

# Genetic Factors that Influence HIV Infection: The Role of the Major Histocompatibility Complex System

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## 1. Introduction

The HIV epidemic continues to be a major world-wide health and human problem as reflected in the AIDS epidemic updates from the World Health Organization (WHO). Highly active antiretroviral therapy (HAART) has improved health management, especially in developed countries, since it was first introduced in the mid-1990s. However, access to antiretroviral therapy in developing countries has been limited. Developing an effective vaccine is an on-going mission, the success of which depends on understanding key aspects of the immune response to HIV. Hence, studying the genetic components of the immune response to the HIV virus is essential.

The existence of genetic factors that modulate immune response to infectious diseases was described more than 10 years ago (Hill, 1998). We recommend various recent and extensive reviews that have focused on the immunobiology of HIV infection (Tripathi and Agrawal, 2007), the immune response to HIV (Chakrabarti and Simon, 2010; Miyazawa, et al. 2008) and specifically the innate response (Borrow and Bhardwaj 2008). Innate and adaptive immune responses play a decisive role during the initial stages of HIV infection and will also affect the progression of the disease. Definitive evidence that host genetics plays a role in the immune response to HIV is the fact that HIV-1 infection does not always progress to AIDS. A small percentage (less than 0.2%) of HIV-1 sero-positive patients is able to control the infection, meaning that they can maintain a viral load of fewer than 50 copies of HIV-1 RNA per ml over 10 years. These patients have been given different names: HIV controllers, HIV elite controllers, long-term non-progressors (LTNPs) or natural virus suppressors (Chakrabarti and Simon, 2010).

This chapter focuses on the influence exerted on HIV infection by the human major histocompatibility complex (MHC) system, also known as the human leukocyte antigen (HLA) system. The effect of the MHC system on HIV infection is crucial for development of an effective vaccine. We recommend several reviews on this subject that complement the present monograph (Carrington and O'Brien, 2003; Stephens, 2005; Miyazawa et al. 2008; Kaur and Mehra, 2009; Singh and Spector, 2009). In this chapter, we will first describe the most important and relevant characteristics of the MHC, then we will review the recent

literature on the influence of the MHC on both horizontal and vertical (mother-to-infant) transmission. Finally, we highlight the molecular basis of the most important associations currently believed to exist between MHC and HIV transmission, with special emphasis on recent theories about how the MHC shapes the cytotoxic T cell (CTL) response and its relation to the appearance of HIV escape variants.

## 2. The human Major Histocompatibility Complex (MHC)

The MHC is located on the short arm of chromosome 6 and contains a large number of genes related to immune system function. Some MHC genes encode proteins that help to distinguish self and non-self components. They were first discovered in transplantation immunology and the gene products were called *antigens*. There are 3 major classes: Class I molecules are encoded by classical genes (A-C) and non-classical genes (E-G). Class II molecules are encoded by classical genes (DP, DQ, DR) and non-classical ones (DM, DOA, DOB). Class III molecules include components of the complement system and other immune system molecules.

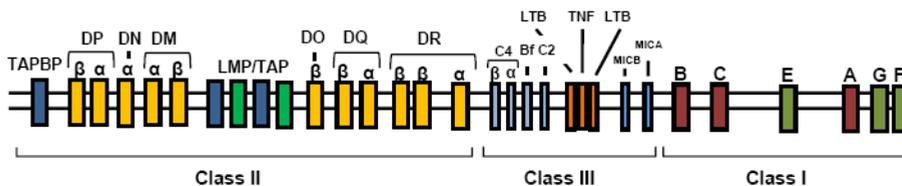


Fig. 1. Schematic of the Human Major Histocompatibility Complex (MHC).

### 2.1 The human MHC class I molecules

The class I protein comprises a  $\alpha$ -polypeptide chain that associates with the invariant  $\beta$  chain  $\beta$ 2 microglobulin ( $\beta$ 2m). MHC class I molecules (A, B, C) present peptides mainly from inside the cell; for example, they present viral peptides when these are found in the cell cytoplasm. These peptides are produced by the proteasome, which breaks down proteins to fragments approximately 9 amino acids (AA) long. Viral, bacterial or self-peptides will be displayed in the binding cleft of the MHC molecule on the cell surface, in a process known as antigen presentation; the displayed fragments are recognized by  $CD8^+$  or cytotoxic T cells (CTLs), which destroy infected cells. Each person expresses 3 MHC class I molecules (A, B, C) from each chromosome. Most nucleated cells express class I molecules. Many viruses reduce the expression of MHC class I molecules to hamper the immune response. This is the case of HIV, which down-regulates CD4 and HLA class I expression through its Nef protein (Greenberg et al., 1998). Compared to the HLA-A and -B loci, the HLA-C locus shows less polymorphism. In addition HLA-C proteins are expressed at lower levels on the cell surface, and seem to bind primarily to natural killer immunoglobulin-like receptors (KIRs).

