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Placental Infection by Trypanosome Cruzi, the Causal Agent of Congenital Chagas' Disease

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1. Introduction

Placenta is a transitory organ which simultaneously separate and connect mother and fetus. It has the major importance in the nutrition of fetus, scavenger waste products from fetus, secretion of hormones and immunological factors, allowing fetus to grow in a sea of maternal immunologic environment and regulating mother metabolism. Also, placenta protects fetus to some infectious agents. It has been described that placental barrier is effective to avoid viral, bacterial and protozoan fetal infections, such as Cytomegalovirus, *Lysteria monocytogenes* and *Trypanosoma cruzi* (Dolcini et al., 2008; Leopardi et al., 1994; Robbins et al., 2010).

Placenta has evolved allowing an independent life to mother. Human placenta is discoidal, villous and hemochorial in structure (Benirschke et al., 2006) meaning it has a particular structure which is not shared with other commonly species employed in biomedical research such as mice. The monkey great apes have similar placenta to human but it is expensive and also needs a special environment and protection of rare species. Guinea pig has a hemochorial placenta similar to human and it would be necessary to study deeper this specie in relation to transmission of infectious agent from mother to fetus at least in Chagas transmission.

To study human placental invasion by infectious agents, such as *Trypanosoma cruzi*, researchers have three possible models, the culture of either isolated trophoblast or chorionic villi explants in interaction with the parasite, or perfusion of placental cotyledons in an extracorporeal system, or to analyze the organ from chagasic women obtained at the end of pregnancy. The aim of this chapter is to study mechanisms and processes of the interaction between placental barrier and the causal agent of Chagas' disease, the *Trypanosoma cruzi*, mainly *in vitro* systems. Most of the studies with human placenta were done in *in vitro* systems approximately the last 15 years.

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2. Chagas' disease: some aspects

Chagas' disease was first described by Carlos Chagas a little more than 100 years ago. He described the causal agent, the vectorial transmission and reservoirs and the clinical manifestations in humans, that is the complete cycle of the disease. Also, Chagas suggested the congenital transmission. Carlos Chagas was nominated twice to the Nobel Prize, but never (unfairly) obtained it (Clayton, 2010).

Chagas disease is an enzootic condition in Latin America, caused by the protozoan *Trypanosoma cruzi*, an obligated intracellular parasite which is transmitted to human by different ways. The most common and important of those ways is by the feces of an infected triatomine which defecate while feeding. Congenital transmission is another important route by which the parasite infects the fetus or the new born, implying in utero or perinatal transmission. This review aimed on transplacental transmission of *T. cruzi*.

The disease has an acute stage mainly seen in children with no symptoms, or mild symptoms or evident ones, such as fever, swelling of lymph nodes, conjunctivitis and skin lesions (Kierszenbaum 2007, Teixeira et al. 2006). It has been also described, myocarditis, encephalitis and meningitis. Death is a rare condition in this period. All symptoms and signals cede spontaneously and patients pass to the indeterminate period of the disease. Approximately 12 million of individuals, who are coursing this stage, are positive to specific serological tests and neither have symptoms and signs of the disease nor ECG and X ray abnormalities, but they are reservoirs for *T. cruzi*. Approximately one third of all of these individuals develop chronic Chagas disease, 20 to 30 years later to acquire it. Chronic Chagas disease is associated to cardiomyopathy or digestive disorders. Death is associated with this stage of the disease.

3. Congenital Chagas transmission (CCT)

3.1 Definition

The transmission of live *T. cruzi* from a chagasic pregnant woman to the fetus implies that the new born has the parasite in his/her tissues at the moment of delivery. To consider a congenital case, it should fulfill the following conditions: Mother should be positive for *T. cruzi* and also new born should have *T. cruzi* in their tissues at delivery. Congenital Chagas should be diagnosed detecting parasites in infants at delivery or later or detecting own antibodies against parasite antigens discarding blood transfusion or vectorial transmission.

The congenital transmission has been described in pregnant women coursing the acute and the indeterminate stages of the disease, even though the incidence of positive transmission were higher when mother was in the acute period with high parasitemias (see 5. Survival of *T. cruzi* in the placental environment) (Schijman 2007). Thus, the amount of parasites could be an important risk factor for CCT.

Positive pregnant women may transmit the parasite to one or all siblings, or to jump a gestation. However, family clustering has been described, and siblings of a congenital case are at high risk that merits testing for Chagas in them (Sanchez-Negrete et al. 2005). Frequently, positive children born to chagasic mothers are asymptomatics (Moya et al. 1979). However, approximately half of the infected new borns depict clinical signs of

congenital Chagas disease (Sanchez-Negrete et al. 2005, Torrico et al. 2004). Clinical manifestation might appear at delivery, or days or weeks later (Freilij et al. 1994). There is an association between premature births and low birth weight with CCT (Azogue 1985, Bittencourt 1992, Sanchez-Negrete et al. 2005) and they should be considered as risk factors. The condition of chagasic in the mother does not have any consequence on the uninfected infant (Schijman 2007). It is controversial if sex participates as risk factor, even though it seems there are more males than females congenitally infected with *T. cruzi* (Bittencourt 1992, Carlier and Truyens 2010, Torrico et al. 2004).

