology, vol. 38, no. 2, pp. 191–198, 1990.

[11] R. P. Prioli, I. Rosenberg, S. Shivakumar, and M. E. A. Pereira, “Specific binding of human plasma high density lipoprotein (cruzin) to Trypanosoma cruzi,” Molecular and Biochemical Parasitology, vol. 28, no. 3, pp. 257–263, 1988.

[12] R. Hoff, R. S. Teixeira, J. S. Carvalho, and K. E. Mott, “Trypanosoma cruzi in the cerebrospinal fluid during the acute stage of Chagas’ disease,” The New England Journal of Medicine, vol. 298, no. 11, pp. 604–606, 1978.

[13] M. A. Miles, “New world trypanosomiasis,” in Trevey and Wilson’s Microbiology and Microbial Infections, K. J. P. Cox and D. WakeLin, Eds., pp. 283–302, Arnold, London, UK, 1998.

[14] K. M. Tyler, C. L. Olson, and D. M. Engman, “The life cycle of Trypanosoma cruzi,” in American Trypanosomiasis, vol. 7, pp. 1–11, Kluwer Academic Publishers, 2003.

[15] K. Tauchi-Sato, S. Ozeki, T. Hougou, R. Taguchi, and T. Fujimoto, “The surface of lipid droplets is a phospholipid monolayer with a unique fatty acid composition,” The Journal of Biological Chemistry, vol. 277, no. 46, pp. 44507–44512, 2002.

[16] P. F. Weller, P. T. Bozza, W. Yu, and A. M. Dvorak, “Cytoplasmic lipid bodies in eosinophils: central roles in eicosanoid generation,” International Archives of Allergy and Immunology, vol. 118, no. 2–4, pp. 450–452, 1999.

[17] C. Bandeira-Melo, P. T. Bozza, and P. F. Weller, “The cellular biology of eosinophil eicosanoid formation and function,” Journal of Allergy and Clinical Immunology, vol. 109, no. 3, pp. 393–400, 2002.

[18] D. J. McGookey and R. G. W. Anderson, “Morphological characterization of the cholesteryl ester cycle in cultured mouse macrophage foam cells,” Journal of Cell Biology, vol. 97, no. 4, pp. 1156–1168, 1983.

[19] H. D’Avila, R. C. N. Melo, G. G. Parreira, E. Werneck-Barroso, H. C. Castro-Faria-Neto, and P. T. Bozza, “Mycobacterium bovis bacillus Calmette-Guérin induces TLR2-mediated formation of lipid bodies: Intracellular domains for eicosanoid synthesis in vivo,” Journal of Immunology, vol. 176, no. 5, pp. 3087–3097, 2006.

[20] Z. Brener and R. T. Gazzinelli, “Immunological control of Trypanosoma cruzi infection and pathogenesis of Chagas’ disease,” International Archives of Allergy and Immunology, vol. 114, no. 2, pp. 103–110, 1997.

[21] C. F. Nathan, “Secretion of oxygen intermediates: role in effector functions of activated macrophages,” Federation Proceedings, vol. 41, no. 6, pp. 2206–2211, 1982.

[22] G. N. R. Vespa, F. Q. Cunha, and J. S. Silva, “Nitric oxide is involved in control of Trypanosoma cruzi-induced parasitemia and directly kills the parasite in vitro,” Infection and Immunity, vol. 62, no. 11, pp. 5177–5182, 1994.

[23] M. Russo, N. Starobinas, R. Ribeiro-Dos-Santos, P. H. Minoprio Eisen, and M. Hontbeyer-Joskowicz, “Susceptible mice present higher macrophage activation than resistant mice during infections with myotropic strains of Trypanosoma cruzi,” Parasite Immunology, vol. 11, no. 4, pp. 385–395, 1989.

[24] R. C. N. Melo and C. R. S. Machado, “Trypanosoma cruzi: peripheral blood monocytes and heart macrophages in the resistance to acute experimental infection in rats,” Experimental Parasitology, vol. 97, no. 1, pp. 15–23, 2001.

[25] S. Revelli, G. Didoli, E. Roggero et al., “Macrophage activity, IL-6 levels, antibody response and heart histology in rats undergoing an attenuated Trypanosoma cruzi acute infection upon treatment with recombinant interferon γ,” Cytokines, Cellular and Molecular Therapy, vol. 4, no. 3, pp. 153–159, 1998.

