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Chagas Heart Disease

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1. Introduction

Chagas disease (CD) or American trypanosomiasis is a complex zoonosis produced by the infection with the intracellular protozoan parasite *Trypanosoma cruzi*. Although the disease was first described in 1909 by the Brazilian physician Carlos Chagas, this disease affects human beings since antiquity as it was demonstrated by paleoparasitology studies which proved the presence of DNA in mummies dating back to 9000 years old (Aufderheide et al., 2004; Guhl et al., 1999). The parasite *T. cruzi* is a hemoflagellate protozoan belonging to the Mastigophora class, Kinetoplastida order, Trypanosomatidae family, genus Trypanosoma, the group Stercoraria. It was named in honor of Oswaldo Cruz, who was the mentor of Carlos Chagas**.**

T. cruzi has a complex life cycle involving two hosts, an invertebrate, especially an insect vector and some vertebrates, including man and domestic and wild reservoirs (Tyler & Engman, 2001). The presence of CD in humans is purely accidental, as when the man came into contact with natural foci and caused ecological imbalances causing the adaptation of vectors to human dwellings and new food sources. Thus three overlapping cycles were established: the wild cycle, the peridomestic cycle and the domestic cycle (Coura, 2007). The parasite occurs in a variety of hosts and infects 150 species from 24 families of domestic (e.g., dogs, cats and guinea pigs) and wild animals (e.g., rodents, marsupials, and armadillos) (Rassi, et al., 2010). The vectors involved in the transmission of CD are insects of the Phylum Arthropoda, Class Insecta, Order Hemiptera, Family Reduviidae, belonging to the subfamily Triatominae. There have been reported approximately 130 species of wild and domiciliary triatomines although only a handful is the competent vector for *T. cruzi* (Schofield, 1981). The domestic species mainly colonize rural homes and peri-urban areas and these species are responsible for most human cases of Chagas disease in endemic areas. Sylvatic species are inhabitants of strict wild habitats such as cracks of rocks, bird nests or burrows of mammals and caves, among others. *Rhodnius prolixus* is the main domestic vector in the northern countries of South America and Central America, *Triatoma dimidiata* in Central America and *Triatoma infestans* in countries of the southern of South America (Guhl, 2007), these species are well adapted to human habitation.

T. cruzi presents four different morphological and biological forms: epimastigote, a replicative form located in the mid gut of the insect vector, it is the predominant form in the axenic culture; metacyclic trypomastigote develops in the posterior intestine and rectum of the insect vector and is the infective form; amastigote replicative stage, is located in the

cytoplasm of mammalian host cells where it replicates by binary fission; blood trypomastigote comes from amastigote differentiation, leading to disruption of the host cell and releases into the bloodstream, where they are taken again by the blood-sucking vector (Brener, 1971) (Figure 1)

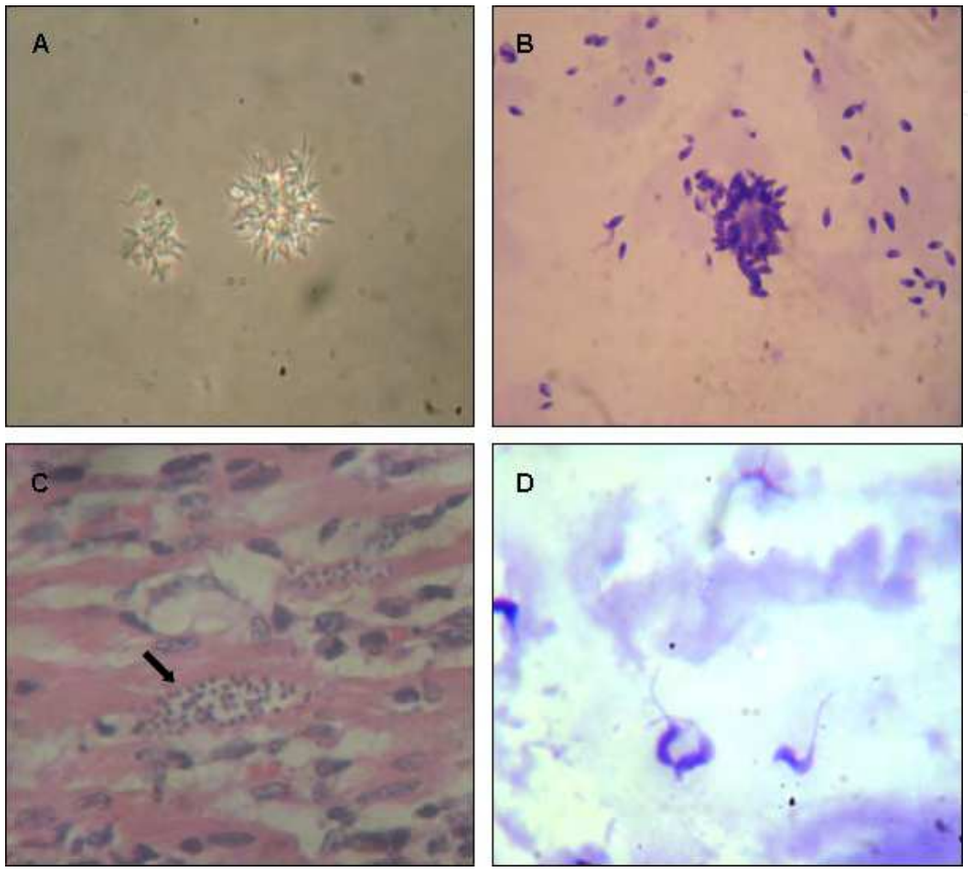

Fig. 1. *Trypanosoma cruzi* different stages. A) Epimastigotes of culture B) Amastigotes in Vero cells C) Nests of amastigotes in cardiac tissue D) Blood trypomastigotes stained with hematoxiylin-eosin.

The classic forms of *T. cruzi* transmission are vectorial, congenital, by transfusion, through organ transplants and labour accident. Vector-borne transmission is the most common and is contaminative by the presence of the infectious form in the faeces of the vector which is released when feeding on the host. The trypomastigotes penetrate through the opening of the bite or loss of continuity due to scratching or active penetration of oral or ocular mucosa. Before screening programs in blood banks, transfusion was the second form of transmission by the presence in donor's blood or blood products infected with parasite forms (Schmunis, 1999). Another important source of transmission is the donation of organs from infected individuals with the development of acute Chagas in the immunosuppressed recipient (Barcan et al., 2005). The passage of the parasite from infected mother to her baby during pregnancy, childbirth or while breast-feeding is high in some endemic regions, specially in Bolivia. The congenital transmission can lead to abortions, premature births or infected babies (Torrico et al., 2004).