Class Ia molecules show greater polymorphism and wider tissue distribution than class Ib molecules. Of the non-classical HLA class I molecules involved in HIV infection, HLA-G is the best studied. Alternative splicing of HLA-G gives rise to 7 isoforms, 4 membrane-bound (HLA-G 1-4) and 3 soluble (HLA-G 5-7). G5 and its membrane-bound counterpart G1 are proteolytically released from the membrane to give rise to the major soluble forms of HLA-

G. HLA-G is expressed in placental trophoblast cells as well as in the thymus, pancreas and other tissues. Its ectopic expression has been reported under various pathological conditions, including viral infections. It is currently accepted that HLA-G molecules exert immunosuppressive functions (Fainardi et al., 2011).

## 2.2 The human MHC class II molecules

These are encoded by three classical genes (HLA-DP, -DQ and -DR) and two non-classical ones (HLA-DM and -DO) (reviewed by (Handunneththi et al., 2010)). This region includes other genes implicated in antigen processing, such as the genes encoding transporter associated with antigen processing protein 1 and 2 (TAP1 and TAP2). Class II molecules comprise  $\alpha$  and  $\beta$  chains. Their expression is restricted mainly to thymic epithelial cells and bone marrow-derived antigen-presenting cells. The latter include B cells, macrophages (M $\phi$ ) and dendritic cells (DCs). Differentiation of B cells into plasma cells, as well as differentiation of dendritic cells, is accompanied by down-regulation of MHC class II expression. On the contrary activation of T cells up-regulates their expression of class II molecules.

In the HLA-DR sub-region the gene DRA encodes 1 unpolymorphic  $\alpha$  chain with only 1 common and 2 very rare alleles. The  $\beta$  chain is encoded by the very polymorphic DRB1 gene. There are 3 DRB1 paralogue genes: DRB3, DRB4 and DRB5, however DRB1 is expressed at a level five times higher than them. The MHC class II is highly polymorphic. For instance, there are over 500 different HLA DRB1 alleles in humans. The DRB loci are classified into 5 major haplogroups according to the number of functional genes (DRB1, 3, 4 and 5) and pseudogenes (DRB2, 6, 7, 8, 9) that are present (Table I).

Halogroup	Genes and Pseudogenes
DR1	DRB1, DRB6 and DRB9
DR8	DRB1 and DRB9
DR51	DRB1, DRB5, DRB6 and DRB9
DR52	DRB1, DRB2, DRB3 and DRB9
DR53	DRB1M DRB4M DRB7, DRB8 and DRB9
Families of DRB1 allelic lineage	Genes
DR1	HLA-DRB1*01 and *10
DR8	HLA-DRB1*08
DR51	HLA-DRB1*15 and *16
DR52	HLA-DRB1*03, *11, *13 and *14
DR53	HLA-DRB1*04, *07 and *09

Table 1. DRB loci classification in halogroups and DRB1 families.

Classical class II MHC genes are:

**HLA-DP:**  $\alpha$ -chain encoded by the HLA-DPA1 locus (16 alleles) and  $\beta$ -chain encoded by the HLA-DPB1 locus (118 alleles).

**HLA-DQ:**  $\alpha$ -chain encoded by the HLA-DQA1 locus (25 alleles) and  $\beta$ -chain encoded by the HLA-DQB1 locus (72 alleles).

**HLA-DR:**  $\alpha$ -chain encoded by the HLA-DRA locus and 4  $\beta$ -chains encoded by the HLA-DRB1, DRB3, DRB4, DRB5 loci.

