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HLA and Infectious Diseases

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1. Introduction

The Human Leukocyte Antigen (HLA) system is the Major Histocompatibility Complex (MHC) in humans, and all knowledge on this system is of great interest to the field of medical sciences. HLA has become an important tool for understanding the pathogenesis of various infectious diseases; the alleles or HLA haplotypes inherited by an individual can predict several risk and protective factors related to infections caused by various agents.

The list of infectious diseases associated with the HLA system is constantly increasing and the level of association is quite variable. New classification methods and frequent nomenclature updates have facilitated the understanding of the role of polymorphisms in this system and the association with various diseases.

The purpose of this chapter is to show the genetic variability of HLA genes and its influence in the immunopathogenesis of diseases caused by different classes of pathogens. The first part of the chapter encompasses aspects of the structure and function of MHC genes and the role of the molecules encoded by these genes. Subsequently, we present some infectious diseases associated with the HLA system that have been highlighted in the global overview.

2. Structure and function of the HLA

MHC is divided into three main regions and has over 200 genes, most of which have functions related to immunity, and are contained within 4.2 Mbp of DNA on the short arm of chromo-

some 6 at 6p21.3 [1]. In the HLA Class I region, near to the telomere, are located the HLA-A, -B and -C classic genes and -E, -F and -G non-classic genes, among other genes and pseudogenes. The HLA Class II region, near to centromere, contains HLA-DR, -DQ and –DP genes. Sub-region DR includes DRA gene which codes for the low-polymorphic alpha-chain and can combine with any beta chains codifying for DRB genes [2]. The Class III region, located between class I and II region contains the C2, C4A, C4B and B genes, that code for complement proteins and tumor necrosis factor (TNF) [1,2].

HLA molecules are polymorphic membrane glycoproteins found on the surface of nearly all cells. Multiple genetic loci within MHC encode these proteins, and one individual expresses simultaneously several polymorphic forms from a large pool of alleles in the population. The overall structure of the HLA class I and class II molecules is similar, with most of the poly-morphisms located in the peptide binding groove, where there is the antigens recognized [3].

Class I molecules are composed of one heavy chain (45kD) encoded within the MHC and a light chain called β2-microglobulin (12kD) whose gene is on chromosome 15. Class II molecules consist of one α (34kD) and one β chain (30kD) both coding within MHC [1]

The class I heavy chain has three domains of which the membrane-distal first (α1) and the second (α2) are the polymorphic ones. These polymorphic domains concentrate three regions: positions 62 to 83; 92 to 121; and 135 to 157. These areas are called hypervariable regions. The two polymorphic domains are encoded by exons 2 and 3 of the class I gene. The diversity in these domains is of great importance as this is where the two domains that form the antigen binding cleft (ABC) or peptide binding groove (PBG) of MHC class I molecule are located [4,5]. The sides of the antigen-binding cleft are formed by α helices, whereas the floor of the cleft is comprised of eight anti-parallel beta sheets. The antigenic peptides of eight to ten amino acids (typically nonamers) bind to the cleft with low specificity but high stability. The α_3 domain contains a conserved seven amino acid loop (positions 223 to 229), which serves as a binding site for CD8 [3,6-8].

Class II molecules comprised of two transmembrane glycoproteins: α and β chains, are restricted to the cells of the immune system (e.g. B cells, dendritic cells), but may also be induced on other cells during immune response. The PBG of class II molecules has open ends which allow the peptide to extend beyond the groove at both ends, and therefore to be longer (12-24 amino acids). The peptide is presented to CD4 T-cells [1]. Both α and β chains are usually polymorphic in class II molecules. In these chains, the α1 and β1 domains are of the PBG and therefore diversity is found mainly in these domains, which are encoded by the exon 2 of their class II A or B genes and the hypervariable regions tend to be found in the groove walls [7].

T cell activation occurs following recognition of peptide / MHC complexes on an antigen-presenting cell (APC). T cell activation can be viewed as a series of intertwined steps, ultimately resulting in the ability to secrete cytokines, replicate, and perform various effector functions. During antigen presentation, the antigen receptors of T cells (TCR) recognize both the antigen peptide and the MHC molecules, with the peptide being responsible for the fine specificity of antigen recognition and MHC residues contributes for the restriction of the T cells (CD4 and

CD8). During antigen presentation, CD4 and CD8 are intimately associated with the TCR and bind to the MHC molecule [9].

3. Haplotype, linkage disequilibrium and HLA genes expression

HLA genes are transmitted for Mendel segregation and allelic variant is expressed in a codominant mode. The set of HLA alleles present in each chromosome of the pair is denominated haplotype. The probability of a sibling having the same HLA haplotype as the other is 25%, different haplotypes is 25% and 50% are share only one haplotype [2].

Moreover, there is a fact that occurs in HLA genes called linkage disequilibrium which denotes that certain alleles occur together with a greater frequency than would be expected by chance (non-random gametic association). Variations in the expected combinations of alleles in the population, more often or less often than would be expected from a random formation of haplotypes from alleles, could be related to linkage disequilibrium [1]. For example, a determined population has a gene frequency of 14% for *HLA-A*01* and 9% for *HLA-B*08*, therefore the expected frequency for this haplotype would be 1.26% (0.14 x 0.09), the actual frequency is however, 8.8% in this population, a higher frequency than expected, characterizing a positive linkage disequilibrium [2].

4. HLA and infection diseases

The frequency and the presence of HLA alleles vary among different populations. Studies suggest that the alleles that can confer resistance to certain pathogens are prevalent in areas with endemic diseases. Furthermore, genomic analysis in families has helped to map and identify the loci related to a number of diseases. Moreover, a number of diseases have been mapped and had their related loci identified thanks to the genomic analysis of families.

4.1. Bacterial diseases

4.1.1. Tuberculosis and leprosy

Leprosy and tuberculosis (TB) have afflicted humanity since time immemorial, and a number of factors converge to a timely discussion on mycobacterial disease. These factors include the re-emergence of human tuberculosis in epidemic proportions on a global scale, and the special position of leprosy among communicable diseases, the frequency of disabilities, and the social and economic consequences of these diseases.

The immunological mechanism involved in the breakdown of host resistance in these individuals remains unclear. A better understanding of the mechanisms that lead to the protective immunity of the host is fundamental in order to develop novel therapies and vaccines.

Cell-mediated immunity is thought to be the major component of host defense against mycobacterium; consequently, the induction of optimal Th1 response is protective immunity against mycobacterial infection.

Whereas exposure to and infection by *M. leprae* are necessary to acquire the disease, heritable factors are equally important in determining who will eventually develop clinical signs of leprosy. Numerous studies that have recently been reviewed support the major role of host genetic factors in the large variability of the host response to bacillus infection.

The extensive polymorphism of the class II genes and molecules results in genetically controlled interindividual differences in antigen-specific immune responsiveness, which in turn may lead to differential susceptibility to or expression of disease. The induction of cytolytic CD4+ Th1-like cells during mycobacterial infections has been extensively documented [10,11]. Thus, under inflammatory conditions it would be conceivable for T cells to access Schwann cells and recognize the HLA/peptide complexes presented by the Schwann cell.