3.2 Epidemiological importance of congenital infection by *T. cruzi*

The prevalence of Chagas' disease in pregnant women in South America ranges between 4% to 64,4% with 0.1% to 7% of these transmitting the infection to their newborns (Romero 2011, WHO 2007). There were 1136 congenital *T. cruzi* reported cases from 1994 to 2001. According to Gurtler et al, (2003) there were more cases than the reported ones; and the estimated for these authors was of 6.3 expected cases per each reported case. So, the real situation in Argentina, at least in those 8 years was of 7157 new cases in Argentina. As it was reported that congenital transmissions was cluster in families, so brothers of congenital children are in risk, drawing a very serious picture for Chagas transmission in endemic countries due to congenital *T. cruzi* transmission.

Congenital transmission has already surpassed the number of vector-mediated acute cases by a factor of 10 in Argentina (Gurtler et al 2003). This form of transmission constitutes an increasing public health problem and is responsible for the urbanization and spreading of the disease to non endemic areas, such as cities of Latin America, United States of America and Europe (Schijman, 2007; Clik Lambert, 2008). The permanence of high prevalence of chagasic pregnant women in some cities of Latin America is worsening the situation.

3.3 Possible routes by which *T. cruzi* reaches the fetus

Congenital transmission of *T. cruzi* has been well documented (Freilij et al., 1995, Schijman 2007). Although this form of transmission was first suggested one hundred years ago by Carlos Chagas, the precise route by which the parasite reaches the fetus has not yet been elucidated, if there was only one.

The chorionic villous offers the major surface for interaction between mother and fetus, therefore is one of the possible routes that *Trypanosoma cruzi* employs to infect the placenta leading to the congenital Chagas' disease. It was described the villous trophoblast as being the first barrier that *T. cruzi* must cross in order to reach the offspring (Bittencourt, 1992, Schijman, 2007). But, Fernandez-Aguilar (2005) and Moya et al. (1979), studying placentas from chagasic mothers, found parasites at the chorionic plate but do not describe parasites at the chorionic villi. These authors therefore suggested that the route by which *T. cruzi* accesses the fetus is by hematogenous route through the marginal sinus, spreading into the chorionic plate rather than by the trophoblast.

It was also described that the genital canal at birth could be another route of connatal transmission (Schijman 2007). A possible fourth route for *T. cruzi* congenital transmission could be through transfusion of blood from mother to fetus in the uterus (Bianchi and

Romero, 2003, Vernochet et al., 2007), mechanism that has not been either studied or described yet to the best of our knowledge.

4. Influence of strains of *T. cruzi* in the congenital transmission

Strains of *T. cruzi* have been involved in different clinical forms of Chagas' disease (Dutra et al. 2005, Zingales et al. 1999), thus implicating a different genetic population in tissue tropism, replication and virulence, and in consequences in disease outcome (Dutra et al., 2005; Macedo et al., 2004; Mejía and Triana, 2005). Maternal conditions, strains of *T. cruzi* and immunological competence of the placenta, might all participate in the congenital Chagas' disease transmission. Whether strains of *T. cruzi* contribute to congenital infection is a matter of controversy. Andrade (1982) found that three different strains of *T. cruzi* had differential tropism to placenta in mice. Epidemiological studies showed geographical differences in the incidence and clinical forms of congenital Chagas' disease (Bittencourt, 1992). These data may indicate that different *T. cruzi* strains and/or host individuality participate, as suggested by the occurrence of family clustering of congenital Chagas disease (Sanchez-Negrete et al., 2005, Schijman 2007). Virreira et al (2006) and Burgos et al., (2007) concluded that congenital transmission of *T. cruzi* is not associated with genetic polymorphism of *T. cruzi*. Recently, Burgos et al. (2007) described that TcIIId is the most prevalent lineage found in pregnant women both in those who transmit and also in those who did not transmit congenitally to their babies and Virreira et al. (2006) found TcIIb, TcIIId and TcIIe in blood in the umbilical cord, indicating there is not a specific strain of *T. cruzi* implicated in congenital transmission. However, Solana et al. (2002) described biological differences among subpopulations of *T. cruzi* in experimental vertical transmission. Furthermore, experimentally in *in vitro* co-cultures of explants of chorionic villi incubated with trypomastigotes of two strains of *T. cruzi*, it was showed that there are biological differences between both strains, surviving more one of the strain with respect to the other (Triquell et al. 2009). The survival of specific strain in the placental environment could be more important than parasitemia itself to amplify possibilities of infection of the placental tissue. Differential susceptibility of different strains of the parasite in the intervillous space might explain those cases of high parasitemia of the mother but without congenital infection. Andrade et al. (1972) in experimental infections found that the level of parasitemia was lower in the two strains of *T. cruzi* associated with human congenital transmission.

The data presented above depict a picture of differences between biological behavior (Andrade et al. 1972, Lujan et al. 2004) and molecular characterization of different populations of *T. cruzi* (Burgos et al., 2007, Virreyra et al. 2006). On one hand different populations of *T. cruzi* have different biological behavior but there is not a specific DTU of *T. cruzi* associated to CCT. These differences merit further investigation in this area, considering individual factors specific to each chagasic pregnant woman (Torrico et al., 2004).

