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Mechanism of Congenital Chagas Disease: Effective Infection Depends on the Interplay Between *Trypanosoma cruzi* and the Different Tissue Compartments in the Chorionic Villi of the Human Placenta

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1. Introduction

American trypanosomiasis, or Chagas disease, a zoonosis caused by *Trypanosoma cruzi* (*T. cruzi*), is endemic in Latin America and ten million people are estimated to be infected (Araújo et al 2009, World Health Organization (WHO), 2010). In the past decades, Chagas disease has been increasingly detected in other non-endemic countries such as Canada, the United States of America, Australia, Japan and in Europe. The presence of Chagas disease outside Latin America is the result of population mobility, notably migration, but also from travelers returning from Latin America and in adopted children (Schmunis, 2007). Subsequent transmission occurs through transfusion, transplantation or vertical routes. More than 10 000 deaths are estimated to occur annually from Chagas disease; its incapacitating effects and mortality are ones of the biggest public-health problems in Latin America. The 10-year mortality rate may range from 9% to 85%, depending on the extent of the cardiac damage induced by the parasite (WHO, 2010).

Chagas disease manifests first with an acute phase, lasting for about 2 months, characterized by high parasitaemia. Most cases are asymptomatic or present nonspecific symptoms. Then, it turns into a chronic phase, the parasites hiding in target tissues, especially in the heart and digestive muscles (WHO, 2010) and in case of pregnancy, also in the placenta (Bittencourt, 1976). During the chronic phase, different clinical manifestations may be observed: 1) the cardiac form; 2) the digestive form, particularly enlargement of the esophagus and the colon; and 3) a mixed form (cardiac plus digestive) (Rassi, 2006).

2. Congenital Chagas disease

Congenital *T. cruzi* infection is associated with premature labor, low birth weight, and stillbirths (Altemani et al, 2000; Bittencourt, 1976; Shippey et al, 2005). Serologic prevalence among pregnant women may reach 80%, and rates of congenital infection vary from 1-21% (Blanco et al, 2000; Burgos et al, 2007; Kirchhoff, 1999; Shippey et al, 2005; Torrico et al,

2005). In Chile, in two of the endemic regions (IV and V regions), the congenital transmission rate of the parasite is 8.4% (Jercic et al, 2010). WHO/PAHO has considered that the number of infected woman at fertile age is of approximately 1.809.000 and that 14.400 neonates are being infected at year (WHO, 2006).

During congenital transmission, the parasite reaches the fetus by crossing the placental barrier (Carlier and Truyens, 2010; Duaso et al, 2010; Kemmerling et al, 2010). The fact that only a percentage of the infected mothers transmit parasites to their fetuses raises the question of the ability of the placenta as well as the immunological status of mother and fetus/newborn to impair the parasite transmission. Therefore, it is thought that congenital Chagas disease is product of a complex interaction between the parasite, the maternal and fetus/newborn immune responses and placental factors (Burgos et al, 2007; Kemmerling et al, 2010).

2.1 The parasite

T. cruzi is a haemoflagelated protozoan of the *Kinetoplastida* Order and *Trypanosomatidae* family (Chagas, 1909). The parasite biological cycle includes three cellular forms characterized by the relative positions of the flagellum, kinetoplast, and nucleus (Prata, 2001): 1) Trypomastigotes: Approximately 20 μm in length and sub terminal kinetoplast. They constitute the non-replicative, mammalian infecting cellular form that is found in the blood and in the posterior intestine of triatomids. In mammals, this is the cellular form that disseminates infection through blood. 2) Epimastigotes: Also 20 μm in length with a kinetoplast anterior to the nucleus. They represent the multiplying parasite form in the triatomid intestine. 3) Amastigotes: Approximately 2 μm in diameter, rounded, with no emergent flagellum. It multiplies within the mammalian host cells, forming "nests", until they rupture after several cell divisions. Before their release from the host cells, amastigotes differentiate into trypomastigotes that invade the blood stream; they may then enter any other nucleated cell. Epimastigotes can be grown in axenic cultures while amastigotes grow in cultured mammalian cells, releasing trypomastigotes that can be harvested to perform *in vitro* assays.