[26] R. C. N. Melo, “Depletion of immune effector cells induces myocardial damage in the acute experimental Trypanosoma cruzi infection: ultrastructural study in rats,” Tissue and Cell, vol. 31, no. 3, pp. 281–290, 1999.

[27] H. D’Avila, G. C. Freire-de-Lima, N. R. Roque et al., “Host cell lipid bodies triggered by Trypanosoma cruzi infection and enhanced by the uptake of apoptotic cells are associated with prostaglandin E2 generation and increased parasite growth,” Journal of Infectious Diseases, vol. 204, no. 6, pp. 951–961, 2011.

[28] C. G. Freire-de-Lima, Q. X. Yi, S. J. Gardai, D. L. Bratton, W. P. Schiemann, and P. M. Henson, “Apoptotic cells, through transforming growth factor-β, coordinately induce anti-inflammatory and suppress pro-inflammatory eicosanoid and NO synthesis in marine macrophages,” The Journal of Biological Chemistry, vol. 281, no. 50, pp. 38376–38384, 2006.

[29] J. S. Silva, D. R. Twardzik, and S. G. Reed, “Regulation of Trypanosoma cruzi infections in vitro and in vivo by transforming growth factor β (TGF-β),” Journal of Experimental Medicine, vol. 174, no. 3, pp. 539–545, 1991.
M. Ming, M. E. Ewen, and M. E. A. Pereira, “Trypanosome infection of mammalian cells requires activation of the TGFβ signaling pathway,” Cell, vol. 82, no. 2, pp. 287–296, 1995.

M. M. Borges, J. K. Kloeetzl, H. F. Andrade Jr., C. E. Tadokoro, P. Pinge-Filho, and I. Abrahamsohn, “Prostaglandin and nitric oxide regulate TNF-α production during Trypanosoma cruzi infection,” Immunology Letters, vol. 63, no. 1, pp. 1–8, 1998.

G. O. Ramirez-Yañez, S. Hamlet, A. Jonarta, G. J. Seymour, and A. L. Symons, “Prostaglandin E2 enhances transforming growth factor-beta 1 and TGF-beta receptors synthesis: an in vivo and in vitro study,” Prostaglandins Leukotrienes and Essential Fatty Acids, vol. 74, no. 3, pp. 183–192, 2006.

S. G. Harris, J. Padilla, L. Koumas, D. Ray, and R. P. Phipps, “Prostaglandins as modulators of immunity,” Trens in Immunology, vol. 23, no. 3, pp. 144–150, 2002.

H. D’Avila, D. A. M. Toledo, and R. C. N. Melo, “Lipid bodies: inflammatory organelles implicated in host-trypanosoma cruzi interplay during innate immune responses,” Mediators of Inflammation, vol. 2012, Article ID 478601, 11 pages, 2012.

A. M. Celentano, G. Gorelik, M. E. Solana, L. Sterin-Borda, E. Borda, and S. M. González Cappa, “PGE2 involvement in experimental infection with Trypanosoma cruzi subpopulations,” Prostaglandins, vol. 49, no. 3, pp. 141–153, 1995.

C. G. Freire-de-Lima, C. G. Freire-de-Lima et al., Uptake of apoptotic cells drives the growth of a pathogenic trypanosome in macrophages, Nature, vol. 403, no. 6766, pp. 199–203, 2000.

R. C. N. Melo, D. L. Fabrino, F. P. Dias, and G. G. Parreira, “Lipid bodies: structural markers of inflammatory macrophages in innate immunity,” Inflammation Research, vol. 55, no. 8, pp. 342–348, 2006.

R. C. N. Melo, H. D. Ávila, D. L. Fabrino, P. E. Almeida, and P. T. Bozza, “Macrophage lipid body induction by Chagas disease in vivo: putative intracellular domains for eicosanoid formation during infection,” Tissue and Cell, vol. 35, no. 1, pp. 59–67, 2003.

N. E. Rodriguez, U. Gaur, and M. E. Wilson, “Role of caveolae in Leishmania chagasi phagocytosis and intracellular survival in macrophages,” Cellular Microbiology, vol. 8, no. 7, pp. 1106–1120, 2006.

R. C. N. Melo and A. M. Dvorak, “Lipid body-phagosome interaction in macrophages during infectious diseases: host defense or pathogen survival strategy?” PloS Pathogens, vol. 8, no. 7, Article ID e1002729, 2012.

E. Anes, M. P. Kühnel, E. Bos, J. Moniz-Pereira, A. Habermann, and G. Griffiths, “Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria,” Nature Cell Biology, vol. 5, no. 9, pp. 793–802, 2003.

