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A review of the roles of Major Histocompatibility Complex (MHC) molecules in infections

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Abstract:

The major histocompatibility complex (MHC) locus is a group of genes located on the short arm of chromosome 6 in human that code for proteins on the cell surface. They have important roles in immune response by the cells of immune system. Using a comprehensive search method on Google Scholar and PubMed databases, literatures on MHC published in English until 2021 were searched with the terms; "MHC", "HLA", "MHC antigen presentation" and "MHC roles in infections". Relevant publications were identified, screened for duplicates and selected per eligibility. The review highlights the different haplotypes of the MHC that either enhance or depress the body immune system to some important viral, bacterial and parasitic infections. The possibility of utilizing this knowledge in genetic engineering and immunomodulation, to prevent infectious diseases and cancers, are discussed.

Keywords: Major histocompatibility complex; human leukocyte antigen; haplotypes; genetic engineering; immunomodulation; review.

Un examen des rôles des molécules du complexe majeur d'histocompatibilité (CMH) dans les infections

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Abstrait:

Le locus du complexe majeur d'histocompatibilité (MHC) est un groupe de gènes situés sur le bras court du chromosome 6 chez l'homme qui codent pour des protéines à la surface des cellules. Ils jouent un rôle important dans la réponse immunitaire des cellules du système immunitaire. À l'aide d'une méthode de recherche complète sur les bases de données Google Scholar et PubMed, les publications sur le CMH publiées en anglais jusqu'en 2021 ont été recherchées avec les termes; "MHC", "HLA", "présentation de l'antigène du CMH" et "rôles du CMH dans les infections". Les publications pertinentes ont été identifiées, examinées pour les doublons et sélectionnées par éligibilité. L'examen met en évidence les différents haplotypes du CMH qui renforcent ou dépriment le système immunitaire de l'organisme contre certaines infections virales, bactériennes et parasitaires importantes. La possibilité d'utiliser ces connaissances dans le génie génétique et l'immunomodulation, pour prévenir les maladies infectieuses et les cancers, est discutée.

Mots clés: Complexe majeur d'histocompatibilité; l'antigène leucocytaire humain; haplotypes; ingénierie génétique; immunomodulation; la revue.

Introduction:

The major histocompatibility complex (MHC) locus is a group of genes that encode proteins on the cell surface that have an important role in immune response [1]. The level of immune responsiveness is often affected or controlled by gene products of the MHC, also known in humans as human leukocyte antigens (HLAs) [2]. Many diseases, as well as host immune reactivity, are associated with the HLAs [3,4]. The MHC were first identified by their potent effect on the immune response to transplanted tissue, reason to which, the gene complex was termed "major histocompatibility complex". The MHC, called the H-2 complex in mice and located on chromosome 17, and on the short arm of chromosome 6p21.31 in humans, has more than 200 genes, and were first recognized in 1937 as a barrier to transplantation in mice [5]. The MHC also functions as tissue allorecognition, an important factor in prevention of successful organ transplantation.

The HLAs were first discovered through antigenic differences between white blood cells in different individuals. Their main role is in antigen presentation where they display peptide fragments for recognition by appropriate T cells which is an important process in the immune system response for destroying invading pathogens. The MHC on the cell surface is necessary for cell self-recognition and the prevention of the immune system targeting its own cells. Certain MHC alleles are associated with an increased risk of autoimmune disease such as Hodgkin's lymphoma and multiple sclerosis [1].

The presence of HLA alleles differs in various human populations. Genomic analysis in families has paved way for the mapping and identification of the HLA loci associated with certain infectious diseases and the role they play in conferring resistance or susceptibility on the host. The MHC has two distinct properties which makes evasion of immune response difficult for pathogens. It is polygenic with several different MHC class I and class II genes, such that a set of MHC molecules with different range of peptide-binding specificities is present in every individual. It is also highly polymorphic, making a population of individuals possess multiple variants of each gene.

There is paucity of data on the roles played by the MHCs in infection and against various pathogens. The extent of actions and involvement of this MHC is sparsely understood, thus limiting application of knowledge and use of these molecules in infectious diseases treatment, prevention and control. Also, information on the impact and functions of the MHC in immune responses are sparse.

Hence, this review was conducted to highlight the functions and impacts of the MHC in human, as well as their roles in modulating infections.

Methodology and Results:

In this review, a combination of free-text terms or phrasal terms of "MHC" and/or "HLA", "MHC types", "MHC antigen presentation", "MHC structure" and "MHC roles in infection" were used in carrying out a comprehensive search of literatures through online database search as shown in Fig 1. Articles published in English language up till October 2021, were screened and duplicates removed after determining the relevant articles. This produced 50 articles but further search led to additional 3 articles, giving a total of 53 articles for the review.
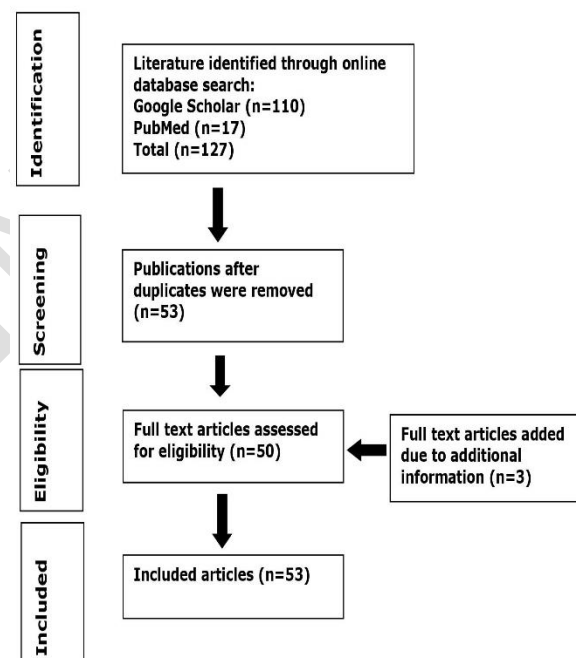

Fig. 1: Process of selection of publications (using PRISMA guide) used for the review

Discussion:

MHC genetic locus

The human major histocompatibility complex (MHC) locus is located on the short arm of chromosome 6 at 6p21.3 (Fig. 2a). Chromosome 6 is estimated to be 150-180 Mb in size and the MHC region on this short arm is a 4-Mb DNA segment that encodes many of the molecules involved in innate and adaptive immune responses. This highly polymorphic DNA region contains nearly 130 genes and approximately 100 pseudogenes but not all of these genes are linked to immunity, and only two sets of genes within the region play central roles in antigen presentation; MHC class I and MHC class II locus

which encode molecules involved in antigen presentation (Fig. 2b). The MHC locus starts at 4954 bp and ends at 3550069 bp.

The MHC locus is made up of three regions; MHC-I, MHC-II, and MHC-III. Each region has specific classical HLA antigens encoded; HLA-A, -B, and -C in the MHC-I region, HLA-DR, -DQ, and -DP in the MHC-II region, while MHC-III region includes several genes involved in the complement cascade (C4a, C4b, C2, and FB), TNF-α and TNF-β (LTa) genes, CYP21 gene that encodes an enzyme in steroid metabolism, HSP70 gene that encodes a chaperone, and many other genes of unknown immunological function. This indicates the important role of MHC in immune-mediated responses, autoimmunity, and infectious diseases (4).

The MHC class I proteins develop a functional receptor on almost all nucleated cells of the body, encoded by 3 major (HLA-A, HLA-B and HLA-C) and 3 minor (HLA-E, HLA-F and HLA-G) MHC class I genes. The genes responsible for encoding α1, α2 and α3-chains of MHC-I and α1, α2 and β1, β2-chains of MHC-II are linked, while the genes for β2-microglobulin in MHC-I and the invariant chain (Ii gene) in MHC-II are located on different chromosomes; chromosomes 15 and 5 in humans, and chromosomes 2 and 18 in mouse respectively.
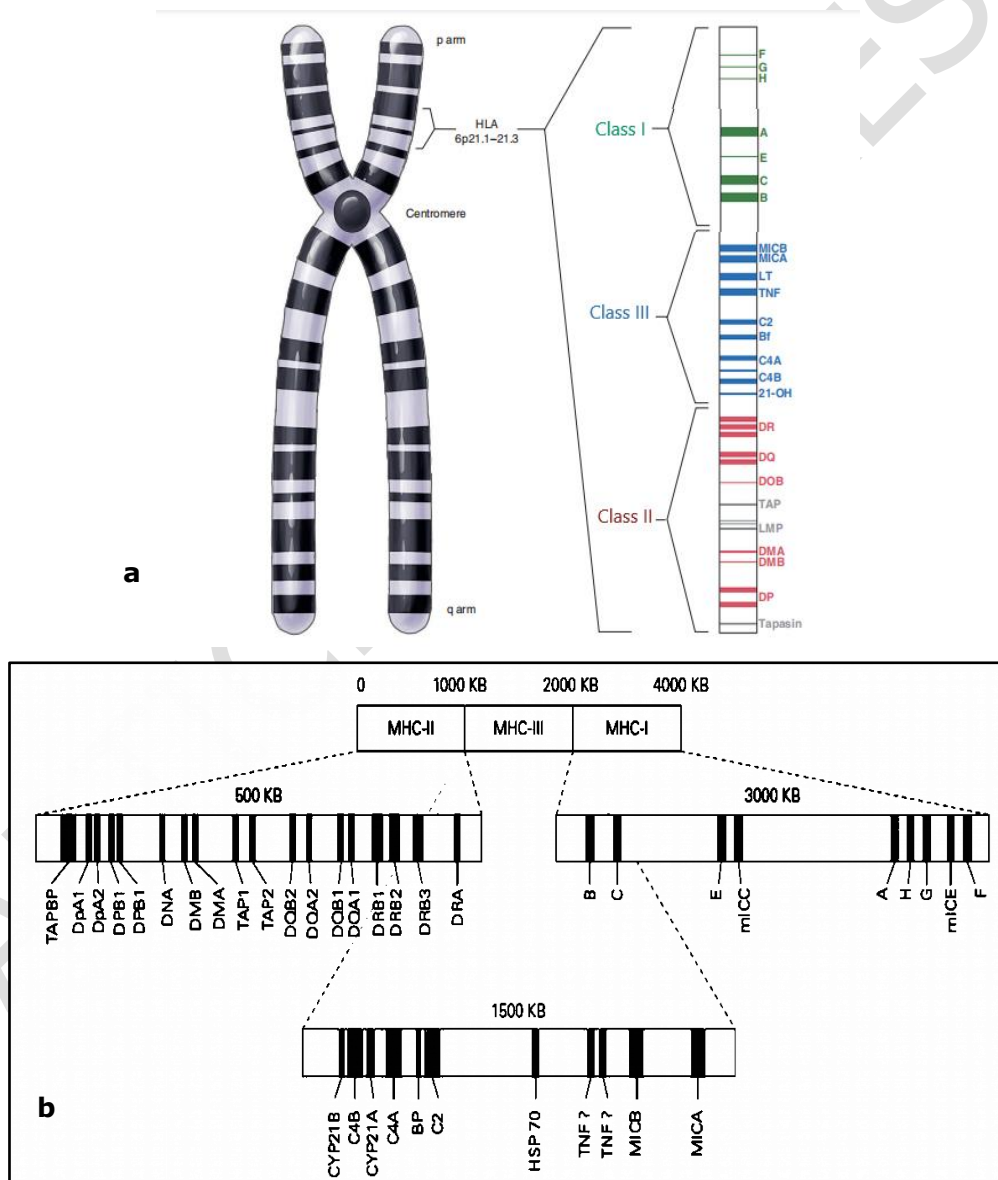