5. Survival of *T. cruzi* in the placental environment

It was demonstrated that trophoblasts and/or other chorionic villi cells produce various immunological agents such as hormones, cytokines, nitric oxide and nitrogen and oxygen derivatives products (Benirschke et al. 2006, Haugel-de-Mouzon and Guerre-Millo 2006). Some of these are also released to the intervillous space. This aspect concomitantly with

maternal low blood flow in the intervillous space where *T. cruzi* might be present in chagasic pregnant women, open the possibility that the parasite could be damaged and consequently the parasitemia could be reduced or cleaned out of the intervillous space. The low flow of the mother blood in the intervillous space might allow the parasitocidal agents to destroy the parasite cell limiting the placental invasion by *T. cruzi*.

The presence and quantity of parasite cells in the intervillous space seems to be an important matter in the congenital transmission of *T. cruzi*. In the acute stage of the disease, the pregnant women have intense and persistent parasitemia (Carlier and Truyens 2010, Freilij et al. 1995, Schijman 2007). The rate of *T. cruzi* transmission from mother to fetus is increased when pregnant women coursed an acute stage of the infection, as was described by Moretti et al. (2005), and reviewed by Freilij et al. (1994), Carlier and Truyens (2010), Bittencourt (1976) and Shijman (2007). Also, in experimental infection, high parasitemia worsen mating and pregnancy outcome, with high resorptions of fetuses (Mjihdi et al. 2002, Mjihdi et al. 2004, Solana et al. 2009). These results are independent of the strains of the mice and of the parasite given that Mjihdi et al. (2002) employed BALB/c mice infected with Tehuantepec population of *T. cruzi*, while Solana et al. (2009) employed C3H/HcN mice with K98 clone derived from the CA-I strain of *T. cruzi*, obtaining similar results.

There were few publications analyzing the survival of *T. cruzi* in the placental environment. This aspect was studied by Triquell et al. (2009) in *in vitro* experiments employing chorionic villi explants. In this work authors employed the whole placental barrier co-cultured with two populations of the *T. cruzi*, one was the laboratory maintained tulahuen strain and the other was isolated from a congenitally acquired new born. To study the effect of placental environment upon *T. cruzi* cell, authors employed two different strategies. In one of them, parasites were collected at the end of co-cultures placental explants – trypomastigotes and their viability were quantified. The population of *T. cruzi* obtained from a congenital case had a significantly higher survival rate than the tulahuen population of *T. cruzi* when parasites were incubated with chorionic villi explants but there was no difference in their survival between both populations when parasites were incubated with Vero cells as control. In the other strategy, authors collected culture media from placental explants and Vero cells (as control) and then treated trypomastigotes for 1h at 37°C with those media and also with fresh medium as control. Again, culture media from placental explants affect both strains of *T. cruzi*, eventhough there were more viable parasites of the congenital strain of *T. cruzi*. These results indicate that the placental environment alters the viability of the parasite cell and that there is a different behavior of different populations of *T. cruzi* in that environment. This aspect is evidently related to the permanence of the parasite in the intervillous space.

Another interesting aspect still poorly analyzed is referred to the time that *T. cruzi* remains in the intervillous space. There is a work that indirectly analyzed this aspect employing a placental perfusion model (Shippey et al. 2005). After the spiral arteries cross the basal plate, the maternal blood is poured into the intervillous space where circulates around the villi outside of the endothelium of the maternal vascular system (Brenishke, 2006). Then, blood return to the basal plate where veins drain the maternal blood into de general circulation of the mother. Differences between arterial-venous pressure is the force by which the maternal blood flows within placenta (Bernishke, 2006). According to a radioangiographic study, maternal blood fills rapidly the centers of the villous trees and then spreads slowly toward

the centrifugal subchorial and peripheral zones. Due the form of the intervillous space as narrow clefts (Bernishke 2006), maternal blood circulates slowly within placenta, allowing *T. cruzi* to interact with placental barrier in chagasic pregnant women. So the question is how much time the *T. cruzi* cell is able to stay in the intervillous space interacting with trophoblast? Shippey et al. (2005) used placental perfusion model to study transplacental passage of the causal agent of Chagas disease. A solution containing a great mass of trypomastigotes of *T. cruzi* (approximately 10^7 cells) was injected as a bolus through the maternal perfusate flow. Authors have not informed the strain of *T. cruzi* they employed. After the bolus infusion of parasites, the fetal and maternal circulations were maintained with sterile saline solution till 2 hs. The PCR (polymerase chain reaction) to detect *T. cruzi* DNA in the fetal and maternal effluents indicated presence of the parasite at 30 min, 60 min and 90 min only in the maternal one and was negative (there was not parasite DNA) in the fetal effluent. These data implicate that *T. cruzi* remains within placenta after several flows of sterile saline perfusion and also that there was not any passage to fetal circulation despite the great mass of parasites injected. This result acquires importance due the differential survival that different strains of *T. cruzi* have in the placental environment and the similar infectivity that these strains of the parasite have upon the placental tissue (Triquell et al. 2009). Thus, the biological characteristics of the parasite may play a role in the permanence of *T. cruzi* in the placental environment and it could be more important than the reproduction rate within the placental tissue.