2. The impact of Chagas disease

CD is currently is recognized by the World Health Organization (WHO) as one of the tropical neglected diseases and the infection with *T. cruzi* is the third parasitic infection after malaria and schistosomiasis (Schmunis & Yadon, 2010). CD is an important public health problem in 21 countries of South and Central America. The Pan American Health Organization (OPS, 2006) estimates that 7.7 million people are infected with *T. cruzi*, 109 million are at risk of infection and 12,500 deaths occur per year. The number of new annual cases of vector-borne infection is 41,000 and congenital Chagas' is 14,000 (WHO 2008).
Although this disease is considered typical of rural areas and poor suburbs with inadequate housing conditions, in recent decades in many Latin American countries there has been a substantial migration from rural to peri-urban areas. Migration has not only occurred from rural to urban areas in Latin America, but also to developed countries of North America, Europe and Asia. Accordingly, further cases have been detected in non-endemic countries like the USA, Canada, Spain, Japan and Australia due to population migration from endemic countries. In the United States have reported more than 300,000 people infected with *T. cruzi* and in Spain from 40 to 60,000 (Bern & Montgomery, 2009; Gascon et al., 2010).
The migration in endemic countries has led to the passive transport of vectors and the emergence of cases in areas considered of low endemicity. Additionally, the national initiatives for the elimination of the domestic vectors, including not only insecticide spraying but also a rural housing improvement, have led to the elimination of traditional vectors. However, a new transmission pattern is being introduced due to the presence of palms and trees located close to houses and sylvatic vectors that are attracted sporadically by light and feeding conditions. Consequentially, transmission by new vectors has arisen and often these vectors often have high rates of infection. This couple with the presence of wild reservoirs in the peridomestic area presenting high rates of infection has led to an alternate form to vectorial transmission in these areas, such as oral transmission (Briceño-León, 2009). This form of transmission is usually associated with acute and fatal outcomes and it has been increasing especially in the Brazilian Amazon where it is considered an emerging disease (Coura et al., 2002). The first report was given in 1960 in Teutonia with five deaths involved (Valente et al., 2009). Since then 600 new cases of acute Chagas have been reported, 50% associated with oral transmission. There are also reports in Venezuela (Alarcon de Noya et al., 2010), Mexico (Salazar-Schettino et al., 2011) and in the last three years in Colombia has increased, especially in Santander with six outbreaks of acute Chagas and three fatal cases (Díaz et al., 2009).

3. Clinical aspects of Chagas disease

3.1 Phases of Chagas disease

3.1.1 Acute phase

The clinic course of CD could have two phases: acute and chronic. The acute phase is characterized by the presence of *T. cruzi* trypomastigotes in the bloodstream, the parasitaemia generally persists for 4–8 weeks and it resolves spontaneously. In the majority of cases, especially in adults, this phase of infection is asymptomatic, however a small percentage of patients develops the acute disease characterized by important manifestations such as malaise, prolonged high fever, headache, edema, hepatomegaly, splenomegaly and generalized lymphadenopathy (Prata, 2001). In the acute form of CD, the first signs appear

7–10 days after infection. The Romaña's sign is observed when the parasite penetrates the conjunctiva; but when the parasite penetrates through the skin the patient develops the chagoma at the site of inoculation. The adjacent lymph nodes to the site of entry of the parasite are generally compromised, which together with the conjunctival or eyelid lesions constitute the ophthalmo - lymphonodal complex. Aproximately the fifty percent of the patients who develop the acute CD has Romaña's sign, and one-quarter has the inoculation chagoma. The Romaña's sign is characterized by painless, unilateral swelling of the upper and lower eyelid, with rose -violet coloration, congestion and edema of the conjunctiva, the submandibular, preauricular or other near lymphonode are enlarged, but not adhering to deep layers, occasionally may appear palpebral and periorbital cellulitis, sometimes with necrosis and abundant parasites. The inoculation chagoma generally appear on the skin of the face or the extremities, and is a forunculoid lesion, with a rose violet tone. In these patients, the initial electrocardiogram is normal, but after 2-3 weeks might show anomalies such sinus tachycardia, low QRS voltage or first grade atrioventricular block, the chest radiograph is also normal, however it might show cardiomegaly (Dias, 1989; Rassi et al., 2010).

The majority of patients, (90% or more) with acute CD survive the initial infection and remain healthy and asymptomatic, but a few individuals, between 2 -10%, generally infants or immunodepressed patients, or many people like children or adults who acquired the infection due to oral contamination, develop an acute and severe disease with myocarditis and cardiac insufficiency or with meningoencephalitis, clinical conditions that maybe cause death (Nobrega et al., 2009). Regarding to the central nervous system (CNS) involvement in CD, in the initial acute phase, the infection is asymptomatic and only a small percentage of cases develops encephalitis in the acute phase of disease; headache, seizure, focal neurologic signs and progressive decrease in consciousness are the notorious symptoms (Cordova et al., 2007).

3.1.2 Chronic phase

The great majority of patients, who were infected with *T. cruzi*, remain asymptomatic in the chronic phase, without abnormalities in the electrocardiogram and the radiological evaluations of the heart, esophagus and colon. This form of the chronic phase of CD is named indeterminate form, it is present in the half of infected people of endemic areas, and may persist until dead in 40-50% of the cases. All patients with the indeterminate form of CD are positive in serological or parasitological examinations, and do not have symptoms or signs of the disease, but using specialized methods such as ambulatory electrocardiographic monitoring or endomyocardial biopsies, may demonstrate that they have at least some degree of cardiac damage. The morphologic features of the indeterminate form of CD in autopsies performed for us in individuals who died of other causes, include discrete focal infiltration of mononuclear cells with lymphocytes predominance, and mild interstitial fibrosis, these changes are notorious in the subendocardical zone, and near to the cardiac conduction system. The change from the indeterminate form to the determinate cardiac or digestive occurs slowly in a lapse of 10 – 20 years after the initial infection, in a few cases, approximately 2-3% per year. In these patients, the CD adopts a slow and benign course, but others develop dilated cardiomyopathy, heart congestive failure or arrhythmias. In sporadic cases the CD progresses directly from the acute form to determinate chronic form of human CD, and is named the subacute form, that generally affects young adults, these patients develop severe cardiopathy with cardiac failure (Marin-Neto et al., 1999).

In the chronic phase of CD, the fundamental morphological feature in patients with chronic chagasic cardiopathy (CCC) is a mixture of cellular infiltration of lymphocytes and monocytes with few plasma cells, and fibrous tissue, that correlate with diverse clinical symptoms and signs, since asymptomatic to a congestive syndrome with damage of conduction system, arrhythmias, disturbances in the ventricular repolarization and the extrasystoles. Thromboembolic phenomens due to cardiac mural thrombosis are also frequent. In the majority of these patients, in the thorax radiographs, the heart contour appears normal. In some cases the lack of symptoms is surprising, and it does not have correlation with damage of tissue detected under microscopical examination. The symptomatic patients with CCC related palpitations by arrhythmias or fatigue by cardiac failure. In the physical examination, the arrhythmias and the extrasystoles are the most frequent clinical features detected. In these patients, the cardiac failure has a slow and progressive course, generally with features of right failure predominating the legs edema, jugular ingurgitation, ascites, and hepatomegaly. The thromboembolic manifestations due to mural thrombosis are frequent, and in autopsies done by us, the pulmonary thromboembolism is the most common anatomopathological feature, although brain embolism is also recognized in a few cases. After the manifestations of cardiac failure, the patients may recover or die in a later episode to one year after the first symptoms of decompensation. In these patients the periganglionitis with reduction of neuronal bodies especially in the sympathetic system, the sinusal node fibrosis, and destruction of tissues of cardiac conduction system and the myocardial cells are related with the early alterations of autonomous nervous system. The described changes can explain the reduction of the response to cardiovagal reflex in the sinusal node, and the reduction of variability of the heart frecuency. The cardiovagal denervation increased the sympathetic tone and could explain why the arrhythmias, blockades and sudden death are the first clinical manifestations in these patients (Samuel et al., 1983; Rassi et al., 2001).