T. cruzi display great biological, biochemical and genetic diversity, therefore different strains of the parasite have been identified and classified into six discrete typing units (DTU) (Telleria et al, 2010; Zingales et al, 2009). *T. cruzi* strains corresponding to different DTUs might have relevant consequences on congenital transmission and fetal/neonatal pathology. Nevertheless, different parasite strains identified in congenitally infected children correspond to the same strain identified in the mother, that is the predominantly *T. cruzi* lineage in the respective geographic region (Carlier and Truyens, 2010). There is no clear evidence that a relationship between *T. cruzi* strains and congenital infection in humans exists. Nevertheless, parasitaemia is associated with the risk of congenital transmission. Thus, a high parasitaemia, as in acute infection, correlates with a higher transmission rate (around 50%). In chronic infected patients, with very low parasitaemia, the transmission rate is between 1-21% (Brutus et al, 2010; Moretti et al, 2005). Though appearing a low rate of infection, chronically infected pregnant women represent a high risk of maintenance of Chagas disease both in endemic and non endemic areas.

2.2 Mother and fetus/newborn immune response

The immune system is fundamental to protect the mother against the environment and to prevent damage to the fetus. During pregnancy the maternal immune system is characterized by a reinforced network of cellular and molecular recognition, communication, trafficking and repair; it raises the alarm to maintain the well-being of the mother and the fetus. On the other side, the fetus provides a developing active immune system that will modify the way the mother responds to the environment, providing a uniqueness of the immune system responses during pregnancy (Mor and Cardenas, 2010).

A crucial factor to stop, limit, or permit the development of fetal/neonatal infection relates to the capacity of the mother and fetus/newborn to mount innate and/or specific immune response(s) against pathogens. Clinical studies have shown a strong association between intrauterine infections and pregnancy disorders such as abortion, preterm labor, intrauterine growth retardation and pre-eclampsia (Koga and Mor, 2010). As described above, congenital *T. cruzi* infection is associated with some of these pathologies (Altemani et al, 2000; Bittencourt, 1976; Carlier and Truyens, 2010; Shippey et al, 2005).

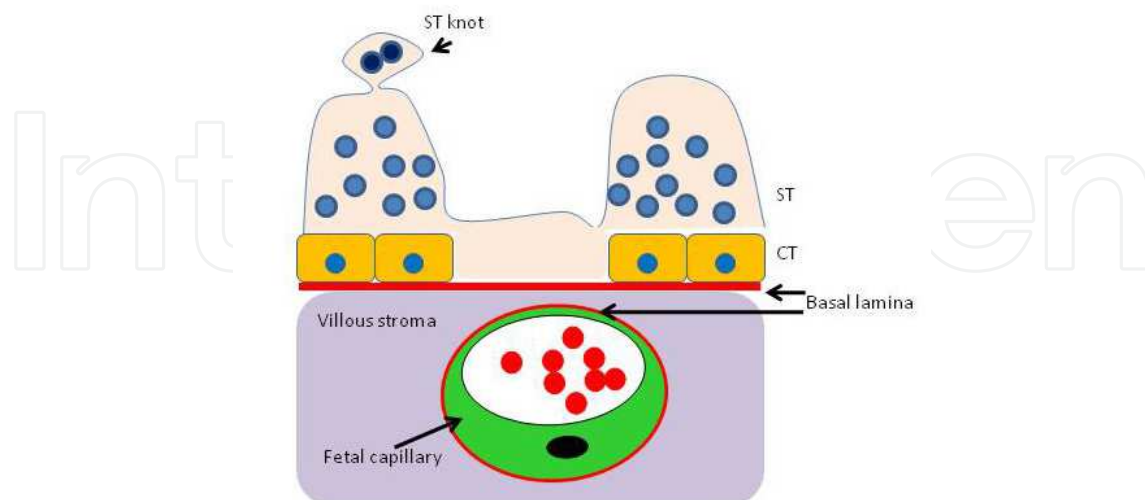
Production of pro-inflammatory cytokines can be observed in uninfected babies born to infected mothers (Carlier and Truyens, 2010). Contrarily, the levels of inflammation markers and activation of NK cells are rather low in congenitally infected newborns (Hermann et al, 2010). These data highly suggest a protective role of such innate defenses in an uninfected newborn from infected mothers. On the other side, maternal *T. cruzi*-specific IgG antibodies play protective roles in mothers and in fetuses when antibodies are transferred through the placenta (Breniere et al, 1983) and also may contribute to a reduction in parasitaemia (Carlier and Truyens, 2010).