C.-I. Suh, N. D. Stull, J. L. Xing et al., “The phosphoinositide-binding protein p40 phox activates the NADPH oxidase during FcyIIA receptor-induced phagocytosis,” Journal of Experimental Medicine, vol. 203, no. 8, pp. 1915–1925, 2006.

M. S. Desruisseaux, M. E. Trujillo, H. B. Tanowitz, and P. E. Scherer, “Adipocytokine, adipose tissue, and infectious disease,” Infection and Immunity, vol. 75, no. 3, pp. 1066–1078, 2007.

S. W. Cushman, “Structure-function relationships in the adipose cell. I. Ultrastructure of the isolated adipose cell,” Journal of Cell Biology, vol. 46, no. 2, pp. 326–341, 1970.

J. R. Koethe, T. Hulgan, and K. Niswender, “Adipose tissue and immune function: a review of evidence relevant to HIV infection,” Journal of Infectious Diseases, vol. 208, no. 8, pp. 1194–1201, 2013.

P. E. Scherer, S. Williams, M. Fogliano, G. Baldini, and H. F. Lodish, “A novel serum protein similar to C1q, produced exclusively in adipocytes,” The Journal of Biological Chemistry, vol. 270, no. 45, pp. 26746–26749, 1995.

Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, and J. M. Friedman, “Positional cloning of the mouse obese gene and its human homologue,” Nature, vol. 372, no. 6505, pp. 425–432, 1994.

C. M. Steppan, S. T. Bailey, S. Bhat et al., “The hormone resistin links obesity to diabetes,” Nature, vol. 409, no. 6818, pp. 307–312, 2001.

V. M. dos Santos, S. F. da Cunha, V. P. Teixeira et al., “Frequency of diabetes mellitus and hyperglycemia in chagasic and non-chagasic women,” Revista da Sociedade Brasileira de Medicina Tropical, vol. 32, no. 5, pp. 489–496, 1999.

M. E. Guariento, M. J. A. Saad, E. O. A. Muscelli, and J. A. R. Gontijo, “Heterogenous insulin response to an oral glucose load by patients with the indeterminate clinical form of Chagas’ disease,” Brazilian Journal of Medical and Biological Research, vol. 26, no. 5, pp. 491–495, 1993.

L. C. Oliveira, Y. Juliano, N. F. Novo, and M. M. Neves, “Blood glucose and insulin response to intravenous glucose by patients with chronic Chagas’ disease and alcoholism,” Brazilian Journal of Medical and Biological Research, vol. 26, no. 11, pp. 1187–1190, 1993.

H. B. Tanowitz, B. Amole, D. Hewlett, and M. Wittner, “Trypanosoma cruzi infection in diabetic mice,” Transactions of the Royal Society of Tropical Medicine and Hygiene, vol. 82, no. 1, pp. 90–93, 1988.

A. Guillerme, J. V. Virbasius, V. Puri, and M. P. Czech, “Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes,” Nature Reviews Molecular Cell Biology, vol. 9, no. 5, pp. 367–377, 2008.

T. P. Combs, S. Mukherjee, C. J. G. de Almeida et al., “The adipocyte as an important target cell for Trypanosoma cruzi infection,” Journal of Biological Chemistry, vol. 280, no. 25, pp. 24085–24094, 2005.

A. V. Matos Ferreira, M. Segatto, Z. Menezes et al., “Evidence for Trypanosoma cruzi in adipose tissue in human chronic Chagas disease,” Microbes and Infection, vol. 13, no. 12-13, pp. 1002–1005, 2011.

Q. Miao, C. Santamaria, D. Bailey et al., “Apolipoprotein A-I truncations in chagas disease are caused by cruzipain, the major cysteine protease of trypanosoma cruzi,” American Journal of Pathology, vol. 184, no. 4, pp. 976–984, 2014.

S. Mukherjee, H. Huang, S. B. Petkova et al., “Trypanosoma cruzi infection activates extracellular signal-regulated kinase in cultured endothelial and smooth muscle cells,” Infection and Immunity, vol. 72, no. 9, pp. 5274–5282, 2004.

S. E. Wilkowsky, M. A. Barbieri, P. Stahl, and E. L. D. Isola, “Trypanosoma cruzi: Phosphatidylinositol 3-kinase and protein kinase B activation is associated with parasite invasion,” Experimental Cell Research, vol. 264, no. 2, pp. 211–218, 2001.