4.1.2. HLA and leprosy

Leprosy is a chronic infection disease caused by *Mycobacterium leprae* (*M. leprae*) (Hansen, 1874), an intracellular parasite of macrophages, with high infectivity and low pathogenicity, which primarily affects the peripheral nerves and the skin [12]. The contact with *M. leprae* occurs mainly through the superior aerial views, but may also occur through the skin and maternal milk. A long period of exposure to the microorganism, between 2 and 5 years, is needed to promote the infection [13].

A global increase in both prevalence and new case detection has been observed as compared to 2011. The prevalence of leprosy in 2012 was 181,941 (0.34), compared to 189,018 (0.33) at the end of the first quarter of 2013, and approximately, 232,857 new cases reported (4.00/100,000 population), in the population were detected during the year of 2012 [14]. Currently, the major prevalence is in the Southeast Asiatic, South American, and African continents.

In 1966, Ridley and Jopling, based on clinical, histological, and immunological criteria, classified the spectra of leprosy into 5 groups: tuberculoid (TT), borderline-tuberculoid (BT), borderline-borderline (BB), borderline-lepromatous (BL) and lepromatous (LL). The Madrid classification was presented to subdivide leprosy patients into four different types (lepromatous, tuberculoid, borderline, and indeterminate), and since the year of 1998, the World Health Organization has recommended a new classification based on the number of skin lesions: paucibacillary (PB) for patients who have up to five skin lesions (lower bacterial load) and multibacillary (MB) for patients who have six or more skin lesions (higher bacterial load) [15].

The major signals of this disease are hypostatical cutaneous lesions, dilation of peripheral nerves, and the presence of acid-resistant bacillus in the skin lesions [16]. The undetermined form is an initial stage where the clinical and histopathological courses are uncertain. In the TT form, the lesions are maculates or infiltrated and can reappear or develop from undetermined macula, whereas in the LL form there are multiple lesions with numerous bacillus detected by skin biopsies [17].

Leprosy has been considered a multifactorial disease; the expression of clinical manifestations reflects the relation between the host and the parasite. The infection evolution depends on to the specific response on behalf of the host to the parasite. There is a good relationship observed *in vitro* and *in vivo* between the immunity mediated by cells (CMI) against antigens of *M. leprae* and the course of the disease. In the located and non-severe form TT, an efficient CMI to *M. leprae* develops with low levels of antibodies. On the other side of the leprosy spectrum are polar LL patients, who have a high humoral immune response and a low cellular response. Most patients, however, are between these two poles and are classified as borderline leprosy cases [18].

The susceptibility to *M. leprae* infection is complex and influenced by several host, parasite, and environmental factors. In 1929, Hopkins and Denny postulated that genetic variability was the basis of family and racial differences regarding the expression and incidence of the disease. Many epidemiologic studies that aimed to identify susceptibility genes have indicated that genetic characteristics of the host play a role in the variability of the clinical response to M. *tuberculosis* and *M. leprae* infection [19].

HLA has been studied in several distinctive illnesses, including infectious diseases. HLA alleles codify class I and II crucial molecules for CMI cell interaction. The HLA system participates effectively in the immune response by promoting the interaction between pathogen epitopes and the host cell T repertory. Consequently, depending on host HLA, different host responses can occur against the same antigen.

Previous investigations demonstrated different class I HLA variants associated to TT and LL forms of leprosy, in several populations. In India, the most important country in number of infected individuals with the bacillus, an important association with leprosy was reported for HLA-B40 antigen and HLA-A2-B40, HLA-A11-B40, and HLA-A24-B40 haplotypes [20]. Further studies in India replicated these findings; HLA-A11 [21] and HLA-B60 (split of B40) [22] antigens were associated to the LL form. Subsequently, with the advent of molecular genotyping, HLA class I alleles were determined in Indian multibacillary leprosy patients, resulting in a positive association with *HLA-A*02:06*, *A*11:02*, *B*18:01*, *B*51:10*, *C*04:07*, and *C*07:03* alleles, and a negative association with *C*04:11* [23]. Moreover, the *A*11-B*40* haplotype was confirmed in multibacillary leprosy patients compared to controls [24].

Recent studies have shown a positive association between LD and *HLA-A*11*, *HLA-B*38*, and *HLA-C*12*, as well as a negative association with *HLA-C*16*. When groups were stratified, *HLA-B*35* and *HLA-C*04* were shown to be protective against lepromatous leprosy, whereas *HLA-C*07* was shown to be a susceptibility variant [25]. Furthermore, the allele *HLA-C*15:05* has been related to the LD phenotype in certain populations from India and Vietnam [26].

However, the main restriction determinants for *M. leprae* seem to reside on DR or DQ molecules. The HLA-DR2 molecule [26-28], later identified as *DRB1*15* and *DRB1*16* variants, is primarily associated with leprosy or different clinical forms [29-33]. Risk for leprosy associated with *DRB1*10* has been described in Turkish, Vietnamese, and Brazilian populations [30,34], whereas *HLA-DRB1*14* has been associated with the TT group in a population from northeastern Brazil [33] and with leprosy *per se* in the Argentinean population [35].

HLA molecules with the highest affinity to peptide produce the greatest T cell proliferation and IFN-γ response [36], and the peptide presentation by low affinity class II molecules may result in muted cell-mediated immunity [36]. Alternatively, peptide presentation by specific class II molecules may result in activation of suppressor/regulatory T-cells [37]. A protective effect against leprosy has been described for *DRB1*04* in Brazilian, Korean, Japanese, Vietnamese, Argentinean, and Taiwanese populations [30,38-40].

In addition to the studies that have been performed to investigate the molecular mechanisms of mycobacterium antigens restricted to HLA, certain Class II HLA genes have been suggested, as the selection of determined groups of antigen peptides and specific T helper cells, can contribute to the development of leprosy polar [41] and also tuberculoses [42].

4.1.3. HLA and tuberculosis

Tuberculosis, or TB, is a chronic disease caused by *Mycobacterium tuberculosis*, considered a major public health problem worldwide. The infection most commonly affects the lungs (Pulmonary Tuberculosis). One-third of the world's population has been in contact with the pathogen, but approximately 90% of the infected persons do not present clinical symptoms [43].

According to the World Health Organization [14], in 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430,000 among people who were HIV-positive. Among the TB high-burden countries (approximately, 80% of all new TB cases arising each year), the highest rates of case detection in 2011 were estimated to be in Brazil, China, Kenya, the Russian Federation, and the United Republic of Tanzania.

A great challenge in immunology is to understand the complexities, mechanisms, and consequences of host interactions with microbial pathogens. The innate immune response to intracellular bacteria involves mainly macrophages and natural killing cells (NK). Bacteria activate NK cells directly or stimulate macrophages to produce cytokines that activate NK cells, which results in a broad and fast antimicrobial response critical to the control of pathogen dispersion. Innate immunity can limit bacterium growth for some time, but in general, it does not succeed in eradicating infections, triggering the acquired immunity mainly through cell action.

Proteins are processed by APCs that interact with surface receptors of T-lymphocytes (T CD4+) as peptides associated with class II HLA molecules. Either the phagocyted bacteria are transported from the phagosome to the cytosol or they escape the phagosome and enter the cytoplasm of infected cells, and their degraded products are expressed on the cell surface associated with the HLA molecule, whose complex interacts with the specific cytotoxic T CD8+ receptors. Thus, the T cell eradicates the target cell. The activation of the macrophage can also result in tissue lesion in the form of late hypersensibility reaction to the protein antigens. Bacteria may resist death within the phagocytes for a long period, producing macrophage and lymphocyte cell infiltration around them and giving rise to granulomes [44,45].