The expression of MHC class II genes is tightly regulated, primarily at the transcriptional level. Their promoter contains regulatory elements collectively called the “SXY module”, to which various proteins bind, including regulatory factor X (RFX) and the class II transactivator (CIITA) (Handunnetthi et al., 2010). Induction of CIITA and subsequent expression of the MHC class II isotype HLA-DR are hallmarks of CD4<sup>+</sup> T cell activation which, paradoxically, favors HIV replication. Interestingly, CIITA is able to inhibit HIV-1 in infected cells by blocking the function of the viral transactivators Tat and Tax (Tosi et al., 2009).

A key question about the influence of MHC on infectious disease is whether allele-specific sequence variation that affects the level of expression of HLA proteins can lead to class II-associated diseases. For instance, transcripts in resting peripheral B cells have been reported to be more abundant within the DR52 haplogroup than within the DR53 haplogroup. A vast number of self-antigens are expressed at high levels in the thymic epithelium. It is postulated that a general reduction of self-antigen expression in the thymus could result in loss of central tolerance, meaning that thymocytes with excessive reactivity to self-antigens escape elimination. Does this increase susceptibility to infectious diseases? In the case of HIV, it seems that MHC-II presentation, at least by monocytes/macrophages, is preserved during infection (Woc-Colburn et al., 2010).

Aside from the genes encoding the major antigens, a large number of other genes are located in the HLA complex (Fig. 1), many of which are involved in immune function. One significant characteristic of the HLA system is its tremendous polymorphism in the human population: there are many different alleles for each locus (ImmunoGeneTics HLA database: <http://www.ebi.ac.uk./imgt/hal/atats.html>). This implies that the chance of two unrelated individuals having identical HLA molecules on all loci is very low.

### 3. Historical perspective: HLA-disease association studies and HIV infection

The first reviews of HLA association with disease are from the late 1970s (Thomson and Bodmer, 1979) and early 1980s (Svejgaard et al., 1983), followed by other studies on HLA susceptibility to HIV infection (Scorza Smeraldi et al., 1986; Just, 1995; Fauci, 1996; Buchacz et al. 1998).

HLA genes exhibit “**linkage disequilibrium**”, meaning that they are found together on the same chromosome at a higher frequency than expected according to their recombination distance. They are defined as a so-called “extended haplotype” or combination of alleles that are transmitted together as a unit. As with any gene frequently found in linkage disequilibrium with others, it is difficult to identify the specific HLA gene that is responsible for a given association observed in a population (Svejgaard et al., 1983).

Studies of HLA associations with infectious diseases must separate HLA effects from many **confounding factors**, which are other factors that independently affect the risk of developing the disease. If the prevalence of these other factors differs between the groups being compared, they will distort the observed association. In the case of HLA/HIV associations, confounding factors include the ethnicity of the population studied, the frequencies of the HLA alleles detected and the resolution of the typing methods used. HLA associations are considered to be “consistent” when a similar or equivalent association is observed across different ethnic groups (Tripathi and Agrawal, 2007).

### 3.1 HIV associations and ancestral haplotypes

Initial association analyses focused on **ancestral haplotypes**. An increased frequency of C4 null alleles was found in HIV-infected individuals, which could in fact reflect an indirect association with a discrete number of ancestral haplotypes (Cameron et al., 1990). At that time a series of studies focused on the A1-B8-DR3-DQ2 haplotype, also known as the 8.1 ancestral haplotype, which has been implicated in disease susceptibility (McNeil et al., 1996; Price et al., 1999). In addition, the HLA-B27 allele was found to be related to slow HIV disease progression (McNeil et al., 1996). Closer analysis of ancestral haplotypes points to a direct role of HLA-B35 in rapid HIV progression, and this allele is thought to be associated with disease susceptibility (Flores-Villanueva et al., 2003).

### 3.2 HIV infection and HLA frequencies of individual alleles

The proliferation of studies on associations between HLA frequencies and HIV infection made it clear to experts that it would be necessary to establish uniform research standards, such as more concrete definitions of HIV disease and its progression (Mann et al., 1992). Focusing on particular aspects of the disease, researchers were able to study a cohort of 106 homosexual men from Amsterdam and correlate certain alleles with different aspects of HIV pathogenesis, including skin rash (HLA-B62), rapid decline of CD4+ T lymphocytes to < 200/microL (HLA-B35), AIDS-related Kaposi's sarcoma (HLA-DR1) and opportunistic infections (HLA-DR3 and DQ2) (Klein et al., 1994). HLA disease associations studies were performed in different populations, such as in India (Shankarkumar, 2004), south India (Selvaraj et al., 2006) and southern Africa (Lombard et al., 2006).