2.3 Placenta

The placenta is the principal site for the exchange of nutrients and gases between the mother and fetus. This organ plays an important role in hormone, peptide, and steroid synthesis necessary for a successful pregnancy (Moore and Perseaud, 2004). The human placenta is classified as a hemochorial villous placenta in which the free chorionic villi, formed by the trophoblast and the villous stroma, are the functional units. The trophoblast contacts maternal blood in the intervillous space and is separated by a basal lamina from the villous stroma, which is connective tissue containing the vascular endothelium, fibroblasts and macrophages (Berniske et al, 2006). Trophoblast, basal *laminae* and villous stroma with the endothelium of fetal capillaries form the placental barrier that must be crossed by different pathogens, including *T. cruzi*, to infect the fetus during vertical transmission (Carlier and Truyens, 2010; Duaso et al, 2010; Kemmerling et al, 2010) (**Figure 1**).

Placentas from mother with acute Chagas disease (high parasitaemia) show severe histopathological changes, such as extensive necrosis, inflammatory infiltrate and amastigote nests (Altemani et al, 2000). Contrarily, placentas from mother with chronic Chagas disease do not present necrotic foci and inflammatory infiltrate. Although parasite antigens can be visualized in the villous stroma, the typical amastigote nests are not present (Duaso et al, 2011b). In accordance with these results, in *ex vivo* infected placental explants although parasite antigens and DNA can be detected (Al Khan et al, 2011; Duaso et al, 2010; Luján et al, 2004), amastigote nests are not observed. Only few individual parasites can be

detected. These evidences suggest that anti-parasite mechanisms may exist in the placental tissue of women suffering chronic Chagas disease.



The placental barrier is composed of syncytiotrophoblast (ST) with ST knots, cytotrophoblast (CT), fetal connective tissue of the villous stroma, fetal capillary and basal lamina between villous stroma and trophoblast as well as around fetal endothelium.

Fig. 1. Human placental barrier

3. *Trypanosoma cruzi* interaction with the trophoblast

The major constituent of the human placenta is the trophoblast, the first cell lineage that develops before any embryonic tissue arises. Between morula and blastocyst stages, the trophoblast lineage forms a cover around the early embryo (the embryoblast) (Berniske et al, 2006; Huppertz and Borges, 2008). The human trophoblast differentiates into two major subtypes (Drewlo et al, 2008; Huppertz and Gauster, 2010; Huppertz and Borges, 2008): a) Cells that invade maternal uterine tissue and differentiate into the *extravillous trophoblast*, and b) Cells that remain within the placenta and differentiate into the *villous trophoblast* forming the epithelial cover of the placental villi and constituting part of the placental barrier (Berniske et al, 2006; Kemmerling et al, 2010) (see **Figure 1**). The *villous trophoblast* is composed of two cellular layers: the *syncytiotrophoblast* (ST) and the *cytotrophoblast* (CT). The CT displays high proliferative properties, whereas the differentiated ST loses its generative capacity and is no longer able to proliferate. The ST is a multinucleated layer that forms the outer surface of placental villi and comes into direct contact with maternal blood (Berniske et al, 2006; Huppertz and Borges, 2008). This cell layer is a typical syncytium with plasma membranes only on the apical and basal sides. The ST is continuous and normally uninterrupted, covering all villous trees of the human placenta. It is generated and maintained through syncytial fusion by incorporation of CT cells (Berniske et al, 2006; Huppertz, 2010).

During congenital infection the first fetal cells exposed to the parasite are those of the syncytiotrophoblast. In human chorionic villi infected *ex vivo* the parasite induces

detachment and destruction of this tissue layer (Duaso et al, 2010). Other pathogen like cytomegalovirus (Chan and Gilbert, 2006), *Plasmodium falciparum* (Maubert et al, 1997) and *Toxoplasma gondii* (Abbasi et al, 2003) also induce syncytiotrophoblast damage.