6. Infection and survival of *Trypanosoma cruzi* in the placental tissue

6.1 Mechanism of infection

Trypanosoma cruzi which could be present in the maternal blood in the intervillous space, cross the trophoblastic barrier, the first placental line of defense or other placental tissues deprived of trophoblastic defenses. The trypomastigotes into the stromal of chorionic villi (the second placental line of defense) and/or chorionic plate constituted by connective tissue fibers and cells such as fibroblasts, myofibroblasts and macrophages (Hofbauer cells), can further multiply within such cells if that have not been destroyed by mesenchymal phagocytic cells. The parasite formed nest o pseudocysts which once rupture, releases new motile parasites. Sequential infection of other cells, finally infecting myocytes and endothelial cells of fetal vessels in villous chorion, chorionic plate and gain access to fetal circulation and infect the fetus causing the congenital form of the disease (Bittencourt 1976, 1992; Carlier 2005; Fernandez Aguilar et al 2005). Some authors believe that the trypomastigote have to find a lesion in the trophoblast in order to penetrate the placental tissue (Bittencourt 1963) because trophoblast may conform a barrier to *T. cruzi* infection. Histopathological analysis of placentas to brazilian infected women showed placental inflammation with villitis and areas of trophoblast destruction or necrosis which induced to release inflammatory cytokines such as TNF- α and production of local inflammatory mediators. These factors can induce a rupture of the trophoblastic barrier facilitating fetal infection (Redline 2004).

The invasion mechanism of the protozoan parasite *T. cruzi* was originally assumed to be similar to the many bacterial pathogens which mobilize the actin cytoskeleton of host cells in a phagocytosis-like process (Galan and Bliska 1996). Works studying in vivo invasion revealed a gradual accumulation of host cell lysosomes at the parasite entry site, and

progressive fusion of these lysosomes with the plasma membrane as invasion proceeded into several cell types (Andrews 1995, Sibley and Andrews 2000, Tan and Andrews 2002). Morphometric and cytochemical analyses have demonstrated increased lysosomes in placentas of women with Chagas disease (Fretes and Fabro 1995)..

The cortical actin cytoskeleton acts as a barrier for lysosome recruitment and fusion. However not polymerized actin was detected around *T. cruzi* containing intracellular vacuoles and invasion was significantly enhanced by disruption of host cell microfilaments (Tardieux et al 1992). Sartori et al. (2003) have observed in cultures of explants of placental villi in vitro that the parasite induced disassembly of the cortical actin cytoskeleton, and authors proposed this is a step in the *T. cruzi* invasion mechanism into placental cells that allowing lysosomes to access to the plasma membrane, and to form the parasitophorous vacuole. Fusion of lysosomes with the plasma membrane is required for parasite entry into several cell types and that the process is triggered by elevations in intracellular free Ca^{2+} concentration (Burleigh and Andrews 1998). *T. cruzi* might be taking advantage of Ca^{2+} -regulated lysosomal exocytosis in the repair of plasma membrane lesions (Redddy et al. 2001) for cell invasion.

The specific signaling pathway and mechanisms for *T. cruzi* entry into placental cells is still not well understood. In order to understand the process, Calderón and Fabro (1983) studied the interaction between syncytial plasma membranes from the human placenta and from the parasites; they found modifications of membrane lipids and proteins of the villi trophoblast. Also modifications in trophoblast enzymatic activity and in chorionic villi have been described (Fretes and Fabro, 1990; Fretes and Fabro, 1994; Fretes and Fabro, 1995). Placental alkaline phosphatase (PLAP) is a trophoblast plasma membrane protein and has been proposed to have a pathogenetic role in the congenital chagas disease. PLAP activity decreased in women with Chagas disease and is related to congenital transmission (Sartori et al, 1997) and also is modified in placental villi cultured with *T. cruzi* (Sartori et al 2002, Fretes and Fabro 1990). PLAP anchored to the cell membrane lipid layer by a glycosylphosphatidylinositol (GPI) molecule participates in the process of *T. cruzi* invasion into placental syncytiotrophoblast cells by hydrolysis of the GPI molecule (Bertello et al 2000). Activation of tyrosin kinase proteins increase cytosolic calcium and rearrangement actin filaments of the host cells (Shijman 2007). Treatment of microvilli with phospholipase C before engagement by *T. cruzi* hinders parasite invasion into placental trophoblast (Sartori et al 2002), probably altering the placental alkaline phosphatase.

6.2 Placental areas of parasite invasion

The trophoblast according to Rassi (1958) and Carlier (2010) constitutes a potential barrier to penetration of *T. cruzi* (Bittencourt 1976; Carlier and Truyens 2010). The histopatological analyses of placentas from congenital cases display intense villitis with parasites in villous trophoblast as well as in villous stromal cells (Bittencourt 1976; Bittencourt 1988; Drut and Araujo 2000). However in other studies villitis was uncommon and parasites were not or hardly identified in trophoblast (Moya et al 1979; Azogue et al 1985; Carlier 2005). Also the parasite was described in the trophoblast but the fetus was free of infection (Bittencourt 1992). Some in vitro studies mention that trophoblastic cells are easily infected by *T. cruzi* (Sartori et al 2002; Shippey et al 2005) but other authors show low multiplication rate of the parasite and the incapacity of *T. cruzi* to produce a sustainable infection in the normal

chorionic villous explants *in vitro* (Luján et al 2004, Triquell et al. 2009). The different results might be referred to different number of parasites employed by researchers, as was demonstrated by Duaso et al. (2010) and also to different strains of *T. cruzi*.