The digestive form of CD is present almost exclusively in Argentina, Brazil, Chile and Bolivia, although they have reported isolated cases in Colombia, Central America and Mexico. The symptoms are the consequence of achalasia. The dysphagia is the first disturbance that may lead to malnutrition and weight loss. Odynophagia and epigastric pain also occurs in cases of megaesophagus, and chronic constipation, abdominal distension and occasionally intestinal obstruction of large bowel in cases of megacolon (Florez et al., 2010).

3.2 Pathological anatomy

The changes described below are the product of the experience gathered in the practice of autopsies of patients who died of various forms of CD, and reflect the interaction between inflammatory response, cellular damage and alterations of the extracellular matrix, three pathologic processes generated by the parasite in the tissues, particularly in the heart, esophagus, colon and central nervous system.

In the acute phase when the infectious forms of *T. cruzi* penetrate in the cell, such macrophages, fibroblasts, Schwann cells, and myocytes, they transform in amastigotes, subsequently reproduce and form the parasitic nest or pseudocyst, after 3 – 5 days the parasite differentiates to trypomastigote, the pseudocyst enlarges, breaks the cell, releasing intact or degenerate forms of the parasite, which act in the interstitium as a particle that promotes the inflammatory response. In these cases the heart is enlarged, congestive, flaccid

with haemorrhagic foci on the epicardic surface, and at the cut, the cardiac chambers are dilated and the myocardium shows areas of haemorrhage and necrosis (Figure 2 A and B). In the microscopic examination, the extent of the inflammatory response is proportional to the number of pseudocyst and damaged cells. A dense interstitial infiltration of lymphocytes, macrophages, with a few neutrophils and eosinophils around the pseudocyst and damaged cells is observed in the acute severe form of CD (Figure 2 C and D).

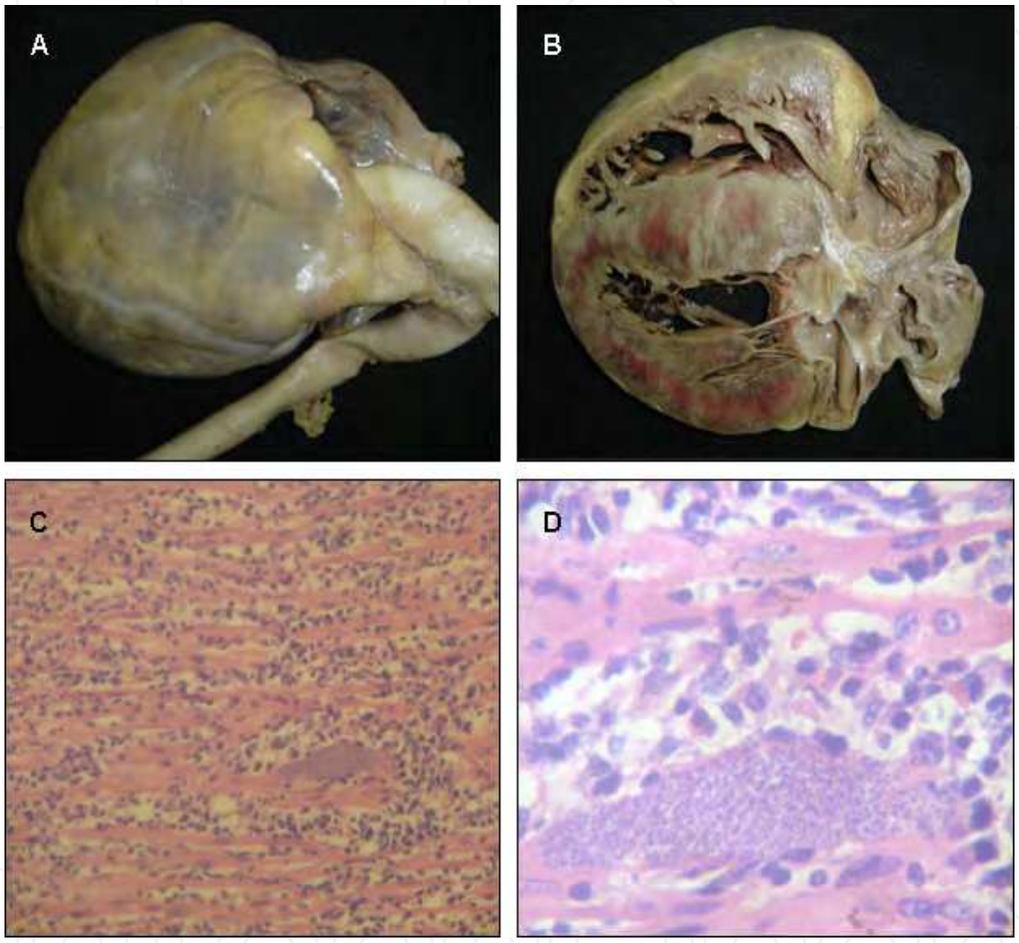

Fig. 2. Acute Chagas heart disease A) Heart enlarged with rounded shape. B) The surface of cut shows dilatation of four chambers, with pale and red areas, which correspond to focus of inflammation, necrosis and haemorrhage C) Nest of *Trypanosoma cruzi*, dense interstitial infiltrate of lymphocytes, plasma cells and monocytes with necrosis of myocardial cells D) Nest of *Trypanosoma cruzi* with rupture of myocardial cell and infiltrate inflammatory of mononuclear cells.

In the chronic phase of CD, the most important feature in chagasic cardiopathy, is the enlarge of heart with dilatation of chambers, mural thrombus (Figure 3A) and the mixture of cellular infiltration of lymphocytes, monocytes with a few plasma cells, and fibrous tissue (Figure 3B). In the adipose tissue of epicardium there are mononuclear cells with predominance of lymphocytes, which are more abundant around the nervous fibers and ganglionar cells (Figure 3C and 3D).