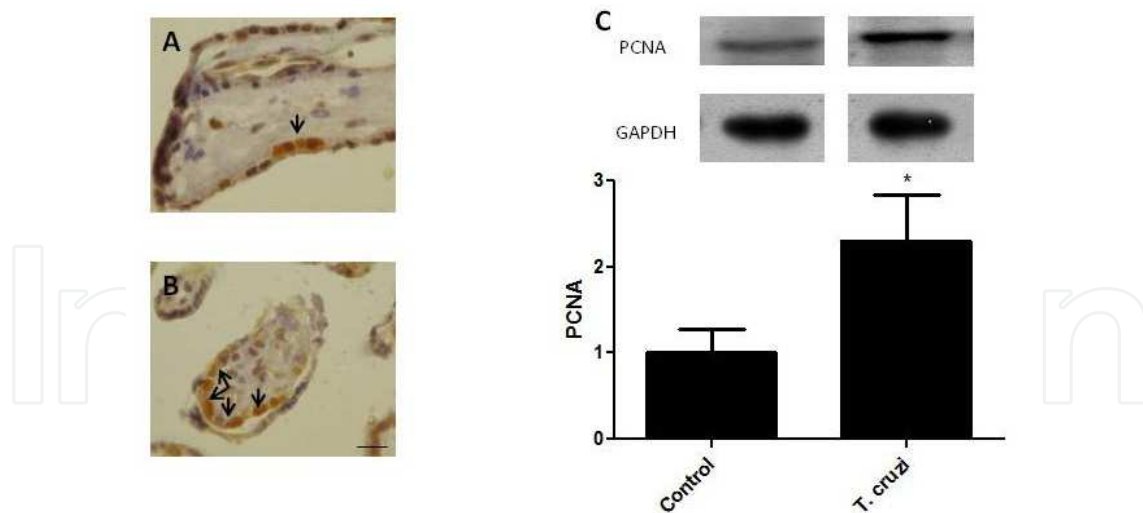
The trophoblast, as covering epithelia, forms a physical barrier to pathogens. On the other hand, the epithelial turnover has been considered part of the innate immune system (Janeway and Traver, 2004) due to the fact that pathogens, prior to cell invasion, must attach to the surface of cells. As these cells are continuously eliminated, the attached pathogens are removed with them.

Trophoblast turnover: Trophoblast turnover implies precise orchestration of different cellular processes that include cell proliferation of the CT, differentiation (meaning the syncytial fusion by incorporating CT cells into a non replicative ST and differentiation of CT cells previous fusion with the ST) and cell death (Berniske et al, 2006; Huppertz, 2010). Cell death in the trophoblast manifests by formation of apoptotic ST knots which are released into the maternal blood. The apoptotic knots counterbalance the continuous incorporation of CT cell into the ST (Berniske et al, 2006).

Cell proliferation: As previously reviewed and described above, cells of the CT are the only ones showing capacity for cell proliferation (Berniske et al, 2006). Importantly, growth, expansion and maintenance of the ST throughout pregnancy depend mainly on the continuous incorporation of CT cells into the ST (Berniske et al, 2006; Huppertz, 2010). Therefore cell proliferation of CT is fundamental for the trophoblast turnover in health and disease. We identified an increase in cell proliferation in the CT upon infection of villous explants with *T. cruzi*, particularly in cells beneath the areas where the ST is detached and destroyed (**Figure 2**).

Cell differentiation in the trophoblast: Trophoblast fusion is dependent on and regulated by multiple factors such as fusion proteins, proteases and cytoskeletal proteins as well as cytokines, hormones and transcription factors (Huppertz 2010; Huppertz and Gauster, 2011). Some of these factors, considered as trophoblast “differentiation markers” or “fusion markers”, are the following:

- a. *Syncytin family proteins:* Syncytins are fusogenic proteins encoded by envelope genes (*env* genes) of the human endogenous retrovirus (HERV)-W (Syncytin-1), (HERV)-FRD (Syncytin-2), and (HERV)-P(b) (Syncytin-3;) (Ruebner et al, 2010). HERVs contribute to genome plasticity, protect the host against infection with related pathogenic and exogenous retroviruses, and play a vital role in the development of the placenta (Black et al, 2010). Knock down of syncytin-1 inhibited syncytialization of primary trophoblasts (Gauster et al, 2009).
- b. *Transcription factors:* Glial cell missing-1 (GCM1), a placenta-specific transcription factor, regulates transcription via two GCM1 binding sites upstream the 5'-long terminal repeat of the syncytin-1 gene (Huppertz and Borges, 2008; Yu et al, 2002). GCM1 is expressed in highly differentiated CT cells (Baczyk et al, 2004; Huppertz and Borges, 2008).
- c. *Other membrane proteins:* Presence of gap junctions is considered as a prerequisite for trophoblast syncytialization (Gauster et al, 2009). Inhibition of connexin 34 expression by antisense techniques impairs cell fusion in primary trophoblast cultures (Frendo et al, 2003).