An important milestone in demonstrating that HIV-1 disease progression is associated with MHC genes was the discovery of **HLA concordance** between hemophilic siblings: pairs that shared one or two haplotypes were significantly concordant in CD4+ T cell decline and AIDS status within 5 years of seroconversion, while no concordance was found in pairs sharing no haplotypes. This is strong evidence that HLA is a determining factor or at least a relevant marker of disease progression.

The expression level of HLA-G during HIV infection was found to be higher in monocytes from patients under HAART than from untreated individuals. Similarly, T cells from infected individuals express HLA-G. Different HLA-G alleles have been associated with protection (G-0105N9) and susceptibility (G-010108) (Fainardi et al. 2011).

Viral load is an important factor determining the progression of HIV-1 infection. The initial peak of infection is followed by a period when the level remains relatively stable; the level during this period is called the "**viral load set point**" (VLS). A recent study addressed the influence of genetic factors, including HLA genotype, on the VLS (Saathoff et al., 2010). The study population was from Tanzania and was composed of three groups: female bar workers and females and males from the general population. HLA alleles were classified as protective (A\*0205, B\*5801, B\*8101, B\*4201, B\*5703), harmful (B\*5802, B\*4501, B\*1801 and B\*1503) or neutral (all others). The prevalence of elevated viral load was 40% lower among individuals with protective alleles than among those with neutral ones. The major conclusion from this study is that male gender and possessing harmful HLA alleles are associated with higher VLS.

HLA class II molecules are involved in presenting antigens to CD4+ T cells, which are central for establishing helper T responses. The HLA class II allele DRB1\*1303 was associated with low plasma viral load in a cohort of 426 black South African females infected

with HIV-1 clade C. This association was confirmed in a larger cohort of 1436 male European Americans infected with HIV-1 clade B, demonstrating that the association was independent of ethnicity and viral subtype. Whether the protective effect exerted by this allele is due to the development of CD4+ T cell responses has yet to be shown (Julg et al., 2010).

### 3.3 Advantage of heterozygous individuals

Heterozygosity of MHC genes has long been thought to confer an advantage in the battle against infectious agents, and possessing different alleles at class I and II loci should therefore represent a benefit for HIV-infected individuals. Carrington et al. (Carrington et al., 1999) corroborated this key immune system dogma by studying HIV infection. They found that maximum heterozygosity of HLA-A, -B, and -C genes delayed progression to AIDS, while individuals who were homozygous at one or more loci progressed rapidly to AIDS. Furthermore, they were able to conclude that B\*35 and Cw\*04 were consistently associated with rapid development of AIDS in Caucasians. This work led to the proposal of a "heterozygote advantage and B\*35-Cw\*04 disadvantage theory" (Carrington et al., 1999). In subsequent work, the researchers studied the role of TAP genes and HLA supertypes in resistance to HIV infection. They found that the B\*35 Px alleles were a risk factor, while the presence of alanine at position 665 in TAP2 was associated with resistance. Whether this resistance was due to a higher efficiency in transporting peptides, or was a consequence of linkage disequilibrium, was not resolved (Liu et al., 2003). Further studies have sought to consolidate our understanding of HLA-B35 alleles as risk factors, and have extended the findings in Caucasians to other populations (Shankarkumar et al., 2003).

### 3.4 HLA supertypes

Several studies have focused on the analysis of HLA supertypes (Sidney et al., 2008), in which HLA alleles are functionally classified according to their peptide-binding specificities (MacDonald et al., 2001). An attempt was made to group different HLA-B antigens (identified in patients by serology) according to their peptide-anchoring pockets, in order to determine whether the abovementioned associations could be explained by differences in the peptide repertoire presented by those molecules (Itescu et al., 1995). Later on, it was proposed that HIV adapts to the most frequent alleles in the population, implying that the expression of rare supertypes confers an advantage (Trachtenberg et al., 2003).

### 3.5 Modern theories

A recent study that, in our opinion, is an important breakthrough in the field, proposed that it is not the contribution of only one "relevant" allele that governs disease susceptibility but rather the sum of small contributions from several alleles (Leslie et al., 2010). The authors of that study justified their reasoning based on the fact that after excluding subjects expressing any of the important HLA-B class I alleles that strongly affect HIV control (B\*57, B\*58, and B\*18), HLA-B alleles continued to play the dominant role in the observed progression (Leslie et al., 2010). If true, this idea would help reconcile some of the disparities reported in the literature.