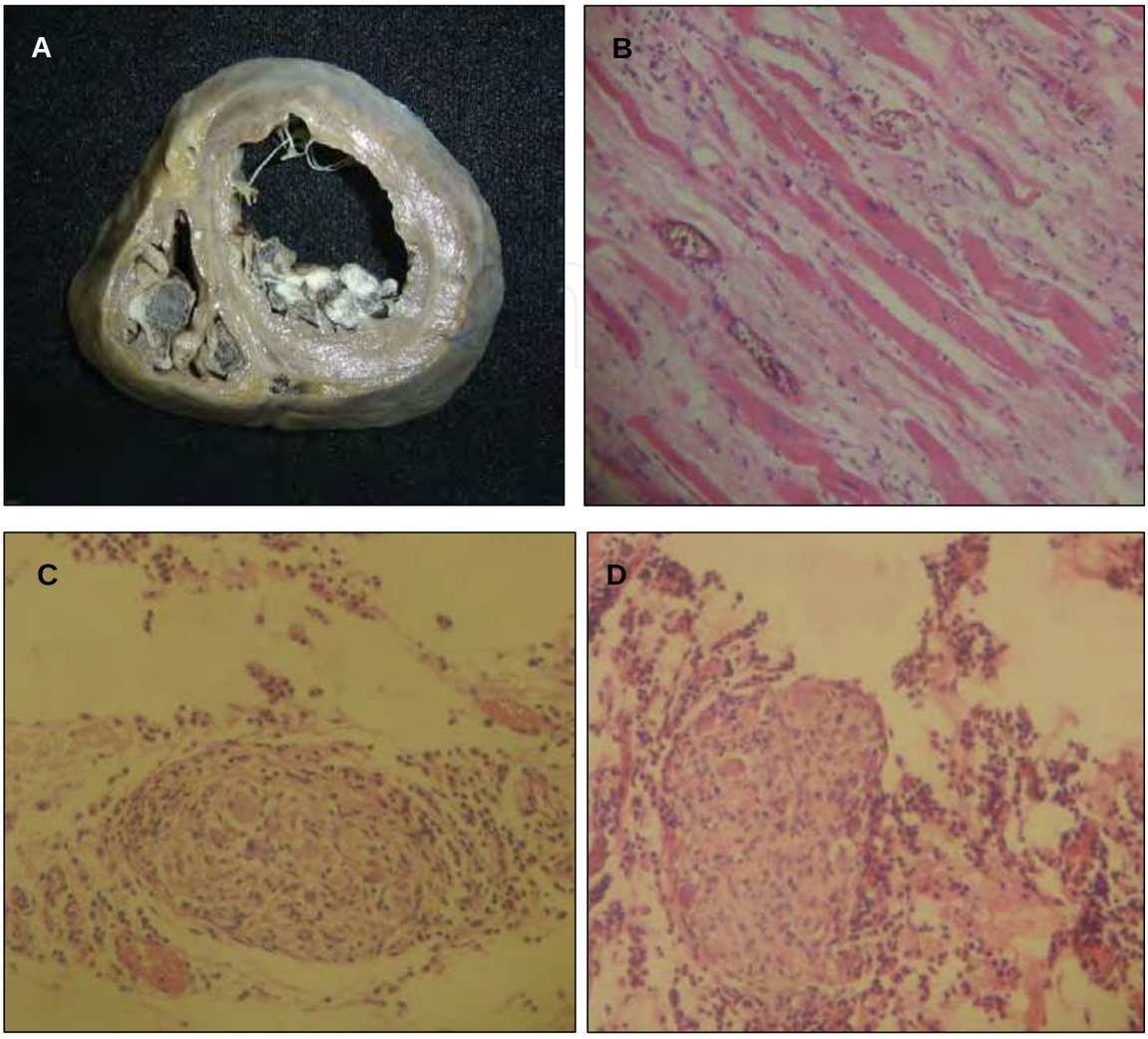

Fig. 3. Chronic Chagas heart disease A) Heart enlarged with dilatation of ventricles and mural thrombus B) Separation of the myocardial fibers, edema, abundant fibroblasts whith extracellular matrix increase, and scarce mononuclear inflammatory cells. C and D) Marked infiltration of lymphocytes and plasma cells around the nervous fibers and ganglionar neurons of cardiac plexus.

In case of oral transmission of the parasite, in the esophagus mucosa there are abundants lymphocytes and histiocytes, but the parasites are scarce or not identified (Zafra et al., 2008; Mantilla et al., 2010). In the digestive form the CD, the megaesophagus and megacolon are the result of destruction of neuronal bodies of intramural autonomic nervous ganglia of Meissner and Auerbach of the digestive tube in these sections.

4. Diagnosis and treatment

4.1 Laboratory diagnosis

The diagnosis of *T. cruzi* infection depends on the phase of infection, in the acute phase the patent parasitemia allows the use of parasitological methods to see or culture the parasite in

the first weeks. The diagnosis is difficult in the chronic phase, mainly due the very low or intermittent parasitemia, therefore, the serological methods are usual. Additionally, CD endemic areas also present endemicity of other parasites especially *Leishmania sp*. and *T. rangeli* (Gomes et al., 2009). This fact leads to the serological methods which present high sensitivity but lack of specificity because of antigenic cross-reactivity. Therefore, the World Health Organization recommends that at least two assays based on different techniques should be used. The serological methods frequently used in the diagnosis of CD are enzyme-linked immunosorbent assays (ELISA), indirect hemagglutination assays (IHA), immunofluorescence indirect assays (IFI), immunoblotting assayss (IB), and immunochromatographic assay. These methods used crude antigens but recombinant proteins and synthetic peptides are being used to improve the specificity (Hernandez et al., 2010; Praast et al., 2011; Umezawa et al., 2001; Umezawa et al., 2004).

On the other hand, molecular methods, in particular amplification by the polymerase chain reaction (PCR), provide an alternative diagnosis of CD (Gomes et al., 1999) specially to confirm diagnosis in case of inconclusive serology; in addition, it has been performed nested-PCR assays (N-PCR) (Marcon et al., 2002), quantitative real-time PCR assays (qRT-PCR) (Piron et al., 2007) and oligochromatography assays (OligoC) (Deborggraeve et al., 2009) to improve the detection of *T. cruzi* DNA.

4.2 Treatment

The treatment of CD is aimed at two main aspects: the removal of the parasite and the symptomatic management of cardiac manifestations. The options for the treatment of CD are restricted to the use of two drugs, the nifurtimox and the benznidazole. These drugs are indicated in the acute phase of infection, congenital forms, reactivation associated with immunosuppression especially in children and young adults with infections transmitted by blood transfusion and organ transplantation. Although the benznidazole have proven to be effective in the early stage of chronic infection its effectiveness at the late stage is limited. Both drugs produce serious complications such as neurological toxicity, depression, anorexia, vomiting and depression in bone marrow. Antitrypanosomal treatment in mild and late stage Chagas disease is under study by the BENEFIT trial (Rassi et al., 2010). The drug resistance is a major problem in the treatment of infectious and tropical diseases. In CD has a strong impact on the increase in the number of therapeutic failure aggravated by the few options of treatment, currently, there are numerous efforts in the search for treatment alternatives.

The amioradone is used in the management of cardiac symptoms especially for patients with sustained ventricular tachycardia, and for those with non-sustained ventricular tachycardia and myocardial dysfunction. Patients haemodynamically unstable, and those resuscitated from sudden death are treated with implantable cardioverter defibrillators (Rassi et al., 2010).

5. Pathogenesis and pathophysiology

The pathogenesis of CD is a process that is not fully understood. Most individuals infected with *T. cruzi* do not develop an acute phase and the injury to the myocardium and nervous system is directly related to tissue parasitism. The rupture of the nests of parasites in the tissues releases antigens of *T. cruzi* sensitizing cardiac and neuronal fibers,

leading to the destruction of these cells by anti-*T. cruzi* response mediates by CD8+ and CD4+ lymphocytes (Palomino et al., 2000). For the chronic phase, different mechanisms have been proposed; it is currently accepted that the inflammatory response generated by the parasite, which has not been eliminated by the immune system induces chronic inflammation in some individuals leading to tissue damage (Tarleton, 2003). There are several factors that directly or indirectly contribute to the progression and therefore evolution of the CD in the host. Some of these factors are inherent to the parasite, as the virulence related to their tissue tropism, their genetic and antigenic features, others are related to the host, such as age, race, nutritional status, immune response and genetic constitution (Dutra & Gollob 2008).