Human chorionic villi incubated with 1×10^5 trypomastigotes DM28c strain for 24 hours (**B**) show increase in PCNA immunoreactivity compared to control tissue (**A**). In control (**A**, arrow) and *ex vivo* infected chorionic villi (**B**, arrows) PCNA immunoreactivity can be observed. Note that PCNA immunoreactivity is increased in cells beneath syncytiotrophoblast detachment (arrows). Chorionic villi were processed for routine immunohistochemistry and Antigen-Antibody complex was stained with DAB. Bar scale: 20 μ m.

In (**C**) upper panel a representative western blot for PCNA detection is shown. The bar graphs under the Western blots represent the ratios, normalized with respect to control values, of PCNA over GAPDH. Values represents means \pm SD, $p \leq 0.05$, $n=3$.

Fig. 2. *T. cruzi* induces cell proliferation in the trophoblast

Cell differentiation and apoptosis: In the trophoblast, cell differentiation and apoptotic cell death are closely related (Huppertz and Gauster, 2010). While seemingly paradoxical, there are strong evidences that initiator caspases, especially caspase-8, are involved not only in apoptosis but in differentiation processes in diverse cell types and tissues. Some examples are the enucleation processes during terminal differentiation of erythrocytes (Carlile et al, 2004) and keratinocytes (Denecker et al, 2008) as well as other differentiation processes such as monocytes into macrophages (Sordet et al, 2002) or formation of myotubes in striated skeletal muscle tissue (Fernando et al, 2002).

Programmed cell death in the trophoblast presents most, but not all, of the classic features of apoptosis (Bernischke, 2006; Huppertz and Gauster, 2010). The most remarkable difference between "classic apoptosis" and "trophoblast apoptosis" is that the latter is a prolonged form of apoptosis (3-4 weeks) (Bernischke, 2006). The following data suggests that this prolonged form of apoptosis drives, at least partially, the stages of trophoblast differentiation and turnover:

- a. Initiation stages of apoptosis are responsible for the CT cell exit from the cell cycle and for its entrance into the differentiation pathway (Bernischke, 2006; Huppertz et al, 2002). The matador/Bcl-2 ovarian killer (Mtd/Bok) regulates human trophoblast apoptosis and proliferation. The main isoform of Mtd/Bok associated with trophoblast proliferation is Mtd-L, the full-length isoform, which preferentially is localized in the nuclear compartment in proliferating cells, whereas during apoptosis it switched localization to the cytoplasm where it is associated with mitochondria. Mtd-L

- expression in proliferating cells co-localized with cyclin E1, a G₁/S phase cell cycle regulator (Ray et al, 2010).
- b. Caspase 8 is activated in highly differentiated CT just prior to fusion and escorts the fusing cell content including the nucleus into the ST; interestingly, it has not been found in proliferating CT cells (Black et al, 2010; Huppertz and Gauster, 2010; Huppertz and Borges, 2008).
 - c. Activation of caspase-8 induces phosphatidylserine “flip”, which is a key signal for syncytial fusion (Huppertz and Gauster, 2010; Huppertz and Gauster, 2011) and for cell death by apoptosis (Savill, 1998). Highly differentiated CT cells display the flip of phosphatidylserine without any signs of apoptosis (Huppertz et al, 1998; Rote et al, 2010). Furthermore, it has been demonstrated that the phosphatidylserine flip is also required for fusion of trophoblast-derived BeWo choriocarcinoma cells (Lyden et al, 1993).
 - d. Caspase-8 is responsible for cytoskeleton rearrangement previous to cell fusion (Rote et al, 2010) by cleaving α -fodrin (Huppertz and Gauster, 2011). α -fodrin belongs to the spectrin protein family of sub-membranous cytoskeletal proteins that carry binding sites for phosphatidylserine. The spectrin network maintains the curvature of the plasma membrane and its degradation affects membrane curvature facilitating fusion (Martens and McMahon, 2008). The expression of α -fodrin is diminished in highly differentiated CT and is entirely missing in the ST (Huppertz and Gauster, 2011).
 - e. Upon syncytial fusion, excess expression of apoptosis inhibitors like bcl-2 and mcl-1 blocks further progression of the apoptosis cascade for 3 to 4 weeks (Bernischke, 2006; Huppertz et al, 1998; Huppertz and Gauster, 2011).