Parasite was found in placental areas deprived from trophoblast at chorionic plate and amastigotes were seen within membranes of amniotic epithelium a fact that may suggest the presence of trypomastigotes in the amniotic liquid in association with chorionitis (Moya et al 1979; Azogue 1985; Carlier 2005; Fernandez Aguilar et al 2005). Biopsies in placentas from infected newborns showed high density of parasites at the level of marginal zone (Carlier 2005) eluding as a consequence, the defenses of the trophoblast (Lujan et al. 2004).

6.3 Survival of *T. cruzi* in the placental tissue: mechanisms of resistance

Considering the lower congenital transmission incidence and also the report of uninfected infants with parasitized trophoblast of chorionic villi (Freillij et al 1994; Bittencourt 1992), it argues for the efficacy of the placenta to control the *T. cruzi* infection.

Previous analysis involves lysosomes in the *T. cruzi* invasion into host cells, and also in Chagas parasite destruction (Carvalho and de Souza 1989; Milder and Klotzel 1980). Fretes and Fabro (1995) described increasing lysosomes and acid phosphatase activity in chagasic placentas without congenital transmission, suggesting that lysosomes population are involved in the processes of placental infection and human congenital transmission of Chagas disease. Modifications of enzymatic activity in the trophoblast and in chorionic villi have been described (Fretes and Fabro, 1990a; Fretes and Fabro, 1990b; Fretes and Fabro, 1994; Fretes and Fabro, 1995). Furthermore, it was demonstrated that normal human placental lysosome subfraction and its supernatant subfractions of normal placentas have deleterious effects upon the *T. cruzi* in *in vitro* placental cell-free system (Frank et al., 2000).

In this way it was determined an absence of productive infection of *T. cruzi* into normal chorionic villi in an experimental system of chorionic villi explants co-cultured with the parasite in contrast to susceptible cells such as VERO cells (Luján et al. 2004). These findings may be in accordance with pathological results found in chagasic placentas, where parasites are found in placental chorionic villi but newborns are free of parasites without congenital transmission (Bittencourt 1992).

All of these data were obtained employing an *in vitro* system of chorionic villi explants co-cultured with infective forms of the *T. cruzi*, as have been previously successfully employed with bacteria, virus and protozoan (Poliotti. et al 2002). The experimental system employed is very similar to the real situation in the uterus where placental villi are floating in the intervillous space bathed by the mother's blood which could contain *T. cruzi* in the pregnant chagasic woman.

Which are the possible mechanisms involved in the control of productive infection of *T. cruzi* in chorionic villi and protective function of the placenta? Placentas express eNOS and iNOS (endothelial and inducible nitric oxide synthases respectively) and produce a large amount of Nitric Oxide (NO) (Conrad 1995; Myatt et al 1993, Soorana et al 1999) which has been implicated as parasitocidal agent to microorganisms, including *T. cruzi* (Villalta1998, Gobert 2000). The causal agent of Chagas disease is affected by NO, according to *in vitro* and *in vivo* studies in cardiomyocytes (Fichera et al 2004).

According to Triquell et al. (2009) eNOS transcription and protein expression was significantly higher when parasites were present in in vitro experimental system. Also, the level of NO in the placental environment contains deleterious NO levels to *T. cruzi* (Triquell et al. 2009, Villalta et al. 1998), with two strains of *T. cruzi* behaving differently in this environment. Although there are several immunological mechanism to eliminate the intracellular pathogens as NO, parasites have elaborated a variety of strategies to escape of the immune response and to make possible their survival and replication in the host. Some parasites modulate the production of several toxic molecules synthesized by the immune system. Interestingly, it has been described that some parasites were able to escape to deleterious NO due to the arginase induction (Stempin and Cerban, 2007). Consequently, only certain strain of the parasite may produce a sustainable infection and offer the subsequent possibility of infecting the fetus in pregnant women with Chagas disease. So, at this time, by contrast with information collected in experimental murine model (Solana et al., 2002) there is no clear evidence of a relationship between *T. cruzi* genotype and congenital infection in humans (Shijman 2007, Burgos 2007).

The capacity of each placenta to produce deleterious agents in the placental environment, the different susceptibility of strains of *T. cruzi* in this deleterious medium (Triquell et al. 2009), the low capacity of the parasite to induce a reproductive infection in chorionic villi (Lujan et al. 2004), as well as the possibility that different placental cells types have differential susceptibility to be infected by *T. cruzi* (work that is on going in our lab) can modulate the success of transplacental transmission for congenital Chagas disease via chorionic villi route.

7. Association of placental infection by *T. cruzi* with other pathological conditions

7.1 Chagas placental alterations and associated pathologies

It is thought that congenital Chagas' disease is a product of a complex interaction among the maternal immunological or nutritional status, obstetrical history, maternal stage of disease, placental factors, and the characteristics of the parasite, such as the strain of *T. cruzi* or the parasitic load (Bittencourt 1992; Carlier, 2005; Burgos, et al 2007), but none of these factors have been conclusively demonstrated yet (Moretti et al, 2005).