5.1 Associated to *T. cruzi*

T. cruzi presents a great heterogeneity both genotypic and phenotypic (Tibayrenc et al., 1993) and consists of different populations which circulate among humans, vectors, domestic animals and wild reservoirs. These populations show different behaviors in terms of parasitaemia, virulence, pathogenicity, interactions with host cells, tissue tropism and sensitivity to drugs. *T. cruzi* has been classified into several groups, initially using biochemical markers (zymodemes) and subsequently molecular markers (esquizodemes, clonets and lineages). The last meeting of experts standardized the nomenclature of *T. cruzi* and accepted the existence of six discrete typing units (DTUs) called TCI-VI (Zingales et al., 2009). The heterogeneity of *T. cruzi* extends to the forms and severity of clinical presentation with a particular geographical distribution. In Brazil, Tc I is present in the sylvatic cycle of transmission with low parasitemia in humans and experimental animals, therefore it is considered non-virulent, except for some reports of the Amazon (Texeira et al., 2006). By contrast, in this country Tc II is involved in the domestic cycle of transmission and causes high parasitemias, human infections and both heart and gastrointestinal diseases (Zingales et al., 1998). The same behavior is observed in other southern countries of South America as Argentina, Chile, Paraguay and Uruguay. By contrast, in the northern countries of South America and Central America predominates Tc I associated with heart disease and involved in both domestic and sylvatic cycle (Higo et al., 2004). Recently, our group reported the presence for both groups for the first time, Tc I and Tc II group in blood of seropositive individuals to antigens of *T. cruzi* associated with chagasic cardiomyopathy (CC) (Zafra et al., 2008, Gonzalez et al., 2010). The two groups were also identified in tissues of deceased patients with CC, with predominance of Tc I (Zafra et al., 2011). One individual presented a mixed infection with Tc I and Tc II, but Tc II was the group associated with cardiac involvement (Mantilla et al., 2009).

5.2 Associated with the host

5.2.1 Innate immune response

In recent years, new data related with interaction between innate immune cells and *T. cruzi* have been presented. This interaction is crucial in controlling parasite replication and removal by the action of phagocytic cells, activation of antigen presenting cells and natural killer cells (NK) in the host tissue. The innate immune cells recognize pathogen associated molecular patterns (PAMPs) through their pattern recognition receptors (PRR). The best characterized PRRs are Toll-like receptors (TLRs), which are expressed in the cell membrane or are located intracellularly. When TLRs recognize microbial components, it induces

signals responsible for the activation and production of inflammatory cytokines and chemokines (Akira & Takeda, 2004). In *T. cruzi*, TLR2 was the first receptor identified which recognizes glycosylphosphatidylinositol (GPI)-anchores mucin-like glycoproteins, distributed to the cell surface membrane of *T. cruzi* trypomastigotes (Campos et al., 2001). This receptor also recognizes the *T. cruzi* protein Tc52 and induces dendritic cell activation (Ouaissi et al., 2002). The TLR4-MD2 complex recognizes glycoinositolphospholipids containig ceramide (GIPL) (Bafica et al., 2006) and TLR9 recognizes DNA rich in CpG sequences. The TLR-mediated MyD88 signaling pathway induces pro-inflammatory cytokines as TNF-α and IL-12 and stimulates the production of nitric oxide (NO) involved in parasite clearance (Bafica et al., 2006). Other mechanisms for the TLR- independent recognition of *T. cruzi* have been described and involved the molecule NOD1 that induces type I IFNs (Kayama & Takeda, 2010). Innate immunity in turn acts as an immunomodulatory specific immune response through the generation of the microenvironment of cytokines that regulates the differentiation of effector T cell subpopulations (Bilate & Cunha-Neto, 2008, Dutra et al., 2009).

5.2.2 Adaptative immune response

The role of the adaptative immune response in the pathogenesis of CD has been subject of much controversy, for decades the role of the autoimmune component was accepted as directly responsible for heart damage (Takle & Hudson, 1989). This was supported by the detection of autoantibodies against cardiac antigens, chronicity and difficulty of finding parasites in affected individuals (Cunha-Neto et al., 1995). However, the development of more sensitive molecular tests that allowed detection of low numbers of parasites, the fact that immunosuppressed patients developed acute and severe CD and experimental models showed that the parasite, even in small amounts was essential for the development of the disease (Zhang & Tarleton, 1999; Tarleton, 2003). The presence of autoantibodies may be explained by the release of autoantigens as the result of the immune response against the parasite (Cunha-Neto et al., 1995).

Currently, the role of chronic inflammation and unbalance of the immune response generated by the parasite is accepted as responsible for the damage and tissue regeneration associated with organ dysfunction (Dutra & Gollob 2008). Although heart inflammatory cells contribute to control parasite growth, they are also involved in perpetuating inflammatory infiltrate. In chagasic patients the cellular infiltrate consists mainly of T lymphocytes with a predominance of CD8+ cells but also contains CD4+ cells and macrophages. Both CD8+ cell and CD4+ exhibit characteristics of activated T cells and correlate with the expression of inflammatory cytokines such as TNF-α and INF-γ and a smaller number of regulatory cells producing IL-10 (Araújo et al., 2007). Patients with chronic CC have higher serum levels of TNF-α and CCL2 compared with asymptomatic individuals (Talvani et al., 2004). In this context, cytokines, chemokines, receptors and signaling pathways associated with activation of pro-inflammatory proteins and with low expression of immunoregulatory proteins will be clearly associated with the immunopathogenesis of CD. This coupled with the fact that most infected individuals remain asymptomatic throughout life and only between 15 to 30% of them developed the disease demonstrates the importance of host genetic component. Thus individuals with genetic predisposition to proinflammatory phenotype in the presence of *T. cruzi* would be those that develop chronic and severe forms of the disease.

6. Chagas disease as a complex disease

6.1 Human genome variation

The variation in the human genome sequence plays an important role, yet little known in the etiology of many diseases. The establishment of the association between genotype and phenotype is crucial for understanding biological processes and in the case of disease, pathogenic mechanisms that lead to their development. For monogenic diseases, the methods of genetic linkage and physical maps facilitated the identification of mutations responsible for the phenotype associated with pathology. Thus numerous Mendelian-type diseases were identified. However, most common diseases are complex and multifactorials therefore, are the result of the effect of multiple genetic variants on the phenotype and their interaction with environmental factors. In the case of infectious diseases is known that not only the genotypic and phenotypic differences of the microorganism determine the development of a particular disease, but also the variation in the host genome may have an important role in the development of resistance or susceptibility.

6.2 Single nucleotide polymorphisms (SNP)

SNP type polymorphisms are the most common forms of genetic variation in the human genome, currently the common SNPs estimated density is about 10 to 15 million (The International HapMap Consortium 2007, http://www.hapmap.org). Its usefulness as genetic markers associated with various infectious and noninfectious diseases has been amply demonstrated (Pacheco & Moraes, 2009). The SNPs have been the markers most commonly used for its stability, low mutation rate and are plentiful throughout the genome, being found in exons affecting the protein function, in introns or regulatory regions affecting gene expression and therefore the processing and maturation of the messenger, or many of them have been identified in intergenic regions with effect unknown over gene expression or phenotype (Frazer et al., 2009). Numerous reports using one or more polymorphisms have been published (Pacheco & Moraes, 2009), but most of them only explain less than 5% of the observed contribution of the genetic component to the risk of disease. This fact substantially limits the use of these markers to predict risk and in some cases the results have been controversial. One of the main problems with these studies is that in many cases it is not known a direct effect on the phenotype and in common diseases the effect is modest. Therefore, it is necessary to identify other variables involved and the interaction among them (Feero et al., 2010). Another limitation in this type of study is related to the number of SNPs, which in an individual genome is from 3 to 4 million and in the human genome it is estimated between 10 to 11 million (Frazer et al., 2009). Thus an individual would require testing thousands of polymorphisms to identify genes involved in susceptibility to a particular pathology.