A number of genes are thought to be important in the pathogenesis of TB [46,47]. HLA class I molecules are involved in antigen presentation to CD8 cytotoxic T-cell response stimulation. However, the participation of these molecules is controversial in tuberculosis. A meta-analysis study reported that subjects carrying HLA-B13 had a lower risk for thoracic TB, whereas other class I antigens could not be related to tuberculosis pathogenesis [48].

Earlier studies revealed that HLA-DR2/DR3, DR2/DR4 and DR2/DR5 are the major heterozygous combinations associated with susceptibility to TB [49]. These same authors have also identified the association of HLA-DRB1 alleles and cytokine secretion in response to live *M. tuberculosis* [50]. An increased IFN-γ response in *HLA-DRB1*03*-positive and a decreased IFN-γ response in *HLA-DRB1*15*-positive patients, an increased level of IL-12p40 in *DRB1*10* and IL-10 in *DRB1*12* positive and an increased level of IL-6 in *DRB1*04* positive patients were observed.

The HLA class II variant, DR2 encoded by *DRB1*15* and *DRB1*16*, is associated with TB in several populations [51,52]. In South Africans [53], a significant interaction between *HLA-DRB1*13:02* allele and susceptibility to TB was observed. A study in Poland [54] related a significant interaction between *HLA-DRB1*16* and *HLA-DRB1*14* and susceptibility to TB. Furthermore *HLA-DRB1*04* and *HLA-DQB1*02:01* were associated with TB in Chinese patients [55].

Hence, whether the presentation of mycobacterial epitopes by HLA molecules is beneficial or detrimental to mounting a protective response to tuberculosis and leprosy conditions has yet to be explored.

4.2. Viral diseases

4.2.1. HLA and dengue

Dengue is a resurging mosquito-borne disease that is often contracted by US travelers visiting Latin America, Asia, and the Caribbean. The clinical symptoms range from a simple febrile illness, called to Dengue Fever (DF), to hemorrhagic fever represented for Dengue Hemorrhagic Fever (DHF) or shock symptoms, called to Dengue Shock Sindrome (DSS) [56].

Nowadays, there are currently four known serotypes: DEN 1, 2, 3 and 4, which are strongly related. The viruses belong to the genus flavivirus, family *Flavaviridae* and are prevalent in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban areas [57].

The pathophysiology of DF viral infections and factors that result in severe clinical disease are poorly understood. Cross-reactive memory T cells and antibodies have been suggested to contribute to the immunopathology by altering the cytokine profiles during secondary infection and are believed to be less effective in eliminating the newly infective virus serotype [58].

However, genetic factors appear to be important in the manifestation of DF as, even in endemic areas, only a small proportion of people develop DF or the most serious forms of the disease.

During infection by DF virus, a series of genes have their regulation mechanisms modified, among them, genes linked to high production of IFN-gamma, as well as MIP-1β, RANTES, MBL2, IL-8 and IL-10 [59,60]. Host genetic polymorphisms involved in innate immune responses have been shown to be correlated with resistance to DHF, such as a variant of the FcGRIIA [61], functional polymorphisms of MBL2 [62], and the polymorphisms the CD209 promoter [63].

Similarly, studies on MHC-encoded transporters associated with antigen processing (TAP) genes have also shown associations with DHF [64, 65]. In addition, the analyses of tumor necrosis factor (TNF) and lymphotoxin alpha (LTA) genes have revealed specific combinations of TNF, LTA, and HLA class I alleles that associate with DHF and production of LTA and TNF [66].

Several aspects of T cell functionality are altered in DHF patients, including proliferation, activation status, production of cytokines, and their survival [67–70]. All these functions are influenced by specific recognition, through TCRs, of the antigen associated with HLA molecules. Thus, polymorphisms of HLA genes may also play an important role in dengue severity. Several genetic variations in HLA class I alleles have been found to correlate with dengue severity in Southeast Asian populations.

Some studies have revealed positive associations, whereas others have reported negative associations between DF and HLA classes I and II alleles. In Mexico and Cuba, *HLA-B*35, DRB1*04, *07, *11*, and *DQB1*03:02* were associated to protection against classical DF [12,13]. Meanwhile in Mexico, Thailand, and Cuban the *HLA-A*02:03, *31, B*15, *51, *52, DQB1*01*, and *02:02* have been associated with susceptibility to the classical disease [71,72].

Results based on a study with 85 dengue fever cases, 29 dengue hemorrhagic fever and 110 health controls (HCs) on Western India population, revealed a significantly higher frequency of *HLA-A*33* in DF cases compared to HCs, the frequency of *HLA-A*02:11* was higher in DHF cases compared to DF cases. The frequency of *HLA-B*18* was significantly higher in dengue (DEN) cases. The frequency of *HLA-C*07* was significantly higher in DEN cases. Significance was observed even when the cases were categorized into DF and DHF [73].

The combined frequency of *HLA-C*07* with *HLA-DRB1*07/*15* genotype was significantly higher in DHF cases compared to DF and HCs. On the other hand, the frequency of combination of *HLA-C*07* without *HLA-DRB1*07* was significantly higher in DF cases compared to HCs. The results suggest that *HLA-A*33* may be associated with DF whereas *HLA-B*18* and *HLA-C*07* may be associated with symptomatic dengue requiring hospitalization. In the presence of *HLA-DRB1*07/*15* genotype, *HLA-C*07* is associated with increased risk of developing DHF whereas in the presence of other HLA-DRB1 alleles, *HLA-C*07* is associated with DF [73].

Our group had previously found a strong association between HLA-DQ1 and classical DF, during an epidemic that occurred in a Southern Brazilian population in 1995, characterized by the presence of DF virus serotype 1, however no association between DF and HLA class I antigens was detected [74].

The statistical analysis revealed however, an association between *HLA-A*01* and DHF in the Brazilian population, whereas analysis of *HLA-A*31* suggested a potential protective role in DHF that should be further investigated. This study provides evidence that HLA class I alleles might represent important risk factors for DHF in Brazilian patients. [75].

In addition, HLA class I and II have been associated to primary and the several forms of DF around the world [76]. The host HLA allele profile influenced the reactivity of DF-specific T cells, and may be responsible for the immunopathology of DF infection [77].