Fig 2: (**a**) is the major histocompatibility complex locus in a region on the short (p) arm) of human chromosome 6; and (**b**) is simplified genetic map of the MHC regions, showing organizational themes within the MHC locus

Structure of and factors affecting cellular expression of MHC molecule

There is an interwoven similar relationship in the structures of MHC class I and class II. In the MHC Class I, the binding platform is composed of two domains, originating from a single heavy α-chain (HC), while it originates from two chains (α-chain and β-chain) in the case of MHC class II (Fig. 3). The two domains evolved to form a slightly curved β-sheet, which creates a base and two α-helices at the top, which are wide apart and able to accommodate a peptide chain in-between. The MHC class I molecules are expressed on all nucleated cells, and their classical function is to display peptide fragments of endogenous antigens and present them to cytotoxic CD8^{+} T cells (6).

All MHC-I and MHC-II molecules can present peptides to T cells, but each protein binds a different range of peptides. Although MHC I molecules always function as ligands, reverse signaling was demonstrated two decades ago and plays important roles in cell apoptosis, activation or function. Cross-linking MHC I on T cells triggers Lck, Zap70, and PLCγ1 activation, which leads to T cell activation (7) or apoptosis. In contrast to MHC class II molecules, MHC I molecules have a longer intracellular tail with approximately 40 amino acids, including a tyrosine site (8)

The peptide-binding unit is supported by two membrane-proximal immunoglobulins (Ig), with one Ig domain found in each chain of the class II MHC while in class I MHC, the second Ig-type domain is provided as a result of the non-covalent association of the invariant light chain beta-2 microglobulin (β-2m) with the heavy α-chain. These domains in both MHC I (heavy α-chain) and MHC II (both chains) are anchored by the transmembrane helices (9).

To be stably expressed at the cell surface, the MHC class I molecule consists of trimer of a heavy chain, a light chain (β2 microglobulin), and an antigen peptide bound within the peptide-binding groove (6,9). The MHC class I molecule heavy chain consists of three subunits (α1, α2 and α3 subunits). The α1 subunit contains the heavy chain amino terminus and, combined with the α2 domain, creates the highly polymorphic MHC class I peptide binding groove. These α1 and α2 domains, along with majority of α3 domain, lie in the extracellular space. The α3 domain also contains the transmembrane segment and carboxy terminal portion of the class I heavy chain. The carboxy terminal tail lies within the cytoplasm of the cell. Unlike most other MHC class-I molecules, the carboxy tail of HLA-G is truncated and contains only six amino acids.