The International HapMap Project (The International HapMap Consortium 2003-2007) has overcome some of the difficulties in mapping SNPs and identification of susceptibility genes in complex diseases. The advances are related with the reduction in the number of SNPs to be genotyped, increased statistical power and the accurate mapping in association studies. This project HapMap anticipates building a database for common haplotypes in different human populations (www.hapmap.org). When the markers are in linkage disequilibrium (LD) in the population, there is redundant information. If two markers are in complete LD, each of the genotypes of a SNP is completely determined by the other, thus the genotyping of one will suffice for the information of the two (Conrad et al., 2006). The selection of non-redundant markers present in an area with high density of markers has been called "haplotype tagging"

and the SNPs selected by this method are called "tag-SNPs" or label SNP (de Baker et al., 2006). The main objective of this haplotype tagging is to reduce the number and cost of genotyping, keeping most of the information that they contain (Daly et al., 2001). The technological progress in the last decade, related to the development of high density maps of markers, maps of linkage disequilibrium and haplotypes (Cardon & Abecasis, 2003), the use of microarrays for genotyping of SNPs (Steemers & Gunderson, 2007) and bioinformatics tools have helped overcome some of these difficulties. Based on these developments, in recent years the genome scans (GWAS) have popularized (Cheung et al., 2005; Galvan et al., 2010). In fact, after 5 years of the first GWAS, which identified the association of complement factor H with macular degeneration related to age (Klein et al., 2005) there have been published more than 450 GWAS and associations with more than 2000 SNPs in numerous human diseases such as type 1 and 2 diabetes, Crohn's disease, rheumatoid arthritis, prostate cancer, breast, tuberculosis and visceral leishmaniasis among many others (Manolio 2010; Ku et al., 2010). Many of these studies have identified markers on genes already known for its role in the pathogenesis of the disease, but others have also identified strong associations with genes that apparently have not relation with the characteristic of the disease process (Frazer et al., 2009).

6.3 Human genome variation in Chagas disease

The chronic CD courses in 70% of individuals without symptoms and only between 15-30% of infected individuals have cardiac involvement and/or digestive, with different levels of severity and mortality. This clearly suggests the role of the individual genetic component in disease development, a fact that is reinforced with the identification of strains of mice with different susceptibility phenotypes. The C3H strain develops cardiac lesions similar to human chagasic cardiomyopathy, the A/J phenotype presents different pathology and DBA/2 is totally resistant (Marinho et al., 2004). The association related with genetic susceptibility or resistance to infection with *T. cruzi* in human has been demonstrated in some epidemiological studies related to the molecules of the major histocompatibility complex (MHC) (Llop et al., 1991; Fernández-Mestre et al., 1998; Nieto et al., 2000; Layrisse et al., 2000; Williams-Blangero et al., 2003; Moreno et al., 2004).

The identification of biomarkers to establish an association with the risk of developing the disease is critical because could be used not only in prevention and prognosis but also as a therapeutic target. It is now clearly accepted that the immune response is crucial in the pathogenesis of CD and especially the role of the chronic inflammation in the tissular damage (Dutra & Gollob 2008). The balance between anti-inflammatory and pro-inflammatory cytokines and their receptors is crucial in determining whether *T. cruzi* parasites will be eliminated without causing tissue damage. Thus, the lack of efficient immunoregulation in cardiomyopathic patients could contribute to clinical forms of CD. In this sense, case-control studies have searched association between onset or severity of the disease and the functional polymorphisms of genes known to participate in host inflammatory response.

6.3.1 Variation in pro-inflamatory cytokines

In CD, it has been observed that patients infected with *T. cruzi* display increased levels of plasma TNF-α compared to non-infected individuals, where plasma TNF-α levels were 4-fold higher in asymptomatic and cardiomyopathic patients with left ventricular ejection fraction (LVEF) >50% and 8-fold higher cardiomyopathic patients with LVEF ≤50% than non-infected individuals (Ferreira et al., 2003). In fact, the measurement of TNF-α level has been suggested as a tool to identify patients with heart dysfunction (Talvani et al., 2004).

Some positive associations have been observed in Mexican and Brazilian populations, between polymorphisms of regulatory region of *TNFA* gene and CC (Rodríguez-Pérez et al., 2005; Drigo et al., 2006; Pissetti et al., 2011). The most studied allelic form (*TNFA* -308) has functional implication because it affects the TNF-α level. However, discrepancies have been observed with Peruvian and Brazilian populations in which the frequencies of genetic variants were similar in asymptomatic individuals and CC patients (Beraún et al., 1998; Drigo et al., 2007). These differences could be affected by some factors. Among the most important factors would be: sample size, genetic differences between populations, criteria for the selection of controls (study design), linkage disequilibrium with HLA genes and influence of other polymorphisms present in the same region. Some polymorphisms of *TNFA* gene show a high level of LD, and the haplotypes formed by these variants could be affecting levels of protein expression (Figure 4). In Colombian population of highly endemic area we also found associations with genetic variants in *TNFA* and *TNFR2* genes (Criado et al., publication process). Unlike other chronic inflammatory diseases such as rheumatoid arthritis in which the blocking of TNF-α has been used successfully in treatment, in CD the experimental evidence using animal models showed that TNF-α blockade enhances left ventricular dysfunction (Bilate et al., 2007). Therefore, it is necessary to understand the regulation of the expression of TNF-α and its receptors and the effect of host polymorphisms for the use of therapeutic strategies with target TNF-α.