## 4. Vertical (mother-to-child) transmission of HIV-1

Perinatal HIV-1 infection constitutes a significant global health problem and prevention of transmission is a high public health priority (Matt and Roger, 2001; Ahmad, 2010; UNAIDS,

2010). Much progress has been made in the development and implementation of strategies designed to interrupt vertical transmission. Antiretroviral therapy in HIV-infected pregnant women has significantly reduced the rate of mother-to-child transmission in developed countries down to 1% (Coovadia, 2004). In developing countries, however, many women still have limited access to antiretrovirals, and HIV-1 infection in children remains a major concern, with approximately 500,000 new HIV-1 infected infants born every year worldwide (Ahmad, 2010; UNAIDS, 2010). Prevention of maternal-fetal transmission of HIV-1 is therefore a global priority, especially in developing countries.

Several lines of evidence suggest that host genetic factors are important determinants of both susceptibility to vertical transmission of HIV-1 and subsequent progression of AIDS in children (Matt and Roger, 2001). The identification of genetic markers linked with transmission and disease progression can help to define risk factors associated with vertical transmission and provide new insights into HIV-1 pathogenesis that can help in the development of an effective HIV-1 vaccine.

In addition, pediatric HIV infection offers a good opportunity to investigate the influence of host genetics on the evolution of HIV, since the virus has first been in contact with the mother's immune system and is then transmitted to a genetically related individual.

In children with perinatally acquired HIV-1 infection, the expression of clinical and immunologic signs of disease seems to follow a bimodal distribution. At the beginning of the original HIV epidemic in the 1980s and 1990s, approximately 15–20% of infected infants showed an early and severe course of disease and died within the first 2 years of life. The remaining children progressed more slowly and had a less severe course, surviving an average of 8 years or more (Blanche et al., 1994). Today, children perinatally infected with HIV-1 reach adolescence, largely because of advances in treatment over the past 10 years (Dollfus et al., 2010).

#### 4.1 Routes of vertical HIV transmission

HIV-1 vertical transmission occurs mainly during the following stages (Ahmad, 2010):

1. *prepartum*, due to transplacental passage in utero,
2. *intrapartum*, due to exposure of infant skin and mucus membranes to maternal blood and vaginal secretions during delivery, and
3. *postpartum*, due to exposure to contaminated breastmilk during nursing

In the absence of prophylactic treatment, it is estimated that one-third of children are infected *in utero* (*prepartum*) and two-thirds are infected *intrapartum* or *postpartum* (Kuhn et al., 1997). Various factors appear to affect vertical transmission throughout the gestation period and it seems probable that an interplay of all factors occurs, with some factors more determinant than others during specific periods. For instance, factors protecting against *in utero* infection may be less efficient against delivery or breast-feeding transmission. A general and global strategy concerning all known factors must be used to prevent vertical transmission (Bongertz, 2001). A greater understanding of the role played by various risk factors for HIV-1 infection is crucial to designing new preventive and therapeutic strategies. The risk of *prepartum* transmission depends on exposure of the fetus *in utero* to free virus or to HIV-infected maternal cells (Mittleman and Shearer, 1996), the risk of which is likely to be very high (Matt and Roger, 2001). Relatively few maternal cells are thought to enter the fetal circulation during gestation under normal circumstances. However, HIV-1 is known to infect cells within the placenta (Kesson et al., 1993). Intrauterine infection has therefore been suggested as a risk factor for mother-to-child transmission (Kuhn et al., 1999).

Certain conditions of delivery such as premature birth, low birth weight, early placental rupture or placental membrane inflammation seem to be related to increased risk of vertical transmission (Bongertz, 2001). Cesarean delivery is associated with a significant decrease in perinatal HIV transmission, from 55% to 80% (Welles et al., 2000). This result is likely to hold only for women with a sufficiently high viral load, since the transmission rate for women with undetectable viral loads is already low.

To avoid *postpartum* transmission, breastfeeding by HIV-infected women is not recommended because it is associated with an additional 15-20% risk of transmission of HIV-1 (Nduati et al., 2000).

In conclusion, it is now clear that the risk for vertical transmission and subsequent immune suppression depends on multiple factors in both the virus and the host (Singh and Spector, 2009). Several factors have been proposed to influence the risk of mother-to-child transmission and disease progression in children infected with HIV. These include high maternal viral load at birth (Shearer et al., 1997) and viral phenotype (De Rossi et al., 1997).