During pregnancy, there is an increased susceptibility to certain autoimmune diseases and intracellular infections (Guilbert, et al 1993; Lin et al, 2005), like Acquired Immune Deficiency Syndrome (AIDS) (Derrien et al, 2005), infections associated with AIDS (Margono et al, 1994), malaria (Gamain, et al 2006), toxoplasmosis (Biedermann, 1995), etc. The restructured placental barrier possibly facilitates the invasion of diverse pathogens. In addition to *T. cruzi*, other congenital diseases caused by parasites have also been described, among which *Plasmodium falciparum*, the agent responsible for causing malaria, (Rogerson, et al, 2007; Desai et al, 2007), *schistosoma* (Friedman et al, 2007), *Toxoplasma gondii* (Biedermann, 1995; Correa et al, 2007) and *Trypanosoma brucei* (Rocha et al, 2004) are of importance (Kemmerling et al, 2010).

7.2 Chagas, Diabetes and Hiperglycemia

Diseases caused by protozoa have been reported to be associated with nutritional deficiencies, wasting and diabetes. An association between human *T. cruzi* infection and

obesity and diabetes, has been suspected and there has been general belief, that the incidence of diabetes may be increased in the chagasic population (Nagajyothi et al, 2009).

Pancreas is one of the organs affected in Chagas' disease. Patients with this disease have plasma pancreatic glucagon and pancreatic polypeptide levels reduced (Long et al, 1980), lower insulin activity (Guariento et al, 1994), and morphometric and morphologic alterations of pancreatic ganglia and islets (Saldanha et al, 2001). Hyperglycemia and abnormal glucose tolerance tests observed in some patients with chronic Chagas' disease suggest the possibility of morphological changes in pancreatic islets and/or denervation (dos Santos et al, 1999; Saldanha et al, 2001). The observed morphometric and morphologic alterations are consistent with functional changes in the pancreas, including glycemia and insulin disturbances (Saldanha et al, 2001).

Experimental infections in hamsters caused pancreatitis, erratic blood glucose levels and a tendency to hypoinsulinemia (Dos Santos et al, 2004). Diabetes in pregnancy is associated with serious abnormalities in the hormonal and metabolic milieu, and in the maternal and fetal blood supply. These changes are likely to initiate structural and biochemical alterations in placental tissue, which may in turn be related to disturbances in placental functions and metabolic performances (Vannini, 1994; Garner, 1995; Desoye & Shafrir, 1996). On the other hand, different authors have reported that diabetics have an increased susceptibility to a variety of infectious agents (Plouffe et al, 1978, Casey J, Sturm 1982). The course of parasitic diseases such as malaria (Tulbert & McGhee, 1960), schistosomiasis (Mahmoud, 1979) and trypanosomiasis (Tanowitz et al, 1988) has been studied in diabetic animals.

Hyperglycemia has been previously observed to increase the morbidity and mortality of murine *T. cruzi* infection (Tanowitz et al, 1988). While *T. cruzi* infection causes hypoglycemia which correlates with mortality, hyperglycemia is associated with increased parasitemia and mortality (Nagajyothi et al, 2009). It has also been observed that women with the chronic cardiac form of Chagas' disease have diabetes mellitus and disturbances in the regulation of glycemic level at a higher frequency than normal controls, probably due to reduced activity of the parasympathetic system (dos Santos et al, 1999). But, according to the analysis of the bibliography, there is not any study analyzing an association between pregnant women affected with both Chagas' disease and diabetes with congenital transmission or with the effect on the new born. Furthermore, there is no marker for placental or fetus infection in Chagas' disease (Mezzano et al, 2012).

T. cruzi crosses the placental barrier and infects the fetus, causing the congenital form of the disease (Bittencourt, 1976). In order to understand the mechanism used by the parasite to cross this barrier, the interaction between syncytiotrophoblast plasma membranes from the human placenta and the parasite was previously studied, with modifications in lipid and protein patterns from trophoblast membranes being found (Calderón, Fabro, 1983). However, the mechanism by which the parasite infects the placenta as well as the effects upon the protein contents of the placental barrier is still not well understood.

Due the effect of the Chagas parasite on some proteins located at the lipid raft of chorionic villi trophoblast (Fretes RE, de Fabro 1990; Priotto et al, 2009); as well as in trophoblast lipids (Fabro AE, Calzolari, 1990), it was analyzed the possible modification of the main glucose transporter located at the syncytiotrophoblast, the GLUT1 protein, produced by placental *T. cruzi* infection. These experiments showed that GLUT1 protein expression was significantly

diminished in normal placental villi cultured under high glucose concentration in vitro infected with *T. cruzi*, compared to controls (Mezzano et al, 2012).

It was reported that *T. cruzi* causes disorganization of the basal membrane of the trophoblast and the stroma of the chorionic villi, in in vitro experiments (Duaso et al, 2010). Similar changes were registered in human placental explants cultured under high glucose concentration, so, both conditions hyperglycemia and *T. cruzi* infection can modify the stroma of the human chorionic villi (Mezzano et al, 2012).