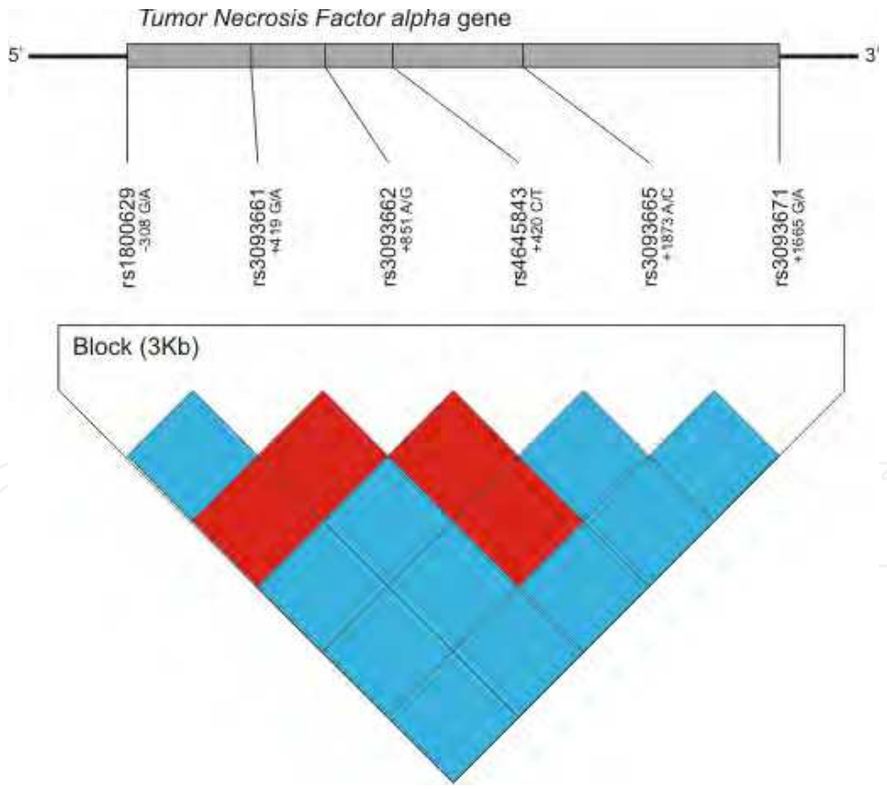

Fig. 4. Plot of LD across the *TNFA* gene. The image shows a high-resolution LD association plot between SNPs located in the *TNFA* gene, D' values are reported in the boxes and represented by color, which ranges from red (higher D' scores) to white (lower D' scores). The SNP nomenclature is presented as numbers that refer to the position of polymorphism in the gene.

In our study population we also found associations of functional polymorphisms present in other pro-inflammatory cytokine genes such as *IL1B* (Flórez et al., 2006), *IL12B* (Zafra et al., 2007), *IFNG* (Torres et al., 2010), and lack of association with *IL6* (Torres et al., 2010) (Table 1).

6.3.2 Variation in chemokines and chemokine receptors

The inflammatory infiltrate of mononuclear cell is driven by a set of specific chemokines that determine the type of cells present in the tissue. Chemokines and chemokine receptors play an important role in mediating the extravasation and accumulation of specific effector and memory cells in chronic inflammatory processes in several diseases. In CD there is experimental evidence in patients with CC and models of *T. cruzi* infection that show that chemokines and chemokine receptors may be relevant mediators of leukocyte influx, which is involved in the pathogenesis of the disease (Teixeira et al., 2002; Marino et al., 2004; Talvani et al., 2004; Machado et al., 2005; Gomes et al., 2005; Guedes et al., 2010; Manque et al., 2011). Genetic variants in genes of chemokine receptors as *CCR5* have been also studied in Peruvian and Venezuelan populations with the identification of a protection marker (Calzada et al., 2001; Fernandez-Mestre et al., 2004). *CCR5* gene polymorphisms had been extensively studied in HIV and have been defined haplogroups which are affecting the transcriptional activity (Gonzalez et al., 1999). These haplogroups are composed by different combinations of *CCR2* and *CCR5* SNPs (Figure 5). Analyzing individual polymorphisms we found association between *CCR5*-2733 polymorphism and CC and also in four variants present in haplogroup HHE (*CCR2* +190, *CCR5* -2733, -2554 and -1835).

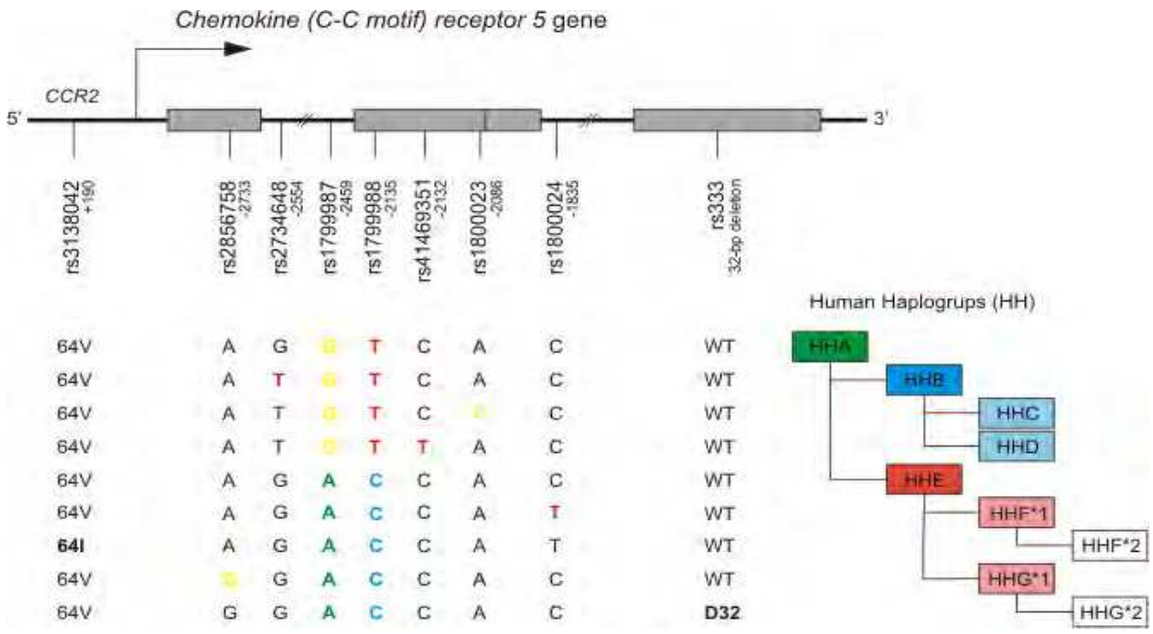

Fig. 5. Human haplogroups of *CCR2* and *CCR5* polymorphisms.

No association was observed with polymorphisms analysed in the chemokines *CCL5* and *CXCL8* genes (Flórez et al., publication process). The genetic variant – 2518 in the chemokine *CCL2/MCPI* promotor gene was associated with CC in Brazilian population (Ramasawmy et al., 2009).

6.3.3 Variation in anti-inflammatory cytokines

Monocytes of patients with the indeterminate form, but not patients with CC showed high expression of interleukin 10, suggesting a lack of immunoregulation in these patients (Costa el al., 2009; D'Avila et al., 2009). The anti-inflammatory cytokines, such as interleukin 4 and IL-10, promote Th2 differentiation and limit Th1 response (Jankovic et al., 2001). This polarization favors the permanence of the parasite in the myocardium but keeps the inflammatory response under control, which appears to be important for avoiding the development of CC (Higuchi et al., 2003; Cunha-Neto et al., 2005). Different groups have found markers associated with decreased production of anti-inflammatory cytokines in patients with CC (Costa et al., 2009). We have analyzed other genes of regulatory proteins, such as *TGFB1* (Calzada et al., 2009), *MIF* (Torres et al., 2009), *IL4*, *IL4RA* and *IL10* (Florez et al., 2011) which are associatted with CC. However, in the latter gene we were unable to demonstrate association between *IL10* gene polymorphism and CD. Other pro-inflammatory and anti-inflammatory genes have been analyzed, such as *BAT1* and *IKBL/NFKBIL1*, *MAL/TIRAP* (Ramasawmy et al., 2006 and 2009), *PTPN22* (Robledo et al., 2007), *CTLA4* (Fernandez-Mestre et al, 2009) (Table 1).