E. Hovsepian, F. Penas, G. A. Mirkin, and N. B. Goren, “Role of PPARs in trypanosoma cruzi infection: implications for chagas disease therapy,” PPAR Research, vol. 2012, Article ID 528435, 8 pages, 2012.

J. M. Alves and W. Colli, “Role of the gp85/trans-sialidase superfamily of glycoproteins in the interaction of Trypanosoma cruzi with host structures,” Sub-cellular Biochemistry, vol. 47, pp. 58–69, 2008.
Mediators of Inflammation

[61] M. E. A. Pereira, “A developmentally regulated neuraminidase activity in Trypanosoma cruzi,” Science, vol. 219, no. 4591, pp. 1444–1446, 1983.

[62] A. Ouaisi, J. Cornette, A. Taibi, P. Velge, and A. Capron, “Major surface immunogens of Trypanosoma cruzi trypomastigotes,” Memorias do Instituto Oswaldo Cruz, vol. 83, supplement 1, p. 502, 1988.

[63] R. R. Tonelli, R. J. Giordano, E. M. Barbu et al., “Role of the gp85/trans-sialidases in Trypanosoma cruzi tissue tropism: preferential binding of a conserved peptide motif to the vasculature in vivo,” PLoS Neglected Tropical Diseases, vol. 4, no. 11, article e864, 2010.

[64] R. Giordano, R. Chammas, S. S. Veiga, W. Colli, and M. J. M. Alves, “An acidic component of the heterogeneous Tc-85 protein family from the surface of Trypanosoma cruzi is a laminin binding glycoprotein,” Molecular and Biochemical Parasitology, vol. 65, no. 1, pp. 85–94, 1994.

[65] P. Velge, M. A. Ouaissi, J. Cornette, D. Afchain, and A. Capron, “Identification and isolation of Trypanosoma cruzi trypomastigote collagen-binding proteins: possible role in cell-parasite interaction,” Parasitology, vol. 97, no. 2, pp. 255–268, 1988.

[66] R. Cavalleresco and M. E. A. Pereira, “Antibody to Trypanosoma cruzi neuraminidase enhances infection in vitro and identifies a subpopulation of trypomastigotes,” Journal of Immunology, vol. 140, no. 2, pp. 617–625, 1988.

[67] G. J. de Grooth, A. H. E. M. Klerkx, E. S. G. Stroes, A. F. H. Stalenhoef, J. J. P. Kastelein, and J. A. Kuivenhoven, “A review of CETP and its relation to atherosclerosis,” Journal of Lipid Research, vol. 45, no. 11, pp. 1967–1974, 2004.

[68] J. Huuskonen, V. M. Ollkonen, M. Jauhiainen, and C. Ehnholm, “The impact of phospholipid transfer protein (PLTP) on HDL metabolism,” Atherosclerosis, vol. 155, no. 2, pp. 269–281, 2001.

[69] M. J. Soares and W. de Souza, “Endocytosis of gold-labeled proteins and LDL by Trypanosoma cruzi,” Parasitology Research, vol. 77, no. 6, pp. 461–468, 1991.

[70] R. P. Prioli, J. S. Mejia, T. Aji, M. Aikawa, and M. E. A. Pereira, “Trypanosoma cruzi: localization of neuraminidase on the surface of trypomastigotes,” Tropical Medicine and Parasitology, vol. 42, no. 2, pp. 146–150, 1991.

[71] M. J. Soares, T. Souto-Brandão, M. C. Bonaldo, S. Goldenberg, and W. de Souza, “A stereological study of the differentiation process in Trypanosoma cruzi,” Parasitology Research, vol. 75, no. 7, pp. 522–527, 1989.

[72] M. J. Soares and W. De Souza, “Cytoplasmic organelles of trypanosomatids: a cytological and stereological study,” Journal of Submicroscopic Cytology and Pathology, vol. 20, no. 2, pp. 349–361, 1988.

[73] M. G. Pereira, E. S. Nakayasu, C. Sant’Anna et al., “Trypanosoma cruzi epimastigotes are able to store and mobilize high amounts of cholesterol in reservosome lipid inclusions,” PLoS ONE, vol. 6, no. 7, Article ID e22359, 2011.

[74] N. N. de Cicco, M. G. Pereira, J. R. Corrêa et al., “LDL uptake by Leishmania amazonensis: involvement of membrane lipid microdomains,” Experimental Parasitology, vol. 130, no. 4, pp. 330–340, 2012.