HLA Allele	Infection	Serotype	Case (n)	Control	Population	Reference
Susceptible						
*A*02:03*	2nd	DV-1	DF (49)	140	Thai	Stephens et al., 2002
*A*02:03*	2nd	DV-3	DF (26)	140	Thai	Stephens et al., 2002
*A*02:03*	2nd	all	DF (106)	140	Thai	Stephens et al., 2002
*B*52*	2nd	DV-2	DF (17)	140	Thai	Stephens et al., 2002
*B*52*	2nd	-	DF (106)	140	Thai	Stephens et al., 2002
*DQB1*01*	-	-	DF (23)	34	Mexican	Falcón-Lezama et. al., 2009
*DQB1*02:02*	-	-	DF (23)	34	Mexican	Falcón-Lezama et. al., 2009
DQ1	-	-	DF (64)	64	Brazilian	Polizel et. al., 2004
*A*24*, codon 70 histidine	-	-	DHF (59)	200	Vietnamese	Lan et. al., 2008
*A*24*, codon 70 histidine	-	-	DHF (117)	250	Vietnamese	Lan et. al., 2008
*A*02:07*	2nd	DV-1	DHF/DSS (32)	140	Thai	Stephens et al., 2002
*A*02:07*	2nd	DV-2	DHF/DSS (36)	140	Thai	Stephens et al., 2002
*A*02:07*	2nd	DV-1, DV-2	DHF/DSS (103)	140	Thai	Stephens et al., 2002
*A*02:07*	2nd	all	DHF/DSS (103)	140	Thai	Stephens et al., 2002
*A*03*	-	-	DHF/DSS (51)	95	Malay, Chinese, Indian	Appanna et. al., 2010
*B*13*	-	-	DHF/DSS (19)	95	Malay	Appanna et. al., 2010
*B*51*	2nd	all	DHF/DSS (103)	140	Thai	Stephens et al., 2002
*B*51*	2nd	DV-1	DHF/DSS (32)	140	Thai	Stephens et al., 2002
*B*53*	-	-	DHF/DSS (51)	95	Malay, Chinese, Indian	Appanna et. al., 2010

HLA Allele	Infection	Serotype	Case (n)	Control	Population	Reference
A*24			DHF/DSS (309)	251	Vietnamese	Fernández-Mestre et. al., 2004
A*02	2nd	-	DSS (41)	138	Thai	Chiewsilp et. al., 1981
A*24, codon 70 histidine	-	-	DSS (152)	250	Vietnamese	Lan et. al., 2008
A*24, codon 70 histidine	-	-	DSS (170)	200	Vietnamese	Lan et. al., 2008
A*24, codon 70 histidine			DSS (96)	200	Vietnamese	Lan et. al., 2008
B blank	2nd	-	DSS (41)	138	Thai	Chiewsilp et. al., 1981
A*31	-	DV-2	DF, DHF/DSS (120)	189	Cuban	Sierra et. al., 2007
B*15	-	DV-2	DF, DHF/DSS (120)	189	Cuban	Sierra et. al., 2007
B*51	2nd	DV-3	DF, DHF/DSS (51)	140	Thai	Stephens et al., 2002
Resistant						
DRB1*11	-	-	DF (47)	34	Mexican	La Fleur et. al., 2002
DQB1*03:02	-	-	DF (23)	34	Mexican	Falcón-Lezama et. al., 2009
DRB1*09:01	1st	-	DHF (59)	200	Vietnamese	Lan et. al., 2008
A*33	-	-	DHF/DSS (309)	251	Vietnamese	Fernández et. al., 2004
B*18	-	-	DHF/DSS (51)	95	Malay, (Chinese, Indian	Appanna et. al., 2010
B*13	2nd	-	DSS (41)	138	Thai	Chiewsilp et. al., 1981
DRB1*09:01	-	-	DSS (170)	200	Vietnamese	Lan et. al., 2008
DRB1*09:01	-	-	DSS (96)	200	Vietnamese	Lan et. al., 2008
B*35	-	-	DF, DHF/DSS (39)	34	Mexican	Falcón-Lezama et. al., 2009
DRB1*04	2nd	DV-2	DF, DHF/DSS (77)	189	Cuban	Sierra et. al., 2007
DRB1*07	-	DV-2	DF, DHF/DSS (120)	189	Cuban	Sierra et. al., 2007

Table 1. Cases vs. healthy controls Adaptated to [78].

4.2.2. HLA and hepatitis C

Hepatitis C virus (HCV) is one of the major causes of chronic liver inflammation worldwide [79,80]. HCV was first identified in 1989 [81] and has since then been the subject of intense

research and clinical investigation due to the role this virus plays in causing liver disease and the ability of HCV to persist despite cellular immune defense.

The majority of the individuals infected by HCV are asymptomatic and only a small number will clear the virus whereas most individuals, approximately 50–85%, end up with persistent chronic viremia. Chronic disease can be evidenced by histopathological changes, which begin with an inflammation of the liver, often associated with fibrosis and which may progress towards cirrhosis, and in some cases, towards hepatocellular carcinoma [82,83]. An estimated 20% of chronic patients develop cirrhosis, especially 20 years after infection, and of these, 0 to 3% develop hepatocellular carcinoma [84,85].

The exact mechanisms responsible for liver damage during chronic hepatitis C have not yet been defined. The factors that influence the disease progression include viral geno-type, age, gender, duration of the infection, concurrent infections and alcohol abuse; these factors taken individually, however, do not explain the reason that many patients sponta-neously recover and escape from persistent infection whereas others progress towards end-stage liver disease [86-89].

In this context, these clinical features appear to be the result of the host's immune response, a complex interaction between the innate and adaptive immune response, involved in the control of viral replication. HLA class I and II play an important role in the immune response against viral infections because they are key proteins to antigen presentation by antigen presenting cells to T lymphocytes. Several studies have analyzed HLA class I and class II in patients with hepatitis C in different populations and there is strong evidence that some, mainly HLA class II, alleles are involved in the control of viral infection by HCV. Table 1 summarizes the various HLA class II specificities that have been associated with HCV infection [90-123].

The most consistent data seems to be related to *HLA-DRB1*11* associated with the asympto-matic disease in individuals hosting HCV in Italy (*DRB1*11:04* allele) [95], and has been associated with normal levels of alanine aminotransferase (ALT) in patients infected in France [105]. In another study in France, *HLA-DRB1*11* has been more frequently detected in patients without cirrhosis when compared to cirrhotic patients [103]. In Europe, *HLA-DRB1*11* has been observed to be less frequent in those individuals who had received transplants for HCV-induced end-stage liver disease compared to blood donors. In fact, *HLA-DRB1*11* seems to be a favorable prognosis factor not only in facilitating spontaneous HCV clearance [96,98,104,115,124,125], but also in increasing resistance against the development of more advanced stages of the chronic HCV infection [121].

Another allele group that has been correlated to self-limiting HCV is *DQB1*03* [101,104,114,124]. *HLA-DQB1*03* is found in linkage disequilibrium (LD) with *HLA-DRB1*11* and, alone or in conjunction with *DRB1*11*, has been strongly associated with spontaneous viral clearance [96,100,115,122] and with the avoidance of further liver damage in chronically infected hepatitis C virus patients. In a meta-analysis, individuals with *HLA-DRB1*11:01* and *DQB1*03:01* had a reduced risk of acquiring chronic HCV infection in 102% and 136%, respectively [126]. *HLA-DQB1*03* once again seems to influence treatment response, *HLA-*

DQB1*03:01 has been associated with sustained viral response (SVR) treated with pegylated interferon-alpha and ribavirin [120]. In another study carried out with patients from Pakistan, an association between *DQB1*03* and improved antiviral defense in patients treated with inferferon-alpha plus ribavirin was detected [100].

Although some studies have been conducted to evaluate the influence of HLA class I in the course of hepatitis C disease and on the treatment response, the data is not yet consistent. The HLA-B35 antigen has been found more frequently in HCV carriers when compared to healthy individuals [111]. *HLA-B*18* has been observed more frequently in patients with advanced stages of fibrosis (F2-F4) [127]. In a study carried out in Spain, this specificity was also more frequently found in patients with hepatocellular carcinoma, suggesting a possible involvement in progression towards more severe forms of the disease and a more unfavorable prognosis [128]. African-American patients with *HLA-A*23* showed a higher susceptibility to develop chronic HCV infection [101].