There are few reports of genome mapping applied to the study of CD in murine models which showed a possible region of susceptibility to the disease directly related with survival to infection in the murine H-2 locus, which corresponds to the human Major Histocompatibility Complex (MHC) located in chromosome 17 (Wrightsman et al., 1984). In a more recent study, the entire genome of mice strains susceptible and resistant were mapping at intervals of 10-15 cM with microsatellite. The regions with marked influence in the severity of CD, are mainly located on chromosome 17 on the murine MHC, but were also identified as candidate regions on chromosomes 5 and 13 (Graefe et al., 2003, 2006). In humans, chromosomal mapping studies on CD have not been reported. All this evidence showing the association of multiple genes and the development of CD, as in other infectious and noninfectious diseases, suggests that susceptibility/resistance to develop CD would be determined by variations in a large number of polymorphic genes. In fact, a single SNP can not fully explain the susceptibility or resistance to a complex disease. Therefore, the genetic susceptibility to *T. cruzi* infection and the development of cardiomyopathy is complex and heterogeneous and likely to involve multiple genes, each with a modest contribution on the pathogenesis of the disease. The availability of high throughput methods enabling of genotyping individual DNA samples at 500,000 or more loci using SNP chip have led to genome wide association studies (GWAS) of more than 40 diseases and human phenotypes (Manolio, 2010). Despite the current limitations and the adjustments of bioinformatic tools for analyzing this vast amount of information, these studies of genomic medicine would allow in a near future obtain the individual genetic profiles and define the genes underlying the phenotype associated with the disease and its severity.

Genes	SNP	Population	Association	Reference
Innate immunity				
TLR 2	R753Q	Colombian	negative	Zafra
TLR4, TLR9	D299G, -1237	Colombian	negative	Zafra
TLR 1,2,4,9	I602S, R753Q, D299G, R392stop codon, -1237, -1486	Brazilian	negative	Ramasawmy
MAL/TIRAP	S180L	Brazilian	CC	Ramasawmy
Pro-inflamatory genes				
NOS	microsatélite	Peruvian	negative	Calzada
NRAMP	-236	Peruvian	negative	Calzada
TNFA	-308	Peruvian	negative	Beraún
		Mexican	CC	Rodriguez-Pérez
		Brazilian	negative	Drigo
		Brazilian	negative	Pissetti
		Colombian	CC	Criado
	-238	Peruvian	negative	Beraún
		Mexican	negative	Rodriguez-Pérez
		Brazilian	negative	Drigo
		Brazilian	CC	Pissetti
	-1031	Colombian	negative	Criado
TNFR2	+676 (M196R)	Colombian	monomorphic	Criado
LTA	+80, +252	Brazilian		Ramasawmy
IL1B	+5810	Colombian	CC	Flórez
	-31,-511, +3954	Colombian	negative	Flórez
		Mexican		Cruz-Robles
IL1RN	+8006, +8061, +11100	Colombian	negative	Flórez
		Mexican		Cruz-Robles
IL1A	-889, +4845	Colombian	negative	Flórez
IL12B	+1188	Colombian	CC	Zafra
IFGN	+874	Colombian	CC	Torres
IL6	-174	Colombian, Peruvian	negative	Torres
CCR5	59029, Δ32	Peruvian	negative	Calzada
	59029, Δ32	Venezuelan	negative	Fernández-Mestre
	-2733, -2554	Colombian	CC	Flórez
CCL2/MCPI	-2518	Brazilian	CC	Ramasawmy
Anti-inflamatory genes				
BAT1	-22, 348	Brazilian	CC	Ramasawmy
IKBL/NFKBIL1	-62, -262	Brazilian	CC	Ramasawmy
IL10	-1082	Brazilian	CC	Costa
	-1082, -819, -592	Colombian	negative	Flórez
PTPN22	1858	Colombian, Peruvian	negative	Robledo
MIF	-173	Colombian, Peruvian	CC	Torres
TGFB	-988, -800, -509, +263	Colombian, Peruvian	negative	Torres
	+10	Colombian, Peruvian	CC	Torres
CTLA4	+49	Venezuelan	negative	Fernández-Mestre
IL4	-590	Colombian	negative	Flórez
IL4RA	+148	Colombian	CC	Flórez
	1124, 1218, 1902	Colombian	negative	Flórez

Table 1. Polymorphisms of immune response genes studied in Chagas Disease

6.4 Host-parasite interaction, changes in gene expression by the infectious process

The infection process involves changes in host cell gene expression caused by the parasite. Therefore, transcriptional profiling is frequently used as a genome-wide tool to screen for the impact of pathogens on host cell functions (Costales et al., 2009). This approach that analyzes the differential expression to identify genes or proteins related with the pathogenesis is widely used in different pathologies. Taking advantages of microarray expression platform comparisons are made between healthy and sick individuals or between strains of susceptible or resistant animal models or between infected and uninfected cells. Currently, two approachs have been integrated so that data from microarrays can be analyzed in the context of the Quantitative Trait Loci (QTLs), a strategy called genetic genomics (Jansen & Nap 2001; Nica et al., 2010). Genetics Genomics is a powerful tool to elucidate the basis of complex traits and disease susceptibility that integrates genotype and phenotype information (Pérez-Enciso et al., 2007).

In CD studies using different cell lines infected with *T. cruzi* or tissues from diseased individuals compared to healthy tissue have been realized. This allowed to identify an increased number of over-expressed genes associated with immune response, such as growth factors, immunoglobulins, cytokines and genes related with cell membrane, lipid metabolism and oxidative phosphorylation (Graefe et al., 2006; Mukherjee et al., 2003; Mukherjee et al., 2006). More recently in several human cell lines was observed overexpression of cytokines with higher overexpression of interferon-stimulated genes and also independent genes of cytokines (Costales, 2009). An analysis of gene expression in heart tissue of five patients with CC and seven with dilated cardiomyopathy suggests that genes of immune response, lipid metabolism and mitochondrial oxidative phosphorylation could be involved in the development of heart failure (Cunha-Neto, 2005). In mice models, myocarditis was associated with immune-inflammatory responses (chemokines, adhesion molecules, cathepsins, and MHC molecules), and fibrosis was associated with extracellular matrix components, lysyl oxidase, and tissue inhibitor of metalloproteinase (Soares et al., 2010). With this approach, our group performed a study for determining differential expression patterns in T lymphocytes of individuals with or without CC. Using the Gen Ontology (GO) tool we could establish the biological pathways associated with over-expression in immune response genes, cell signaling and structure of cardiac tissue. Therefore, genetic genomic strategy could allow establish and identify the risk genotype and phenotype of the patient. In addition would make it possible to identify gene interaction networks responsible for the development of CD.

7. Perspectives

For the control of CD should be used not only the traditional approachs of public health with campaigns to eradicate the domiciled vector, control of transmission in blood banks, and now oral transmission, but implement and promote the use of new developments in genomics, proteomics and pharmacogenomics. The association studies and genetic genomic can provide information to identify genes related with disease development and so develop not only prevention and control programs but identify potential targets for treatment and vaccine design.

8. References

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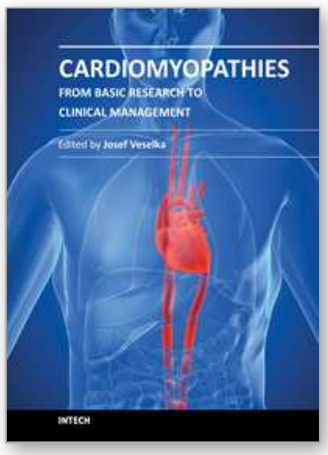

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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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