Furthermore, *T. cruzi* produces plasmatic membrane modifications, by altering their lipid (Fabro AE, Calzolari 1990, Calderón RO, Fabro 1983) and protein components, such as Placental Alkaline Phosphatase (Sartori et al, 2003; Lin et al, 2004; Lin et al, 2005; Mezzano et al, 2005, Fretes RE, Fabro 1990, Sartori et al, 2005), and Glut1 protein (Mezzano et al, 2012). On the other hand, we observed in our laboratory, that Gamma glutamyltranspeptidase, another enzyme present in the placenta's brush border, is not affected in cells co-cultured with *T. cruzi* (Priotto et al, 2009), suggesting that the parasite affects molecules inserted in lipid microdomains of the membrane, as PLAP (Salamon et al, 2005) and GLUT1 (Sakyo et al, 2007). As the hyperglycemia characteristic of diabetes mellitus also affects these membrane components, it was suggested that both the parasite and the high glucose conditions could have been provoking, by different ways, a lower placenta efficacy as a barrier against infections (Mezzano et al, 2012). Reduced GLUT1 expression observed in placental cultures with parasites could imply a down-regulated GLUT1 activity in pregnant women with Chagas' disease. If this disease is causing damage to pancreas islets (Long et al, 1980; Guariento et al, 1994; Saldanha et al, 2001), or happens together with a previous diabetic condition, the adverse effects of reduced GLUT1 activity may be exacerbated. As a consequence, it is of importance to perform a systematic study analyzing new born from pregnant women who have both conditions diabetes and Chagas (Mezzano et al, 2012).

It has been described that chorionic villi in vitro has low susceptibility to infection by *T. cruzi* in normal D-glucose concentration (Luján et al, 2004, Triquell et al, 2009). Nagajyothi et al. (2010) have been studied the effects of hyperglycemia on *T. cruzi* infection rekindled by the increased incidence of obesity and diabetes mellitus, which have the potential to worsen the disease, in areas where *T. cruzi* infection is endemic. In recent years, there have been several studies indicating that diabetes and obesity may be more common in the population of individuals at risk for *T. cruzi* infection (dos Santos et al, 1999; Guariento et al, 1993; oliveira et al, 1993; Geraix et al, 2007; Nagajyothi et al, 2009; Nagajyothi et al. 2011; Saldanha et al, 2001).

7.3 Chagas and HIV

The reactivation of *T. cruzi* infection is observed in individuals who undergo immunosuppressive therapy for malignancies and organ transplantation as well as in individuals with human immunodeficiency virus (HIV) infection and AIDS (Tanowitz et al, 2009; Sartori et al, 2007; Vaidian et al, 2004; Barcán et al, 2005).

HIV and parasitic infections interact and affect each other mutually. Whereas HIV infection may alter the natural history of parasitic diseases, impede rapid diagnosis or reduce the efficacy of antiparasitic treatment, parasitoses may facilitate the infection with HIV as well as the progression from asymptomatic infection to AIDS. There are data on known

interactions for malaria, leishmaniasis, Human African Trypanosomiasis, Chagas' disease, onchocerciasis, lymphatic filariasis, schistosomiasis and intestinal helminthiasis. The common immunopathogenetic basis for the deleterious effects of parasitic diseases may have on the natural history of HIV infection seems to be a particular type of chronic immune activation and a preferential activation of the T helper (Th)2 type of help. Control of parasitic diseases should complement the tools currently used in combating the HIV pandemic (Harms and Feldmeier, 2002).

While for Human African Trypanosomiasis, as well as for onchocerciasis and lymphatic filariasis there is little evidence for an interaction with HIV as yet, *T. cruzi* clearly behaves as an opportunistic agent in the presence of HIV infection (Harms and Feldmeier, 2002). In analogy to the mechanisms in *Leishmania*/HIV co-infections, the ongoing immunosuppression allows *T. cruzi* to multiply, particularly in the chronic stage of Chagas' disease (Perez-Ramirez et al. 1999). Clinically, it may be difficult to differentiate Chagas' disease reactivation as a consequence of HIV infection and chronic chagasic disease. However, reactivation of Chagas' disease in HIV-positive individuals is always associated with high parasitaemia, while in chronic disease, parasitaemia is very low and can only be detected by xenodiagnosis (Perez-Ramirez et al, 1999). Treatment of *T. cruzi* infection in HIV-positive individuals is recommended to be started early in the reactivation process when irreversible alterations have not yet occurred (Sartori et al, 1998).

Almeida and col. (2010) studied the prevalence of Chagas' disease among HIV seropositive patients, registering that the prevalence of co-infected subjects was 1.3% (Almeida et al, 2010). Dolcini and col. (2008) demonstrated that the presence of an intracellular pathogen, such as *T. cruzi*, is able to impair HIV-1 transduction in an in vitro system of human placental histocultures. Direct effects of the parasite on cellular structures as well as on cellular/viral proteins essential for HIV-1 replication might influence viral transduction in this model. Nonetheless, additional mechanisms including modulation of cytokines/chemokines at placental level could not be excluded in the inhibition observed. Further experiments need to be conducted in order to elucidate the mechanism(s) involved in this phenomenon. Therefore, coinfection with *T. cruzi* may have a deleterious effect on HIV-1 transduction and thus could play an important role in viral outcome at the placental level (Dolcini et al 2008).