Interestingly, diverse pathogens, including *T. cruzi*, induce apoptosis in the placenta, especially in the trophoblast (Duaso et al, 2011a).

Regulation of trophoblast differentiation: Cytokines and growth factors derived from the maternal and fetal environment are involved in regulating trophoblast turnover (Gauster et al, 2009). Epidermal growth factor (EGF) (Morrish et al, 1987), colony-stimulating factor (CSF) (Garcia-Lloret et al, 1994), granulocyte-macrophage colony stimulating factor (GM-CSF), leukemia-inhibitory factor (LIF) (Yang et al, 2003), transforming growth factor (TGF)- α and vascular endothelial growth factor (VEGF) (Crocker et al, 2001; Gauster et al, 2009) induce syncytialization of CT and secretion of human chorionic gonadotropin (hCG) as well as of human placental lactogen (hPL). Interestingly, hCG secreted by the ST can act in an autocrine manner to increase syncytium formation (Shi et al, 1993; Yang et al, 2003). The secretion of hCG and hPL are the main biochemical markers of trophoblast differentiation *in vitro* (Drewlo et al, 2008). In contrast, tumor necrosis factor (TNF)- α (Leisser et al, 2006) as well as transforming growth factor (TGF)- β impaired syncytium formation in chorionic villi explants *in vitro* and inhibited secretion of hCG and hPL (Morrish et al, 1987; Huppertz and Gauster, 2011).

Trophoblast and inflammatory response: Expression of all 10 described TLRs, as well as of various co-receptors and accessory proteins, has been described in the human placenta (Koga and Mor, 2010). TLRs 1-2 and 4-6 are membrane receptors while TLRs 3 and 9 are cytoplasmic receptors and recognize extracellular and intracellular signals, respectively.

Following ligation, the majority of TLRs recruit the intracellular signaling adapter protein, myeloid differentiation factor 88 (MyD88), leading to a subsequent kinase cascade, which triggers the activation of NF κ B pathway, with resultant generation of an inflammatory response. TLR3 and TLR4 can also signal in a MyD88-independent manner (Yamamoto et al, 2003). This signaling occurs through an adapter protein Toll/IL-1 receptor domain-containing adaptor inducing IFN- β (TRIF), which not only activates the NF κ B pathway, but also results in the phosphorylation of IFN regulatory factor-3 (IRF-3). This alternative pathway generates a response associated with the production of type I IFNs and IFN-inducible genes (Hemmi et al, 2000; Koga and Mor, 2010). The expression of TLR varies during pregnancy, but TLR-2, TLR-4 (Ma et al, 2006) as well as TLR 9 (Komine-Aizawa, 2008) are expressed in human term placenta and recognize *T. cruzi*. The principal *T. cruzi* mediated TLR activation is induced by members of GPI-anchored mucins located on *T. cruzi* trypomastigote surface that activates TLR-2 and by CpG-rich parasite DNA that activates TLR-9 (DosReis, 2011; Tarleton, 2007). The most important cytokines secreted after TLR-2, -4 and -9 activation are IL-1 α , IL-6, IL-8 and TNF- α . TLR-4 also mediates the production of IFN- β (Koga and Mor, 2010). Interestingly, activation of TLR-2 also induces activation of caspase 8 (Abrahams and Mor, 2005), an enzyme that is fundamental in apoptotic cell death as well as in trophoblast differentiation (see above).

4. *Trypanosoma cruzi* interaction with the villous stroma

To reach fetal capillaries, the parasite must cross the villous stroma. The villous stroma is a connective tissue that contains mesenchymal cells, fibroblasts and macrophages inserted in the extracellular matrix (ECM).

T. cruzi invades preferentially macrophages and fibroblasts, both present in the villous stroma. However, during tissue invasion the parasite not only must internalize into the cells but also have to deal with the ECM.