#### **4.2 Maternal viral load and vertical HIV transmission**

Higher maternal virus load is associated with an increase in the vertical HIV transmission rate (Cao et al., 1997; Rogers and Shaffer, 1999), although the correlation is modest. Treating HIV-infected pregnant women with the antiretroviral drug zidovudine was associated with a reduced rate of transmission (Connor et al., 1994), though the drug may not produce this effect by reducing viral load: a recent study found that zidovudine reduced vertical transmission despite a minimal effect on viral load (Melvin et al., 1997; Newberry and Kelsey, 2003). Whatever the mechanism of zidovudine, it remains generally true that risk of vertical transmission can be minimized if therapies known to reduce the patient's serum and vaginal viral loads are continued during pregnancy. Indeed, even if the risk of mother-to-child transmission is very low in women with low viral load, vertical transmission has been reported in women with all viral load levels (Newberry and Kelsey, 2003).

#### **4.3 Viral phenotype and vertical HIV transmission**

Viral phenotype is also a risk factor for vertical transmission. Genetic variability within HIV-1 is generated by reverse transcriptase during replication of the viral genome. The enzyme lacks 3' proofreading ability. Consequently, rapid replication result in a high degree of virus polymorphism (Wei et al., 1995). This variability among virus phenotypes may allow the appearance of viral escape forms, so-called because they can escape the immune response (Pillay and Phillips, 2005), as well as allow the emergence of viral strains resistant to antiretroviral therapy (Biggar et al., 2002). Both of these viral forms may then be transmitted to the child. Viral phenotype is also a risk factor independent of reverse transcriptase: the frequency of appearance of resistance mutations depends on the HIV subtype (A, C and D) (Kantor et al., 2002).

#### **4.4 Cytotoxic T lymphocytes (CTLs) and vertical HIV transmission**

Various components of the immune system affect viral replication and therefore may participate in vertical transmission. Induction of suppressor and **cytotoxic T lymphocytes (CTLs)** and **neutralizing antibodies (NABs)** are considered fundamental for a protective immune response against HIV (see Section 6) and have also been implicated in protection against vertical transmission (Bongertz, 2001).

Class I-restricted CTLs exert significant immune pressure on HIV-1 and may be an important factor in mother-to-child transmission (Pillay and Phillips, 2005). Recognition of peptide-MHC complexes by CTL receptor triggers a response that ends in the recognition and lysis of HIV-infected cells by CTLs, which blocks the propagation of HIV-1. There is an inverse correlation between plasma RNA viral load and levels of HIV-specific CTLs in patients infected by HIV-1 (Ogg et al., 1998). CTLs detect viral antigens that have been processed intracellularly. Peptides are cleaved and presented on the cell surface by MHC I molecules. Recognition of the peptide-MHC complex triggers a response that results in lysis of the infected cell. HIV-1-specific CTLs seem to contribute to the control of HIV-1, as do certain HLA class I alleles that encode the MHC molecules required for the presentation of these peptide fragments to CTLs. In particular, HLA-B27 and HLA-B57 are predicted to be involved in the control of both HIV infection and AIDS progression, while HLA-B35 is associated with rapid disease progression (Kaslow et al., 1996; Carrington et al., 1999).

The impact of CTL responses on vertical transmission in HIV-infected pregnant women has been investigated since the 1990s (Matt and Roger, 2001). CTL activity in the maternal peripheral circulation is similar to that in the non-pregnant state and CTLs can appear early in infants, where their presence correlates with slow progressive HIV disease (Pillay and Phillips, 2005). Consequently, an indirect role for CTLs in mother-to-child transmission has been proposed (Polycarpou et al., 2002). Moreover, levels of CTL precursor frequencies specific for *pol* and *nef* HIV variants were more frequently found during pregnancy in non-transmitting mothers than in transmitting ones (Jin et al., 1998). Because *nef* is transcribed early during the replication of HIV, a strong *nef*-specific CTL response may be important for the clearance of HIV soon after viral protein expression, thereby limiting further viral transmission. Interestingly, a *nef*-specific CTL response has also been observed in uninfected children born to HIV-positive women (De Maria et al., 1994). Importantly, CD4<sup>+</sup> T cells are critical in maintaining CTL activity against HIV-1 (Kalams and Walker, 1998), and their importance in vertical transmission has also been demonstrated (Plaeger et al., 1999).