Some HLA class I alleles have been described in treated patients: *HLA-C*07* has been associated with SVR in patients on interferon-alpha therapy in Croatia [129]. The HLA-B55, B62, Cw3 and Cw4 antigens have been associated with improved response to interferon-alpha treatment in Japanese's patients [130]. In Taiwan, the HLA- *A*11*, *B*51*, *C*15* and *DRB1*15* allele groups were related to a sustained response to interferon-alpha treatment, whereas *A*24* was linked to non-response to treatment [108]. In addition, *HLA-A*24* and *B*40* as well as haplotypes *B*40-DRB1*03*, *B*46-DRB1*09*, *C*01-DQB1*03* and *C*01-DRB1*09* were associated with SVR in Taiwan [131]. Furthermore, in Caucasian Americans, *HLA-A*02* was associated with SVR [132].

This lack of consensus in the literature may be result of the variations in the methodology of each study, such as different criteria or treatment response diagnoses, sample size, ethnic differences, mixing viral genotypes during analysis, and differences in treatment.

Associated HLA class II specificity	Population/Country	Outcome	Reference
DRB1*04:05 and *DQB1*04:01*	Japan	Viral persistence	Aikawa et al. (1996)
DRB1*03:01	Germany	Viral persistence	Hohler et al. (1997)
DRB1*11 and *DQB1*03*	France	Viral clearance	Alric et al. (1997)
DRB1*04:05 and *DQB1*04:01*	Japan	Viral persistence	Kuzushita et al. (1998)
DRB1*07	Caucasians/France	Nonresponders to IFN-a therapy	Alric et al. (1999)
DQB1*06	Caucasians/France	Sustained virological response	Alric et al. (1999)
DRB1*10:01 and *DRB1*11:01*	Italy	Viral persistence	Asti et al. (1999)
DRB1*11:04 and *DRB3*03*	Italy	Protection	Asti et al. (1999)
DQB1*05:02	Italy	Viral persistence	Mangia et al. (1999)

Associated HLA class II specificity	Population/ Country	Outcome	Reference
DRB1*11:04 and *DQB1*03:01*	Italy	Viral	Mangia et al. (1999)
DRB1*07:01, and *DRB4*01:01*	European (UK)	Viral persistence	Thursz et al. (1999)
DRB1*01	Ireland	Spontaneous clearance	Fanning et al. (2000)
DRB1*03:01 and *DQB1*02:01*	Thailand	Viral persistence	Vejbaesya et al. (2000)
DRB1*11 and *DQB1*03*	Caucasians/UK	Viral clearance	Harcourt et al. (2001)
DQB1*03:01	Black/USA	Viral clearance	Thio et al. (2001)
DRB1*01:01 and *DQB1*05:01*	Caucasians/USA	Viral clearance	Thio et al. (2001)
DRB1*03:01 and *DQB1*02:01*	Caucasians/USA	Viral persistence	Thio et al. (2001)
DRB1*13	Poland	Viral persistence	Kryczka et al. (2001)
DQB1*02:01	France	Viral persistence	Hue et al. (2002)
DRB1*11	Turkey	Protection	Yenigun & Durupinar (2002)
DRB1*11	France	less severe liver disease	Renou et al. (2002)
DR14 and *DR17*	Italy	Viral persistence	Scotto et al. (2003)
DQB1*05:03	Japan	Viral persistence	Yoshizawa et al. (2003)
DRB1*15	Taiwan	Sustained virological response	Yu et al. (2003)
DQB1*02:01	Ireland	Viral persistence	McKiernan et al. (2004)
DRB1*07	China	Sustained virological response	Jiao & Wang (2005)
DRB1*08:03, DQB1*06:01 and *DQB1*06:04*	Korea	Viral persistence	Yoon et al. (2005)
DRB*40:01	Taiwan	High viral load	Wang et al. (2005)
DRB1*15	Tunisia	Viral persistence	Ksiaa et al. (2007)
DRB1*08	Tunisia	Spontaneous clearance	Ksiaa et al. (2007)
DRB1*03	Brazil	Viral clearance	Cursino-Santos et al. (2007)
DRB1*11, DQB1*03 and *DRB3*02*	USA	Viral clearance	Harris et al. (2008)
DRB1*04 and *DQB1*02*	Egypt	Viral persistence	El-Chennawi et al. (2008)
DQB1*06	Egypt	Protection	El-Chennawi et al. (2008)
DRB1*07	Brazil	Viral persistence	Corghi et al. (2008)
DRB1*08 and *DQB1*04*	Brazil	Protection	De Almeida et al. (2011)

Associated HLA class II specificity	Population/Country	Outcome	Reference
DRB1*11	Brazil	Viral clearance	De Almeida et al. (2011)
DRB1*11 and DQB1*03	Brazil	Protection	Cangussu et al. (2011)
DQB1*03:01	Spain	Sustained virological response	Rueda et al. (2011)
DRB1*11	Brazil	Protection	Marangon et al. (2012)
DRB1*11-DQA1*05-DQB1*03	Brazil	Protection	Marangon et al. (2012)
DRB1*11	Brazil	Sustained virological response	Marangon et al. (2012)
DRB1*04	Pakistan	Protection to HCV	Ali et al. (2013)
DRB1*11 and DQB1*03	Pakistan	Viral clearance	Ali et al. (2013)
DRB1*07 and DQB1*02	Pakistan	Viral persistence	Ali et al. (2013)
DQB1*02, DQB1*06, DRB1*13 and DRB1*15	Egypt	Sustained virological response	Shaker et al. (2013)

Table 2. HLA class II specificities associated with hepatitis C infection

4.2.3. HLA and hepatitis B

Similar to HCV, Hepatitis B virus (HBV) is a hepatotrophic virus considered a serious public health problem. HBV infection is endemic in many parts of the world and more than 2 billion people are estimated to be infected with HBV [133-134].

The clinical features of the disease can vary from virus clearance to fulminating hepatitis. Some HBV carriers have an unapparent self-limiting hepatitis and others develop chronic hepatitis, which may lead to cirrhosis and in some cases to hepatocellular carcinoma [133-134].

Persistent HBV infection or HBV clearance is influenced by many factors such as level of viral replication, age at infection, gender, chronic alcohol abuse, co-infection with other hepatitis viruses, and genetic makeup, with most studies having identified susceptibility loci at HLA class II [133-134].

A meta-analysis demonstrated that *HLA-DR*03* and *HLA-DR*07* were associated with an increased risk of persistent HBV infection in 18 individual case-control studies including 9 Han Chinese cohorts, 3 Korean cohorts, 2 Iranian cohorts, and 1 cohort each of Caucasian, Gambian, Taiwanese, Thai, and Turkish subjects [135].

In Chinese Han populations, *HLA-DR*01* was associated with clearance of HBV infection, whereas in other ethnic groups there was no association between *HLA-DR*01* and HBV infection.

The haplotypes *HLA-DQA1*01:02-DQB1*03:03* and *HLADQA1*03:01-DQB1*06:01* were associated to persistent HBV infection, whereas *HLA-DQA1*01:02-DQB1*06:04* and *HLA-DQA1*01:01-DQB1*05:01* were protective to HBV infection [135].