The MHC class II molecule is a dimer of two heavy chains, α and β. The α1 and β1 domains of the heavy chains combine to create the class II peptide-binding groove, while the α2 and β2 domains contain the transmembrane segments and the intracellular carboxy-terminal tails (9).
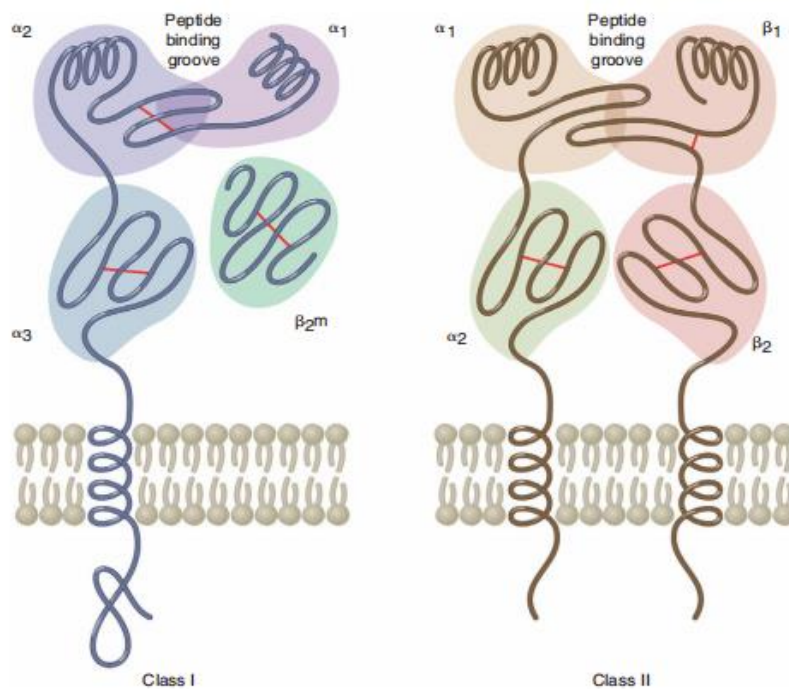

Fig 3: The structures of MHC Class I and Class II, showing the peptide bonding grooves and various helixes

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Antigen presentation by MHC class I and class II molecules

For the purpose of antigen-presentation, MHC Class I and II function specifically for distinct purposes; MHC Class I proteins present foreign peptides to cytotoxic (CD8^{+}) T cells, and MHC Class II proteins present foreign peptides to helper (CD4^{+}) T cells. In general terms, it could be said that the MHC class I and class II molecules are similar in function during antigen presentation in that, they both deliver short peptides to the cell surface allowing these peptides to be recognized by CD8^{+} (cytotoxic) and CD4^{+} (helper) T cells respectively. The difference is that the peptides originate from different sources-endogenous or intracellular for MHC class I and exogenous or extracellular for the MHC class II (10).

Cytotoxic T cells recognize foreign peptides in association with class I MHC proteins, whereas helper T cells recognize foreign peptides in association with class II MHC proteins. In both cases, the peptide-MHC complexes are recognized on the surface of an antigen-presenting cell (usually a dendritic cell) or a target cell (Fig 4).

1 A bacterium is engulfed by phagocytosis into a dendritic cell and is encased in a phagosome.

bacterial pathogen

2 Lysosomes fuse with the phagosome and digest the bacterium.

antigen

dendritic cell

MHC II

3 Immunodominant epitopes are associated with MHC II and presented on the cell surface.
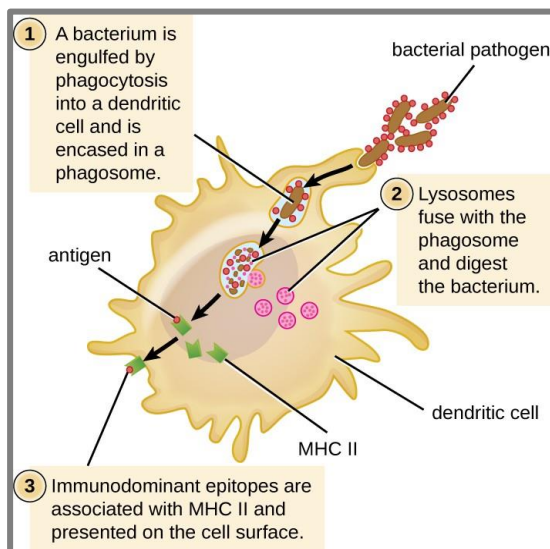
Fig. 4: A dendritic cell and MHC II identifies the most antigenic epitopes from a foreign antigen, select and present on the cell surface for T cells to be recognized and activated

A typical peptide binds in the groove of a class I MHC protein in an extended conformation with its terminal amino group bound to an invariant pocket at one end of the groove and its terminal carboxyl group bound to an invariant pocket at the other end of the groove. Other amino acids (called "anchor amino acids") in the peptide bind to "specificity pockets" in the groove formed by polymorphic portions of the MHC protein (11). The side chains of other amino acids of the peptide point outward, in a position to be recognized by receptors on cytotoxic T cells. Because the conserved pockets at the ends of the binding groove recognize features of the peptide backbone that are common to all peptides, each allelic form of a class I MHC protein can bind a large variety of peptides of diverse sequence. At the same time, the differing specificity pockets along the groove, which bind particular amino acid side chains of the peptide, ensure that each allelic form binds and present a distinct characteristic set of peptides. Thus, the six types of class I MHC proteins in an individual can present a broad range of foreign peptides to the cytotoxic T cells, but in each individual they do so in slightly different ways.