Although it induces the CTL response, the virus cannot always be completely controlled. This is often due to mutations in viral peptides that allow virus to **escape CTL recognition via MHC class I molecules** (Pillay and Phillips, 2005). Vertical transmission of HIV-1 may imply that the transmitted virus is a CTL escape form; such forms have indeed been detected in infants (Pillay and Phillips, 2005). Mothers share at least 50% of their HLA alleles with their children but children may still respond differently than their mothers, depending on their HLA and their concordance with the mother's alleles. For example, if the mother and the child share the protective HLA-B27, transmission of virus to the child will be effective: since the virus is adapted to escape B27 recognition, the allele will not confer protection from HIV-1 on the child (Goulder et al., 2001). In contrast, if the child inherits the HLA B27 allele from the father, the child will be able to generate a strong response to viral epitopes. The viral escape mutation can be maintained in the HIV-1 population if it does not imply a fitness cost; if it does, the mutation will revert in the absence of immune pressure (see Section 6) (Allen et al., 2004).

#### **4.5 Neutralizing antibodies (NABs) and vertical HIV transmission**

Although the CTL response is an important mediator of protective immunity and has been implicated in controlling virus load, the maternal CTL response is insufficient to determine the fate of HIV vertical transmission (Matt and Roger, 2001). Several other factors are

important, including the ability of the mother to generate antibodies, particularly neutralizing antibodies (NAbs) that are able to block viral replication. In individuals infected with HIV-1, high levels of antibodies against the envelope viral proteins gp120 and gp41 are synthesized (Fig. 2). However, these antibodies do not seem to be very effective against HIV since they are not able to neutralize it *in vitro*. This is probably due to the high degree of glycosylation of these proteins (Reitter et al., 1998; Wyatt et al., 1998; Rudd et al., 2001). Nevertheless, there are other Nabs that can be generated rapidly in primary HIV infection (Richman et al., 2003). NABs are thought to protect against vertical transmission, since they can pass through the placental barrier, they have been detected in mother's milk, and they are believed to be present during delivery (Bongertz, 2001). In general the presence of high amounts of NABs is correlated with chronic, non-progressive disease (Pillay and Phillips, 2005).

High levels of NABs are detected during pregnancy. Nevertheless, whether maternal NABs and maternal humoral immunity in general play a role in vertical HIV transmission remains controversial. Several early reports indicated an association between maternal NABs and protection against vertical transmission (Rossi et al., 1989; Devash et al., 1990; Louisirirochanakul et al., 1999), but these observations were not confirmed (Bal et al., 1996; Hengel et al., 1998). Since selection for escape HIV-1 variants occurs during transmission, it is possible that non-neutralized variants are transmitted to the infant (Okamoto et al., 1997). Moreover it appears that the timing and mechanism of NAb activity during vertical transmission is important. A strong local NAB response is probably effective at controlling HIV multiplicity during pregnancy, but ineffective at blocking transmission of HIV-1-infected cells (Bongertz, 2001).

#### 4.6 HIV coreceptors and vertical HIV transmission

In this section of the chapter, we will briefly describe non-MHC genetic factors that influence vertical transmission and then we will focus on the association between HLA polymorphism and vertical transmission.

In addition to CD4, HIV-1 uses other coreceptors to enter the T cell, and these have been identified as chemokine receptors (Cairns and D'Souza, 1998). The CCR5 chemokine receptor is mainly used by non-syncytium-inducing (NSI) HIV-1 strains, whereas syncytium-inducing strains use the SDF1 chemokine receptor CXCR4. Some strains also use additional chemokine receptors such as CCR2 and CX<sub>3</sub>R1 (Cairns and D'Souza, 1998; Singh and Spector, 2009). A mutant CCR5 allele carrying a 32-bp deletion (CCR5-Δ32) was identified independently by several groups, and found to cause the loss of coreceptor activity (Dean et al., 1996; Liu et al., 1996; Samson et al., 1996). This allele has been identified as a natural polymorphism that reduces the risk of acquiring HIV-1 infection (McNicholl et al., 1997). Nevertheless, several studies about the role of this allele in mother-to-child transmission showed that CCR5-Δ32 heterozygosity alone does not protect against vertical transmission (Matt and Roger, 2001). Conversely, another genetic polymorphism, CCR5-59356-T, was strongly associated with a higher rate of vertical transmission of HIV-1 among black infants (Kostrikis et al., 1999).