Maternal viral load and immunological status are the main factors that determine the risk of HIV- Mother-to-child transmission (MTCT) (Bongertz 2001; Scarlatti, 2004). Other risk factors are coinfections of the mother (WHO/UNAIDS 1999, Hotez et al, 2006), an important issue since world regions with the highest prevalence of HIV-1 infection are also affected by other infections. Thus, HIV positive pregnant women are usually infected with other pathogens, and such placental coinfections may have consequences on mother to child transmission of the pathogens.

Data from HIV-*T. cruzi* coinfecting patients indicated reactivation of parasite infection with exacerbation of clinical signs and unusual clinical manifestations (Ferreira MS, Borges 2002; Harms G, Feldmeier, 2002; Sartori et al, 2002; Sartori et al, 2007). Even if no evidence exist of coinfection in the mothers, MTCT of both pathogens with severe outcome for the children (Freilij H, Altcheh , 1995) and congenital transmission of *T. cruzi* without confirmation of HIV-1 MTCT (Nisida et al, 1999) were reported. However, little is known about interaction of both pathogens on an in vitro cellular or ex vivo tissue model.

As a result of the significant burden of the HIV pandemics in resource-poor regions, a number of potential epidemiological, biological, and clinical interactions between HIV and other tropical pathogens gained relevance and need to be studied. The interactions between HIV and tropical infectious agents are complex. Each pathogen has the potential to alter the epidemiology, natural history, and/ or response to therapy of the other pathogens (Karp & Auwaerter, 2007); therefore, it is unpredictable to establish the outcome of such coinfections.

In Latin America, one of the most significant endemic protozoonoses is Chagas' disease, and several clinical studies from HIV-T. cruzi coinfecting patients have been reported (Ferreira MS, Borges 2002; Harms G, Feldmeier, 2002; Sartori et al, 2002; Sartori et al, 2007). MTCT is one way of transmission shared by both pathogens. The exact mechanisms involved in MTCT of both pathogens are not clear. Hence, the study of their interaction at the placental level is critical for designing strategies that abolish MTCT. In in vitro culture system of term placental histocultures, as well as in the trophoblast cell line BeWo, it was demonstrated that acute coinfection with T. cruzi and HIV-1 pseudotyped virus decreases HIV-1 replication. This is the first report about interaction of these pathogens at the placental level (Dolcini et al, 2008).

A great impairment of HIV-1 replication was observed in coinfection with viable T. cruzi trypomastigotes purified from mouse blood (BT). Moreover, when other source of viable trypomastigotes was used, such as those grown in cell culture (CT), the same effect on HIV-1 replication was observed. In all cases, hCG secretion was measured in histoculture supernatants and no significant differences were observed between control, viral infection, or treatment with trypomastigotes. These results indicate that placental tissue remains viable and that parasite impairment of HIV-1 replication was not associated with direct cell toxicity caused by T. cruzi. Previous data indicate that the parasite induces rearrangement of cortical cytoskeleton of syncytiotrophoblast with actin microfilament depletion during human placental invasion (Sartori et al, 2003). Considering that after entering the cell, the HIV-1 virion interacts initially with actin filaments which assist binding to microtubules and transport to the nuclear periphery (Warrilow and Harrich, 2007), modifications in trophoblast cytoskeleton might impair viral replication at an early phase in the case of active T. cruzi invasion. However, the inhibition of HIV replication seems to be caused not only by viable trypomastigotes but also by soluble factors shed by the parasite, either from BT or CT (Dolcini et al, 2008).

Dolcini et al. (2008) evaluated whether the parasite or its soluble products were able to modify the placental environment. In fact, many soluble factors, including cytokines and hormones, with regulatory activities are essential for establishing and maintaining pregnancy (Saito, 2000; Bowen, 2002). HIV-1 and antiretroviral treatment in pregnant women have an impact on the pattern of placental soluble factors (Faye et al, 2007; Pornprasert 2006). Little is known about the changes in human fetal-maternal interface in T. cruzi infection (Dolcini et al, 2008).

8. Conclusion

Spreading of Chagas to non-endemic cities of the world due mainly to congenital Chagas transmission put this form of the disease in one of the top public health problem, needing more attention for researchers, epidemiologists and governmental officials. There are still

many questions not answered yet that need more support to elucidate them. Data from chorionic villi-resistance to *T. cruzi* could lead to obtain mechanisms that lead to prevention of fetal infection.

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10. References

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This book contains the total of 19 chapters, each of which is written by one or several experts in the corresponding field. The objective of this book is to provide a comprehensive and most updated overview of the human placenta, including current advances and future directions in the early detection, recognition, and management of placental abnormalities as well as the most common placental structure and functions, abnormalities, toxicology, infections, and pathologies. It also includes a highly controversial topic, therapeutic applications of the human placenta. A collection of articles presented by active investigators provides a clear update in the area of placental research for medical students, nurse practitioners, practicing clinicians, and biomedical researchers in the fields of obstetrics, pediatrics, family practice, genetics, and others who may be interested in human placentas.

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