Class II MHC proteins have a three-dimensional structure that is very similar to that of class I proteins, but their antigen-binding groove does not narrow at the ends, therefore, it can accommodate longer peptides, which are usually 13–17 amino acids long (Fig 5). Moreover, the peptide is not bound at its ends. It is held in the groove by parts of its peptide backbone that bind to invariant pockets formed by conserved amino acids that line all class II MHC peptide-binding grooves, as well as by the side chains of anchor amino acids that bind to variable specificity pockets in the groove (12). A class II MHC binding groove can accommodate more heterogeneous set of peptides than can class I MHC groove. Thus, although an individual makes only a small number of class II proteins, each with its own unique peptide-binding groove, together these proteins can bind and present an enormous variety of foreign peptides to helper T cells, which have a crucial role in almost all adaptive immune responses.
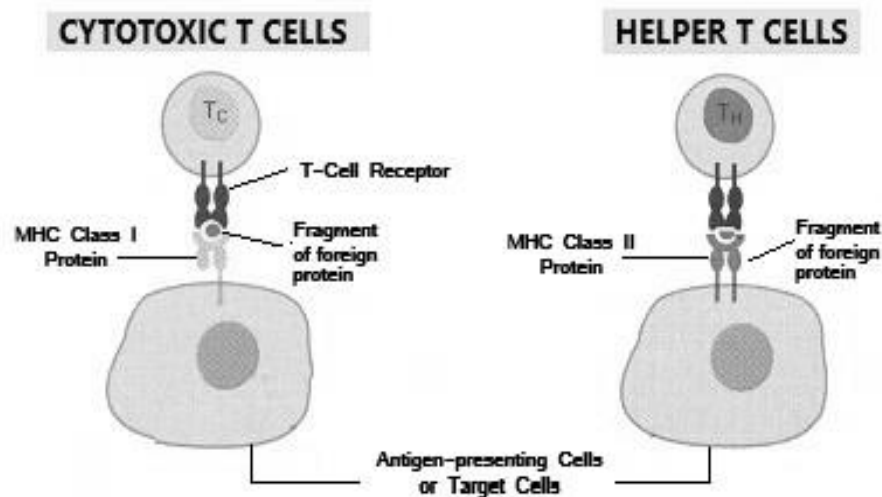
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Fig. 5: MHC I and II proteins presenting antigen of foreign peptides to T Cells for recognition

HLA association with infections

Human leucocyte antigen (HLA) alleles and single nucleotide polymorphisms (SNPs) are known to be associated with several infectious diseases and the type of response produced or initiated varies from individuals to individuals, those responses are determined by a lot of factors (13). SNPs in the HLA-B region are likely playing a role in viral suppression during herpes zoster infection, and three SNPs have been identified with infection in HLA-DRA.

MHC and viral infections

The immune system continuously protects its host against pathogens (14). Antigens are often categorized according to whether they are derived from endogenous pathogens (viruses, intracellular bacteria or protozoans) or from exogenous pathogens that replicate outside of the cell. The MHC molecules play a major role in age-related response to infections, as most of the diseases during aging have an immunological pathogenesis associated with the decline of T cell responses and increased propensity to autoimmune reactivity. Intracellular antigens are presented to T cells by any nucleated cell because MHC-I expression is ubiquitous. During viral infections, both innate and adaptive immune cells contribute to effective immune response. T-cells recognize foreign antigens in the form of short peptides that have been processed and displayed on the cell surface bound to MHC-I or MHC-II molecules. In contrast, exogenous antigens are taken up by professional APCs, which process the antigens and present them in the context of MHC-II molecules. An important function of a professional APC, e. g. dendritic cell (DC), is to deliver a second signal (co-stimulation) to

the T-cell to alert it to the presence of an infectious agents

The recognition of peptide-MHC class I (pMHC-I) complexes by CD8^{+} T cells plays an important role in mediating antiviral immunity (15). CD8^{+} T cells are essential effectors in antiviral immunity, recognizing short virus-derived peptides presented by MHC class I (pMHC-I) on the surface of infected cells. However, the fraction of viral pMHC-I on infected cells that are immunogenic has not been shown for any virus. There is paucity of studies on the associations of viral diseases with HLA alleles. Nevertheless, in the bid to develop safe and efficient virus vaccines, much work has been done on the mechanisms with which HLA molecules determine the immune response to viral peptides. Since antiviral cytotoxic T-lymphocytes (CTLs) are induced by viral peptides presented within the peptide binding grooves of HLA class I molecules on the surface of infected cells, the aim is to produce virus vaccines that would induce a cellular immune response that leads to the destruction of virus-infected cells by CD8^{+} CTLs.

The HLA also play an essential role in activation of both natural killer (NK) cells and T cells (13). Natural Killer cell activation is regulated by a variety of activating and inhibitory receptors, including killer-cell immunoglobulin-like receptors (KIRs). KIRs bind to HLA class I molecules, which are expressed on all nucleated cells. As HLA and KIR molecules are highly polymorphic, each individual expresses a unique set of these molecules. The wide range of combinations of HLA and KIR expression results in differences in binding strengths and variations in NK cell activation (16).

The association of HLA and KIR polymorphisms was demonstrated in the experimental simian immunodeficiency virus infec-

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tion in rhesus macaques, a model used to study human immunodeficiency virus (HIV) infection (17). Not only do these associations show which interactions contribute to disease resistance, they also pinpoint combinations that increase susceptibility to disease. Such associations of HLA and KIR with disease progression have also been found in hepatitis C virus (HCV) infection (18). In HCV infections, some HLA molecules (e. g. HLA-B27 and HLA-B57) are significantly associated with viral clearance. The force driving these NK cell expansions is largely unclear.