The basal lamina, a specialized structure of ECM molecules located between trophoblast and the fetal connective tissue, is one barrier that the parasite must cross. *T. cruzi* presents surface molecules, such as gp85 (Marino et al, 2003) and gp83 (Nde et al, 2006) glycoproteins that bind to laminin and fibronectin (Marino et al, 2003; Nde et al, 2006) and to sulfated glycosaminoglycans such as heparan sulphate (Lima et al, 2002). We have previously shown that the parasite induces a decrease of glycosylated molecules of the basal lamina, specifically laminin and heparan sulphate (Duaso et al, 2010; Duaso et al 2011b).

Collagen IV, other basal lamina components, is also destroyed by the parasite, as evidenced by the decrease in the immunoreactivity of this macromolecule. The decrease in immunoreactivity could also be explained by a change in the epitope as a result of this binding. Interestingly, fibronectin, another principal basal lamina component, is not altered during *ex vivo* infection. The selective destruction of the basal lamina could be part of the mechanism of connective tissue invasion, after an effective epithelial infection.

Basal lamina is also present between the fetal endothelium and the connective tissue. This basal lamina is the last barrier that any pathogen should cross to reach fetal circulation. As expected, *T. cruzi* trypomastigotes induce a similar decrease of laminin and heparan

sulphate in the basal lamina located around the fetal capillaries, as compared to that observed in the basal lamina beneath the trophoblast (Duaso et al, 2010).

Collagen IV is an exception to this since no change is observed. Possibly, the destruction of collagen IV around fetal endothelium is not necessary for the parasite invasion of fetal capillaries or occurs at a later time (Duaso et al, 2010). In other studies, an increase of laminin expression in cardiac tissue has been reported (Scharfstein and Morrot, 1999; Marino et al, 2003). The increase of laminin expression could be induced by the parasite, which needs to attach to ECM molecules for cellular invasion (Marino et al, 2003). The silencing of the laminin gene inhibits cell invasion of the *T. cruzi* (Nde et al, 2006). The parasitic protease cruzipain degrades collagen IV and fibronectin, exposing epitopes to which *T. cruzi* binds (Scharfstein and Morrot, 1999), facilitating also the binding to laminin and consequently the cell invasion. On the other hand, the breakdown of the ECM facilitates the penetration of the parasite through basal lamina and connective tissue of villous stroma.

Between the trophoblast and fetal capillaries, the fetal connective tissue is another important barrier for the parasite. *Ex vivo* infection of human chorionic villi induces a severe collagen I disorganization as seen by Picrosirius red-hematoxylin staining (Duaso et al, 2010). The same effect can be observed in placentas from woman with chronic Chagas disease (Duaso et al, 2011b). The collagen I degradation is probably due to the presence of cruzipain that degrades this type of ECM component (Scharfstein and Morrot, 1999). In other tissue, specifically the lamina propria of seminiferous tubules in mice, *T. cruzi* infection also induces collagen I disorganization (Carvalho et al, 2009). Other enzymes which may participate in collagen I destruction are the metalloproteinases MMP-2 and MMP-9. These proteases are induced by *T. cruzi* in the myocardium of mice with acute Chagas' disease; and its inhibition reduces myocarditis and improves survival during the acute phase of infection (Gutiérrez et al, 2008). Preliminary studies of our laboratory indicates that the parasite increase the activity of the MMP-2 and MMP-9. Collagen I constitute a basic component of the tri-dimensional network of ECM, formed by different types of collagen and elastic fibers, proteoglycans and glycoproteins. If the "basic skeleton" of the ECM is destroyed, the normal conformation of ECM is disorganized, a condition which may facilitate the mobilization of the parasite inside the tissue to its target. Additionally, it has been proposed that ECM alterations produced by the parasite's presence not only promote its motility in tissues and its entrance into cells, but also alter the presence of cytokines and chemokines, which in turn permits *T. cruzi* to modulate and escape both the inflammatory response and the immune response (Marino et al, 2003; Duaso et al, 2010; Duaso et al, 2011b).

5. Conclusion

T. cruzi induces trophoblast destruction and detachment, selective disorganization of the basal lamina and of collagen I in the connective tissue of villous stroma and apoptosis in the chorionic villi. These results suggest that the penetration of this parasite in the placenta is a consequence of its proteolytic activity on the basal lamina and on the connective tissue. Together with the induction of apoptosis these may be part of the mechanisms of infection and tissue invasion by this parasite.

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