A genome-wide association study identified a significant association of chronic hepatitis B in Asians with 11 SNPs in a region including HLA-DPA1 and HLA-DPB1 and subsequent analyses revealed risk haplotypes (*HLA-DPA1*02:02-DPB1*05:01* and *HLA-DPA1*02:02-DPB1*03:01*) and protective haplotypes (*HLADPA1* 01:03-DPB1*04:02* and *HLA-DPA1*01:03-DPB1*04:01*) for HBV infection [136].

HLA haplotype analysis indicated that *HLA-DQA1*01:02-DQB1*03:03* and *HLADQA1*03:01-DQB1*06:01* were risk types for persistent HBV infection, whereas *HLA-DQA1*01:02-DQB1*06:04* and *HLA-DQA1*01:01-DQB1*05:01* were protective types for HBV infection [137].

4.2.4. HLA and HIV

Human immunodeficiency virus (HIV) infection has indeed spread worldwide with over 30 million people living with HIV/AIDS. HIV infection represents a major challenge for physicians and scientists and is typically associated with an acute viral syndrome, with an asymptomatic period until the development of acquire immunodeficiency syndrome (AIDS). When left untreated the infection causes a decline in the CD4+ T cell number to less than 200 cells/mm^3, resulting in immunodeficiency, opportunistic infections, and death [138].

A great number of disease-protective and disease-susceptible HLA alleles have been well characterized in HIV infection and the strongest associations seems to be related to HLA class I alleles (mainly HLA-A and B alleles) with differential rates of HIV disease outcome. Herein, we intend to review and discuss the HLA alleles related to HIV infection.

The virologic and immunologic outcomes in patients with HIV infection can be highly variable, with only a small number of individuals capable of controlling HIV replication without therapy [138]. Despite the mechanism involved in control and progress of HIV infection not yet being fully understood, the implication of some host immunogenetic factors, as the HLA molecules, in the course of disease has been well established.

Earlier studies revealed a relationship between *HLA-B*27* and *HLA-B*57* and the slow progression to AIDS [139]. Since then, a great number of studies have investigated the influence of HLA class I and class II alleles in both acute and chronic HIV infection and the strongest associations seem to be related to HLA class I alleles.

Regarding the association of HLA class I alleles and protection against HIV infection, the *HLA-B*44* and *B*57* have been described as favorable factors in both the acute and chronic phases of sub-Saharan Africans seroconverters [140]. In China, *HLA-A*03* has been described as a protective factor against HIV-1 infection and disease progression [141].

In another study, *HLA-A*32, A*74, B*14, B*45, B*53, B*57* have been associated with disease control in African Americans infected by HIV-1 subtype B [142].

A large multiethnic cohort with HIV-1 controllers and progressors found diverse alleles associated with virologic and immunologic control: *HLA B*57:01, B*27:05, B*14/C*08:02, B*52,*

and *A*25* [143]. Furthermore, *HLA-B*13:02* [144,145] and *B*58:01* [146-148], have also been described as favorable prognostic factors.

Although all these alleles seem to be implicated in HIV infection the most consistent data are related to three HLA-B specificities: *HLA-B*57* (*HLA-B*57:01* in European population, *57:02* and *57:03* alleles mainly in African population) [140,143,147-152], *HLA B*27* (*HLA-B*27:05*) [139,143,145,150] and also *HLA-B*81* (*HLA-B*81:01*) [140,143,146,148]. These variants are strongly associated with viral load control and slow disease progression in different populations. In fact, the HLA-B molecules have impact on HIV infection as the majority of detectable HIV-specific CD8+T-cell responses described seems to be restricted by HLA-B alleles.

Regarding HIV susceptibility and rapid disease progression, *HLA-B*35* (*B*35:01*, *B*35:02* and *35:03*) seems to have the greatest impact on the disease: patients with these alleles seem to have less effective control of viral replication and progress towards AIDS more rapidly [143, 153].

Other unfavorable alleles have been described: *B*18/*18:01* [148,151], *B*45/*45:01* [140,148], *B*51:01* [148], *B*53:01* [143,153], *B*58:02* [140,146,148], *A*36:01* [140,148], and *B*07:02* [143], however with no actual consistency.

In addition, some HLA-C alleles have been described in association with HIV. *HLA-C*08* and *C*18* have been associated with viral load [142]. In 2010 and 2011 respectively, HIV escape mutants within cytolitic T lymphocytes (CTL) epitopes restricted of to two different HLA-C alleles were reported: *C*03* [154] and *HLA-C*12:02* [155]. In HLA-C associations, some HLA-C alleles tend to be in linkage disequilibrium (LD) with HLA-B alleles and the results could be due to the presence of these HLA-B alleles, such as *B*81:01-C*04:01*. To elucidate the genetic factors predisposing to AIDS progression, the first genomewide association study (GWAS) identified several new associations, all of them involving HLA genes: MICB, TNF, RDBP, BAT1-5, PSORS1C1, and HLA-C: This study underscores the potential for some HLA genes to control disease progression soon after infection [151].

4.2.5. HLA and papillomavirus infection

Infection by human papillomavirus (HPV) is a common sexually transmitted infectious disease and most sexually active women have been infected during their lifetime. HPV infections frequently occur in healthy individuals and the high carcinogenic risk (HR) HPV types are a major causal factor for cervical cancer (CC). Persistent infection with one among approximately 15 genotypes of carcinogenic HPV causes almost all cases of cervical cancer; type 16 and HPV-18 account for more than 70% of the cervical cancers detected worldwide [156,157].

A number of genetic risk factors have been identified, but their effects are generally weak. The most prominent among the known risk factors is the HLA complex, which plays a critical role in susceptibility to CC [3]. Since the first reported association of HLA-DQ3 with CC, a large number of studies of HLA association with cervical cancer have been published with variable results depending on the ethnic group [157,158].

A study with CC described that *DRB1*04:07-DQB1*03:02* and DRB1*15:01-DQB1*06:02* were clearly associated with susceptibility to HPV-16 positive invasive CC, high squamous intrae-

pithelial lesion (HSIL), and carcinoma in situ [159]. Studies with Honduran women showed *HLA-DQA1*03:01* in linkage disequilibrium with all HLA-DR4 subtypes in Mestizos, as an increased risk of developing high squamous intraepithelial lesion and CC [160]

Some DR-DQ haplotypes containing *DQB1*03:01* have been positively associated with CC susceptibility: *DRB1*11:01-DQB1*03:01* in Senegalese and US Caucasian Europeans, and *DRB1*04:01-DQB1*03:01* in US Caucasian Europeans and British females. *DRB1*11:02-DQB1*03:01* was also increased in Hispanics with carcinoma in situ or HSIL.

Protection has been mainly linked with the *HLA-DRB1*13* group: *DRB1*13:01* in patients from Costa Rica, and *DRB1*13:01-DQB1*06:03-DQA1*01:03* in Swedish, French and Dutch women with CC. A protective effect against CC progression was also claimed to be correlated with *DQB1*05, DQA1*01:01/04, DRB1*01:01* and *DRB1*13:02* in Brazilians. In Caucasians, *HLA-DRB1*13* and HPV-16/18-negative status, were independently associated with an increased probability of regression of low squamous intraepithelial lesion (LSIL), also suggesting a protective effect against CC progression [161-163].