The importance of HLA class I molecule expression levels in host defense using data derived from transporter associated with antigen processing (TAP)-deficient individuals who express less than 10% of normal HLA class I molecules, demonstrate that self-HLA class I molecules shape the KIR repertoire of NKG2C⁺ NK cells, but are not a requirement for expansion (19). MHC I molecule promotes viral replication independent of suppressing type I IFN production. MHC I molecules are not only key to adaptive CD8⁺ T-cell responses, but are also involved in the fine-tuning of innate inflammatory cytokine production and antibacterial immunity (15,17,20).

i. HLA association with measles

Infection with measles virus is known to induce a strong T cell response (21), but information regarding the specific measles virus antigens that are responsible for activation of these cells is limited. Schellens et al., (22) investigated which measles peptides are presented by HLA class I molecules by eluting naturally presented peptides from virus-infected cells. They show that a broad spectrum of measles peptidome is presented by different HLA class I molecules.

ii. HLA association with Dengue fever

Heritable factors are likely to be significant in the clinical manifestation of DF such that even in areas of endemicity, only a minute percentage of individuals develop DF or the most severe types of the disease. In an infection caused by DF virus, arrays of genes are associated with an increased synthesis of IFN-γ, IL-8 and IL-10. Investigations on MHC-encoded transporters linked to antigen processing (TAP) genes have also demonstrated interaction with DHF. Furthermore, the study of tumor necrosis factor (TNF) and lymphotoxin alpha (LTA) genes have shown specific combinations of TNF, LTA, and HLA class I alleles which associate with DHF and synthesis of LTA and TNF (23).

iii. HLA association with HCV infection

Many studies have conducted analysis of HLA class I and class II in individuals with hepatitis C virus infection among diverse populations and there is a strong link that some alleles, majorly HLA class II, play a role in the control of HCV infection (24). The most reliable evidence-based data is likely to be related to *HLA-DRB1*11* associated with asymptomatic disease in people with HCV in Italy (*DRB1*11:04* allele) and has been associated with normal serum levels of alanine transaminase (ALT) in infected individuals in France (25). In another separate research in France, *HLA-DRB1*11* has been more commonly found in individuals without cirrhosis when juxtaposed with cirrhotic patients (26).

Across Europe, *HLA-DRB1*11* has been reported to be less common in those people who had received liver transplants for HCV-induced end-stage hepatic disease compared to healthy blood donors. Furthermore, *HLA-DRB1*11* is likely to be a good prognostic indicator, not only in helping spontaneous HCV clearance, but also to increase immunity against progression to more advanced and life-threatening stages of chronic HCV infection (27).

Another allele that has been associated with self-limiting HCV infection is *HLA-DQB1*03* which is found in linkage disequilibrium (LD) with *HLA-DRB1*11* and, standing alone or in partnership with *DRB1*11*, has been strongly linked with spontaneous HCV clearance and with prevention of further hepatic injury in chronically infected HCV patients (28). In multiple scientific studies, people with *HLA-DRB1*11:01* and *HLA-DQB1*03:01* had minimal predisposition to developing chronic HCV infection in 102% and 136%, respectively. *HLA-DQB1*03* is also likely to influence response to treatment as *HLA-DQB1*03:01* has been linked to sustained viral response (SVR) in infected patients treated with pegylated interferon-α and ribavirin (29). Also, in another study carried out among infected patients in Pakistan, a link between *HLA-DQB1*03* and good antiviral immune response in patients who were treated with interferon-α plus ribavirin was detected (30).

iv. HLA association with HBV infection

A meta-analysis showed that *HLA-DR*03* and *HLA-DR*07* were linked to a high risk of persistent HBV infection in 18 individual case-control studies which included 9 Han Chinese cohorts, 3 Korean cohorts, 2 Iranian cohorts, 1 cohort each of Caucasian, Gambian, Taiwanese, Thai, and Turkish subjects (31). Among the population of Han Chinese, *HLA-DR*01* was linked to clearance of HBV infection, however, in other ethnic groups, there was no link between *HLA-DR*01* and HBV infection (32). The haplotypes *HLA-DQA1*01:02 - DQB1*03:03* and *HLA-DQA1*03:01 - DQB1*06:01* were linked to persistent HBV infection, however, *HLA-*

DQA1*01:02 - DQB1*06:04 and *HLA-DQA1 *01:01 - DQB1*05:01* provided protection against HBV infection (32).