[75] B. R. Carr and E. R. Simpson, “Lipoprotein utilization and cholesterol synthesis by the human fetal adrenal gland,” Endocrine Reviews, vol. 2, no. 3, pp. 306–326, 1981.

[76] J. E. Vance, “Assembly and secretion of lipoproteins,” in Biochemistry of Lipids, Lipoproteins and Membrane, J. E. Vance and D. Vance, Eds., pp. 505–526, Elsevier, Amsterdam, The Netherlands, 2002.

[77] D. K. Strickland, S. L. Gonias, and W. S. Argraves, “Diverse roles for the LDL receptor family,” Trends in Endocrinology and Metabolism, vol. 13, no. 2, pp. 66–74, 2002.

[78] A. Kumar, A. Middleton, T. C. Chambers, and K. D. Mehta, “Differential roles of extracellular signal-regulated kinase-1/4 and p38(MAPK) in interleukin-1β- and tumor necrosis factor-α-induced low density lipoprotein receptor expression in HepG2 cells,” The Journal of Biological Chemistry, vol. 273, no. 25, pp. 15742–15748, 1998.

[79] A. C. Nicholson and D. P. Hajjar, “Transforming growth factor-β up-regulates low density lipoprotein receptor-mediated cholesterol metabolism in vascular smooth muscle cells,” Journal of Biological Chemistry, vol. 267, no. 36, pp. 25982–25987, 1992.

[80] X. Z. Ruan, Z. Varghese, R. Fernando, and J. F. Moorhead, “Cytokine regulation of low-density lipoprotein receptor gene transcription in human mesangial cells,” Nephrol Dialysis Transplantation, vol. 13, no. 6, pp. 1391–1397, 1998.

[81] P. André, F. Komurian-Pradel, S. Deforges et al., “Characterization of low- and very-low-density hepatitis C virus RNA-containing particles,” Journal of Virology, vol. 76, no. 14, pp. 6919–6928, 2002.

[82] V. Agnello, G. Ábel, M. Elfahal, G. B. Knight, and Q.-X. Zhang, “Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor,” Proceedings of the National Academy of Sciences of the United States of America, vol. 96, no. 22, pp. 12766–12771, 1999.

[83] F. Nagajothy, L. M. Weiss, D. L. Silver et al., “Trypanosoma cruzi utilizes the host low density lipoprotein receptor in invasion,” PLoS Neglected Tropical Diseases, vol. 5, no. 2, article e953, 2011.

[84] L. R. Portugal, L. R. Fernandes, V. S. Pietra Pedrosco, H. C. Santiago, R. T. Gazzinelli, and J. I. Alvarez-Leite, “Influence of low-density lipoprotein (LDL) receptor on lipid composition, inflammation and parasitism during Toxoplasma gondii infection,” Microbes and Infection, vol. 10, no. 3, pp. 276–284, 2008.

[85] C. Johndrow, R. Nelson, H. Tanowitz et al., “Trypanosoma cruzi infection results in an increase in intracellular cholesterol,” Microbes and Infection, vol. 16, no. 4, pp. 337–344, 2014.

[86] E. Cunha-Neto, M. Duranti, A. Gruber et al., “Autoimmunity in Chagas disease cardiopathy: biological relevance of a cardiac myosin-specific epitope crossreactive to an immunodominant Trypanosoma cruzi antigen,” Proceedings of the National Academy of Sciences of the United States of America, vol. 92, no. 8, pp. 3541–3545, 1995.

[87] M. A. Rossi, “Aortic endothelial cell changes in the acute septicemic phase of experimental Trypanosoma cruzi infection in rats: Scanning and transmission electron microscopic study,” The American Journal of Tropical Medicine and Hygiene, vol. 57, no. 3, pp. 321–327, 1997.

[88] R. B. Bestetti, M. T. Arioli, J. L. do Carmo et al., “Clinical characteristics of acute myocardial infarction in patients with Chagas’ disease,” International Journal of Cardiology, vol. 35, no. 3, pp. 371–376, 1992.

[89] D. Sunnemark, R. A. Harris, J. Frostegård, and A. Örn, “Induction of early atherosclerosis in CBA/J mice by combination of Trypanosoma cruzi infection and a high cholesterol diet,” Atherosclerosis, vol. 153, no. 2, pp. 273–282, 2000.

[90] P. Niewelstein-Post, G. Mottino, A. Fogelman, and J. Frank, “An ultrastructural study of lipoprotein accumulation in cardiac...