Continuing trials pursue an explanation for the relationship between HLA and HPV infection. Silva (2013) showed that *HLA-DQB1*05:01* allele might be associated with susceptibility of HPV reinfection in Mexican women, allele frequency of *HLA-DRB1*14* was particularly reduced in patients with cancer when compared with the HPV–persistent group (p=0.04), suggesting that this allele is a possible protective factor for the development of cervical cancer.

A study analyzed the associations between HLA-G polymorphisms and HPV infection and squamous intraepithelial lesions (SIL) in Inuit women from Nunavik, northern Quebec. The group demonstrated that *HLA-G*01:01:01* was associated with an increased risk of period prevalent alpha groups 1 and 3 [164]. The *HLA-G*01:04:01* genotype was associated with a decreased risk of alpha group 3 infection period prevalence. No HLA-G alleles were significantly associated with HPV persistence. *HLA-G*01:01:02, G*01:04:01* and *G*01:06* were associated with HSIL, however the association did not reach statistical significance. In this trial, HPV genotypes were classified according to tissue-tropism groupings of alpha-papillomavirus species: alpha group 1 including low risk (LR) cervical species, group 2 including high risk (HR) cervical species, and group 3 including LR vaginal species.

One Korean study related the relationship between HLA and recurrent respiratory papillomatosis (RRP) and showed that the gene frequencies of *HLA-DRB1*11:01* and *DQB1*03:01* and the haplotype frequency of *DRB1*11:01-DQB1*03:01* were higher in RRP patients than in controls. *DRB1*11:01* and *DRB1*11:01-DQB1*03:01* haplotype were strongly associated with disease susceptibility to severe RRP in Koreans [165]. In Brazil, the *HLA-A*02-HLA-B*51* haplotype presented a reduced frequency in HPV patients compared to controls; and was associated with resistance against the disease [156].

In China population, HLA-DRB alleles were associated with cervical cancer and HPV infections [166]. For the assessment of these genotypes, 69 cervical cancer patients and 201 controls were examined. *HLA-DRB1*13* and *DRB1*03(17)* were associated with an increased risk of cervical cancer, and *DRB1*09:012* and *DRB1*12:01* were associated with a decreased risk. The

risk associations of HPV infection were increased in women carrying *HLA-DRB1*09:012* and *DRB3(52)*01:01* alleles.

Among cervical cancer patients, the association risks differed between HPV positive and negative cases for several alleles; an increased risk of cervical cancer was observed in patients with *DRB3(52)*02/03* and *DRB1*3(17)* and a decreased risk was observed with *DRB1*09:012* and *DRB5(51)*01/02* [166].

4.3. Parasitic diseases

4.3.1. HLA and Chagas disease

Many genetic linkage and association studies have attempted to identify genetic variations that are involved in immunopathogenesis of Chagas disease. However, the causal genetic variants underlying susceptibility remain unknown due to parasite and host complexity [167]. Susceptibility or resistance to Chagas disease involves multiple genetic variants functioning jointly, each with small or moderate effects. To identify possible host genetic factors that may influence the clinical course of Chagas disease, the role of classic and non-classic MHC genes will be addressed.

Chagas disease is an infection caused by the protozoan *Trypanosoma cruzi*, described in 1907 by Carlos Chagas. The disease is endemic and is characterized by acute and chronic phases, which develop into the indeterminate, cardiac and/or gastrointestinal forms [168,169]. Ten million people are estimated to be infected with *T. cruzi* worldwide, mostly in Latin America (WHO, 2012) with a total estimated incidence of 800,000 new cases per year [170].

The mechanisms of the transmission of Chagas infection include transmission through insect vectors mainly, but blood transfusion, contaminated food, congenital and secondary transmissions mechanism may occur [171].The phases of infection include the early or acute phase, characterized by high parasitaemia or trypomastigote circulating forms in the blood for two to four months [170]. Mortality, during this period, ranges from 5% to 10% due to episodes of myocarditis and meningocefalite [172,173].

The clinical signs are a local inflammatory reaction with formation of strong swelling at the site of entry of the parasites (chagoma or Romaña sign), fever, splenomegaly and cardiac arrhythmia [174]. During the acute phase, the majority of the infected individuals develop a humoral and cellular immune response responsible for the decrease of parasites in the blood.

Following this phase, patients progress to the chronic asymptomatic stage which affects most individuals (50 to 60%): this condition characterizes the indeterminate clinical form (IND) of the disease, and may remain in effect for long periods of time [175]. Approximately 20% to 30% of the individuals develop cardiomyopathy, which reflects a progressively damaged myocardium due to extensive chronic inflammation and fibrosis and, in terminal phases, usually presents as dilated cardiomyopathy. Chronic Chagas cardiomyopathy (CCC) is the most relevant clinical manifestation leading to death from heart failure in endemic countries. Eight to 10% have the digestive form (DF), characterized by dilation of the oesophagus or colon

(megaoesophagus and megacolon). Some patients have associated cardiac and digestive manifestations, known as the mixed or cardiodigestive form [176-178].

There is a consensus that during *T. cruzi* infection the host immune system induces complex processes to ensure the control of parasite growth. The immune response is crucial for protection against the disease; however, immunological imbalances can lead to heart and digestive tract lesions in chagasic patients. Several studies have evaluated the innate, cellular and humoral immune responses in chagasic patients in an attempt to correlate immunological findings with clinical forms of Chagas disease. However, in all clinical forms of Chagas disease the involvement of cell-mediated immunity is undoubtedly of major importance [179- 189].

The spectrum of expression of Chagas disease brings strong evidence of the influence of the genetic factors on the clinical course of the disease, and the polymorphic genes involved in the innate and specific immune response is being widely studied such as the molecules and genes in the region of the HLA.

The polymorphic HLA class I (A, B and C) and II (DR, DQ and DP) molecules determine the efficiency of presentation of the *T. cruzi* epitopes to CD8+ and CD4+ T-cells, respectively. The type of the presentation could affect the clinical course of diseases because patients may respond differently to the same antigen, depending on their HLA repertoire [190]. Several HLA alleles and haplotypes have been reported to be associated with Chagas disease.

Regarding the association of HLA and Chagas disease, HLA-Dw22 was firstly associated to the susceptibility of developing the disease in Venezuelans [191]. A subsequent study compared class II allele frequencies between patients and controls and identified a decreased frequency of *DRB1*14* and *DQB1*03:03* in patients, suggesting protective effects unrelated to chronic infection in this population [192]. A study in southeastern Brazil showed that *HLA-A*30* confers susceptibility to Chagas disease, whereas *HLA-DQB1*06* confers protection, regardless of the clinical form of the disease [193] and, in a South Brazilians population, HLA-DR2 antigens were related to susceptibility to chronic Chagas disease [194]. HLA-DR4 and HLA-B39 were associated with the infection by the *T. cruzi* in the Mexican population [195] and *HLA-DRB1*04:09* and *DRB1*15:03* in Argentineans [196,197]. In the latter study, *DRB1*11:03* allele was associated with disease resistance [197]. The haplotype *HLA-DRB1*14-DQB1*03:01* was involved in resistance to *T. cruzi* infection in the rural mestizo population of Southern Peru [198] and the *HLA-DRB1*01-B*14-MICA*011* haplotype was associated with resistance against chronic Chagas disease in Bolivian individuals [199].