A genome-wide association study (GWAS) revealed a significant correlation of chronic hepatitis B in Asians with 11 SNPs in a region including *HLA-DPA1* and *HLA-DPB1* which subsequent analyses identified risk haplotypes; *HLA-DPA1*02:02 - DPB1*05:01* and *HLA-DPA1*02:02 - DPB1*03:01* and protective haplotypes; *HLA-DPA1*01:03 - DPB1 *04:02* and *HLA-DPA1*01:03 - DPB1*04:01* for HBV infection (33). Further analysis of *HLA-DQA1* and *HLA-DQB1* haplotypes showed that *HLA-DQA1*01:02-DQB1*03:03* and *HLA -DQA1*03:01-DQB1*06:01* were risk types for persistent HBV infection while the *HLA-DQA1 *01:02-DQB1*06:04* and *HLA-DQA1*01:01- DQB1*05:01* were protective haplotypes for HBV infection (33).

v. HLA association with HIV infection

Several of disease-protective and disease-susceptible HLA alleles have been well described in HIV infection and the greatest link is likely to be related to HLA class I alleles (majorly HLA-A and B alleles) with variable rates of HIV disease outcome (34). The virologic and immunologic outcomes in individuals with HIV infection can be highly different, with only a few infected individuals capable of controlling viral replication without institution of treatment (35).

Previous studies showed a relationship between *HLA-B*27* and *HLA-B*57* with slower progression and development to AIDS. Ever since, other studies have explored the importance of HLA class I and class II alleles in both acute and chronic HIV infection and the greatest link was identified to be related to HLA class I alleles (36). Related to the association of HLA class I alleles and protection against HIV infection, *HLA-B*44* and *HLA-B*57* have been identified as favorable factors in both the acute and chronic phases of sub-Saharan Africans who are seroconverts. In the Peoples Republic of China, *HLA-A*03* has been identified as a preventive factor against HIV-1 infection as well as disease progression (37). Also, in a study in the USA, *HLA-A*32, HLA-A*74, HLA-B*14, HLA-B*45, HLA-B*53,* and *HLA-B*57* have been associated with disease control in Americans of African descent who are infected by HIV-1 subtype B (38).

In a cohort study among a multi-ethnic population with HIV-1 controllers and progressors, it was reported that there are various alleles associated with virologic and immunologic control of the infection; *HLA-B*57:01, HLA-B*27:05, HLA-B*14/C*08:02, HLA-B*52,* and *HLA-A*25*. In addition, *HLA-B*13:02* and *HLA-B*58:01* have been identified as good prognostic indicators (39). In as much as all these alleles are likely to play a role in HIV infection, the most reliable information is linked to three HLA-B specificities; *HLA-B*57* (*HLA-B*57:01* in the European population, and *HLA-B*57:02* and *HLA-B*57: 03* mainly in the African population), *HLA-B* 27* (*HLA-B*27:05*), and *HLA-B*81* (*HLA-B*81 :01*) (39). These alleles are closely related with viral load control as well as delayed disease progression among the various populations. More so, the HLA-B molecules have a significant influence on HIV infection as the many of detectable HIV-specific CD8+T-cell responses identified is likely to be restricted by HLA-B alleles (40).

Concerning HIV susceptibility and the rapid disease progression, *HLA-B*35* (*HLA-B* 35:01, HLA-B*35:02* and *HLA-B*35:03*) is likely to have the highest effect on HIV disease. Individuals who have these alleles seem to have poorer control of viral replication and progress towards AIDS faster (41). Other alleles associated with poor prognosis have been identified and include; *HLA-B*18/*18 :01*, *HLA-B*45/*45:01*, *HLA-B*51:01*, *HLA-B*53:01*, *HLA-B*58:02*, *HLA-A*36:01*, and *HLA-B*07:02* in no specific order (41).

vi. HLA association with HPV infection

A few heritable predisposing factors to the development of cancer following HPV infection have been enumerated, and chief among them is the HLA complex, which performs a major role in susceptibility to cervical carcinoma. Since the first report of a correlation of *HLA-DQ3* with cervical carcinoma (42), a lot of studies of HLA correlation with cervical carcinoma have been peer reviewed and published with different results based on the ethnic group. One of such studies showed that *HLA-DRB1*04:07-DQB1 *03:02* as well as *HLA-DRB1*15:01-DQB1 *06:02* were closely linked to susceptibility to HPV-16 positive invasive carcinoma of the cervix, high squamous intraepithelial lesion (HSIL), as well as carcinoma in situ (43). In Honduran women it was determined that *HLA-DQA1*03:01* in linkage disequilibrium with all HLA-DR4 subtypes in Mestizos, has a greater risk of having high squamous intraepithelial lesion as well as cervical carcinoma (44).

A few *HLA-DR-DQ* haplotypes containing *DQB1*03:01* have been directly correlated with susceptibility to cervical carcinoma; *DRB1*11:01-DQB1*03:01* among Senegalese population and American whites. *HLA-DRB1*11:02-DQB1*03:01* was also commoner among Hispanics with carcinoma *in situ* or HSIL (44). Immunity has been closely associated with *HLA-DRB1*13* group; *HLA-DR B1*13:01* in individuals from Costa Rica, and *HLA-DRB1*13:01-DQB1*06:03-DQA1*01:03* among Swedish, French and Dutch adult

females with cervical carcinoma (44). A protective effect against the progression of malignancy of the cervix has also been correlated with *HLA-DQB1*05, HLA-DQA1*01:01/04, HLA-DRB1*01:01* and *HLA-DRB1*13:02* among Brazilians (44).

In the Caucasians, *HLA-DRB1*13* and HPV-16/18-negative status, have been independently associated with an increased probability of regression of low squamous intraepithelial lesion (LSIL), also indicating a protective effect against the progression of cervical carcinoma (44). Also, in individuals who have cervical carcinoma, the predisposing risks differed between HPV positive and negative cases for several alleles; a higher risk of cervical cancer was seen in patients with *HLA-DRB3(52)*02/03* and *HLA-DRB1*3 (17)-DRB1*3(17)* while a reduced risk was observed with *HLA-DRB1*09:012* and *HLA-DRB5 (51)*01/02* (44).

HLA and parasitic diseases

i. HLA association with Chagas disease

There is a common belief that during *Trypanosoma cruzi* infection, the host immune mechanism induces complex processes to enhance the control of parasite growth. The immune response is important for defense against the disease however, immunological disequilibrium can lead to heart and digestive tract lesions in infected individuals. The spectrum of clinical manifestation of Chagas disease highly suggests the influence of the genetic factors on the clinical progression of the disease, and the variations of genes involved in both the innate as well as the specific immune response is being extensively researched, like the molecules and genes in the region of the HLA (45).

Both the polymorphic HLA classes I (A, B and C) and II (DR, DQ and DP) molecules influence the efficiency of presentation of the *T. cruzi* epitopes to CD8$^+$ and CD4$^+$ T-cells respectively. The type of the presentation is likely to affect the clinical course of diseases because infected individuals are likely to respond in different ways to the same antigen, depending on their HLA repertoire. Many HLA alleles and haplotypes are known to be associated with Chagas disease (46).

Concerning the link between HLA and Chagas disease, *HLA-Dw22* was first linked to the risk of developing the disease in infected people in Venezuela. Another study further compared class II allele frequencies between patients and controls and this study found a reduced frequency of *HLA-DRB1*14* and *HLA-DQB1*03:03* in infected individuals, indicating protective effects not associated with persistent infection in this population (47).

In southeastern Brazil, a study demonstrated that *HLA-A*30* confers risk of contracting Chagas disease, while the *HLA-DQB1 *06* confers immunity notwithstanding the clinical stage of the disease. Also, HLA-DR2 antigens were associated with increased risk of contracting persistent Chagas disease in a South Brazilian population (48). HLA-DR4 and HLA-B39 were linked to the disease in Mexico and *HLA-DRB1*04:09* and *HLA-DRB1 *15:03* in a population in Argentina (48). Another study showed that *DRB1*11:03* allele was associated with immunity against Chagas disease. *HLA-DRB1*14-DQB1*03:01* haplotypes were associated with immunity against *T. cruzi* infection in the rural population in southern part of Peru (49). *HLA-DR B1*01-B*14-MICA*011* haplotypes have been linked to immunity against persistent Chagas disease in Bolivia (50).

ii. HLA association with malaria

A strong link between the HLA class I (*HLA-B53*) and immunity against life threatening forms of malaria has been clearly elucidated, and said to be regulated by HLA class I restricted CTLs during the hepatic stage of the parasite's life cycle (50). Certain genes on the HLA complex possibly protect individuals in endemic regions against the serious forms which are caused by both *Plasmodium falciparum* and *Plasmodium vivax* (13).

The antibody mediated immune response that occurs in malaria infections is of special interest, because the production of specific IgG antibodies is mandatory for acquired immunity. However, variations in antibody responses could result from multiple genetic types of the HLA class II molecules. With more concentration on the production of subunit vaccines, studies of the role of class II alleles in the immune defense response in ethnically different populations is critical, before the implementation of vaccine trials.

It has been demonstrated that the *HLA-DRB1*04* alleles were linked to an increased frequency of humoral responses to five out of the nine recombinant proteins tested in Brazil, Nigeria and Ghana (51,52). In Mumbai, India, a study showed that *HLA-B49* and *HLA-DRB1*08:09* were directly associated with complicated severe malaria (53). Contrastingly, *HLA-A19*, *HLA-B5* and *HLA-B13* provided protection against malaria in infected individuals with high parasite index (>2%). The results from this study indicate the significance of ethnicity, which should be considered when producing ideal malaria vaccine (53).

Conclusion:

This review shows that there is a cor-

relation of HLA-DQ haplotypes with cervical carcinoma and primary liver cell cancer. It could therefore be postulated that genetic modification of HLA genes associated with increased susceptibility to infections by HPV and HBV could be useful in preventing the development of cancers resulting from such infections. Such haplotypes include, but not limited to *HLA-DRB1*04:07 - DQB1*03:02, HLA-DRB1*15:01 - DQB1*06:02* and *HLA-DQ B1*03:01,* which have been directly correlated with susceptibility to cervical carcinoma. Haplotypes *HLA-DQA1*01:02 - DQB1* 03:03* and *HLA-DQA1*03:01 - DQB1*06:01* were also linked to persistent HBV infection and primary liver cell carcinoma. In addition, a strong link has been described between HLA class I (*HLA-B53*) and immunity against life threatening forms of malaria. The gene products of *HLA-B53* should be considered for use in immunomodulation to prevent severe forms of malaria such as cerebral malaria and nephrotic syndrome among children in malaria endemic zones.

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