As to the association of HLA and the clinical form of CCC, the first publication related HLA-B40 antigen, in the presence of Cw3, with a resistance to cardiac manifestations in Chilean patients [200], which was later confirmed [201]. However, *HLA-C*03* was associated with susceptibility to cardiomiopathy in the Venezuelan *T. cruzi* serologically positive individuals [202]. An increase of HLA-A31, B39, DR8, HLA-DR16 and *DRB1*15:03* and *HLA-DPB1*04:01* alleles and a decrease of HLA-A68, DR4, DR5, DQ1, DQ3 and *DRB1*15:01* were observed in several Latin American mestizos from different countries with CCC [192,195,203,204]. *DPB1*04:01-HLA-DPB1*23:01* and *DPB1*04:01-DPB1*39:01* haplotypes were susceptibility factors in this clinical form [204].

The studies conducted with the mixed or cardiodigestive form revealed that *DRB1*01*, *DRB1*08* and *DQB1*05:01* was more frequent in patients conferring susceptibility to the disease [192], as occurs with the *HLA-DPB1*04:01* allele in homozygous or in combination with *HLA-DPB1*23:01* or *DPB1*39:01* [204]. Contrarily, a decreased frequency of *DRB1*15:01* was found in patients with arrhythmia and congestive heart failure, conferring resistance against these disorders [192,204]. Recently, resistance conferred by *HLA-DRB1*01* and *HLA-B*14:02* was associated with the patients suffering from megacolon, as well as in those with ECG alterations and/or megacolon when they were compared with a group of patients with indeterminate symptoms [199].

Another study showed that contrarily, the polymorphism of HLA-DR and -DQ molecules did not influence the susceptibility to different clinical forms of Chagas' disease or the progression to severe Chagas' cardiomyopathy [205].

The polymorphism of MICA may be involved in the susceptibility to various diseases; however this association has been suggested to be secondary, due to the strong linkage disequilibrium with HLA-B alleles. *MICA*011*, which was closely linked to *HLA-B*14* and *DRB1*01*, might stimulate Tγδ cells in the gut mucosa, a phenomenon that could be related to megacolon [206]. In Chagas disease the same *HLA-DRB1*01-B*14-MICA*011* haplotype was associated with resistance against the chronic form [199]. *MICA-A5* and *HLA-B35* synergistically enhanced susceptibility to CCC [207].

These different results between the HLA allele and haplotypes and Chagas disease could be the result of the variability of HLA allele's distribution in different ethnic groups, the selection of the patients and the clinical form, and the biological variability of the parasite, among other factors. Nevertheless, genetic factors related to the HLA system reflect an important role in susceptibility or protection to Chagas disease and its clinical forms.

4.3.2. HLA and malaria

Malaria is an infectious disease caused by intracellular protozoan of the genus *Plasmodium*. Genes located in the HLA complex appear to protect populations in endemic areas against the severe forms caused by *Plasmodium falciparum* and *Plasmodium vivax*.

The antibody response generated during malaria infections is of particular interest, since the production of specific IgG antibodies is required for acquisition of clinical immunity. However, variations in antibody responses could result from genetic polymorphism s of the HLA class II genes. Given the increasing focus on the development of subunit vaccines, studies of the influence of class II alleles on the immune response in ethnically diverse populations is important, prior to the implementation of vaccine trials. Junior et al.(2012) showed that *HLA-DRB1*04* alleles were associated with a high frequency of antibody responses to five out of nine recombinant proteins tested in Rondonia State, Brazil [208].

The Fulani of West Africa have been shown to be less susceptible to malaria and to mount a stronger immune response to malaria than sympatric ethnic groups. *HLA-DRB1*04* and -*DQB1*02* have been shown to be implicated in the development of several autoimmune

diseases, to be present at high frequency in the Fulani, suggesting their potential involvement in the enhanced immune reactivity observed in this population [209].

Trials have been performed seeking to determine the associations between HLA-A, B, and DRB1 group of alleles and severe malaria in northern Ghana. *HLA-DRB1*04* was analyzed in 4,032 subjects from a severe malaria case-control study, 790 severe malaria cases, 1,611 mild malaria controls, and 1631 asymptomatic controls. The presence of *HLA-DRB1*04* was associated with severe malaria. The frequency of *DRB1*04* was similar in the two major ethnic groups in the study population, Kassem (4.4%) and Nankam (4.7%), and the OR for the association between *DRB1*04* and severe malaria was similar in both ethnic groups. These findings were consistent with results from Gabon suggesting that *DRB1*04* to be a risk factor for severe malaria [210].

To test for associations between HLA alleles and the severity of malaria in a Thai population, polymorphisms of HLA-B and HLA-DRB1 genes were investigated in 472 adult patients in northwest Thailand with *Plasmodium falciparum* malaria. In the study, malaria patients were classified into three groups: mild malaria, non-cerebral severe malaria, and cerebral malaria. The results revealed that the allele frequencies of *HLA-B*46*, *B*56*, and *DRB1*10:01* were statistically different between non-cerebral severe malaria and cerebral malaria, between mild malaria and cerebral malaria (P = 0.032), and between mild malaria and non-cerebral malaria [211].

Individuals from Mumbai, an area of low and seasonal *Plasmodium falciparum* transmission, were investigated for HLA associations. A cohort of 171 severe *P. falciparum* malaria patients were compared with that of 101 normal gender, age, and ethnically matched control samples. Significant differences were observed between patients with malaria and controls in the following HLA: A3, B27, B49, *DRB1*04*, and *DRB1*08:09,* which were increased, whereas A19, A34, B18, B37, and *DQB1*02:03* were decreased. HLA B49 and *DRB1*08:09* were found to be positively associated with the complicated severe malaria patients. HLA-A19, B5 and B13 were protective in patients with high parasite index (> 2%). These observations revealed the importance of ethnic background, which has to be taken into consideration when developing an ideal malaria vaccine. Furthermore, when compared to HLA associations of other world populations the study indicated the relative importance of different HLA alleles that may vary in different populations [212].

5. Concluding remarks

Many genetic linkage and association studies have attempted to identify HLA variations that are involved in immunopathogenesis of infection diseases. However, in the infection diseases multiple genetic variants functioning jointly, each with small or moderate effects, may protect against diseases, or could contribute to aggression and tissue damage. Different results between the alleles and haplotypes HLA and infection diseases could be caused by: variability of HLA alleles distribution in different ethnic groups; the typing test (serological or molecular techniques); the methods of statistical analyses (chi-square test, logistic or linear regression)

and interpretation (*p* or *pc* values that apply the Bonferroni correction for multiple comparations); the selection of the patients and the clinical form; the numbers of individuals; linkage disequilibrium that vary among populations; and biological variability of the parasite.

The characterisation of the susceptibility genes and their variants has important implications, not only for a better understanding of disease pathogenesis, but for the control and development of new therapeutic strategies for infectious diseases. Using the basic knowledge acquired in the studies of the influence of genetics upon the immune response against parasite in different populations, one can look for proteins that induce the immunological phenotype needed for protection. At present, vaccination is an effective preventive measurement for these disorders, and researches for peptides with the best-predicted binding affinities for HLA molecules are an alternative. Overall, this type of analysis could potentially define high-risk patient groups, and result in effective therapeutic strategies for infectious disorders.

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