The CCR2-64-I allele was shown to confer long-term protection in adults (Smith et al., 1997), but it was not associated with mother-to-child transmission (Mangano et al., 2000). A genetic polymorphism in the untranslated region of the SDF-1 gene in mothers was associated with increased risk of vertical transmission of HIV-1, mainly through breastfeeding (John et al., 2000).

#### 4.7 MHC and vertical HIV transmission

Although vertical transmission of HIV-1 has been correlated with a wide range of viral and maternal features, the factors affecting this transmission have yet to be definitively identified (Matt and Roger, 2001). Efforts to explain why only a proportion of children born to HIV-infected mothers become infected have led to the discovery of important host genetic and delivery variables. One of the most relevant genetic factors is the MHC system, which, as mentioned above, plays a critical role in HIV transmission in both horizontal and vertical transmission. Since the 1990s, it has been known that certain HLA types are more susceptible or resistant to HIV-1 infection. In principle, HLA genotype may influence disease susceptibility *in utero* by affecting CTL response or other immune responses. HLA association with mother-to-child transmission has been found with class I, class II, and non-classical HLA alleles. A serologic HLA typing study of Scottish infants by Kilpatrick et al. (Kilpatrick et al., 1991) found that specific HLA haplotypes were associated either with protection or increased susceptibility to HIV-1 vertical transmission. In particular, the HLA-A3-B7-DR2 haplotype was associated with protection against HIV-1 infection, whereas the HLA-A1-B8-DR3 haplotype was associated with HIV-infected children. RFLP HLA-DRB1 analysis performed by Greggio et al. showed that certain DRB1-13 allele subtypes were associated with protection against vertical transmission of HIV-1 (Greggio et al., 1993). These findings were subsequently confirmed using molecular HLA typing methods. The HLA-DR2 allele (DRB1\*1501) was not associated with mother-to-child transmission of HIV-1, while the HLA-DR3 (DRB1\*03011) allele was positively associated with the occurrence of HIV-1 infection among American Caucasian infants (Winchester et al., 1995).

Among infected infants, MHC alleles can influence disease progression. For instance, the HLA DR3 haplotype (DRB1\*0301-DQA\*0501-DQB1\*0201) was associated with the development of severe clinical manifestations and death in African-Americans, DPB1\*0101 was associated with survival to at least two years of age, and DQB1\*0604 was related with increased risk of infection (Just et al., 1995a). A study with Spanish children in Catalonia confirmed the association between the DQB1\*0201 allele and severe clinical outcomes, but found that the DRB1\*0301 allele showed a tendency to protect against disease progression (Just et al., 1996). The differences observed between these studies may be explained by ethnic differences among the children studied (Winchester et al., 1995; Just et al., 1996). Indeed, ethnicity appears to be an important variable for interpreting the effect of HLA alleles. For instance, the DRB1\*13011 allele is significantly associated with a diminution in vertically transmitted HIV-1 infection in African-American children but not in American Caucasian children. Moreover, other HLA DR13 alleles (DRB1\*1301, \*1302, \*1303) are associated with protection against HIV-1 transmission in African-American but not in Caucasian children (Winchester et al., 1995).

Altogether, these data suggest that the HLA DR3 haplotype is associated with both increased risk of vertical transmission of HIV-1 and pediatric disease progression (Just et al., 1995b; Winchester et al., 1995), while the HLA DR13 allele is associated with protection against HIV-1 infection (Winchester et al., 1995). However, the HLA DR3 (DRB1\*03011) and HLA-A2 alleles show discordant effects between African-American and Caucasian ethnic groups.

These observations suggest that variations in the transport of virally encoded peptides to, or presentation by, MHC molecules may significantly influence the host response to HIV infection and mother-to-child transmission. However, the identity of the HLA alleles by itself does not determine risk of mother-to-child transmission. Rather, the concordance or

discordance of HLA alleles between mother and child seems to be a key factor for vertical transmission.

HLA-G is a non-classical HLA molecule from MHC class Ib with a limited distribution in tissues, and it is selectively expressed in placental trophoblast cells in the maternal-fetal interphase (Kovats et al., 1990). HLA-G has been identified as a molecule involved in immune tolerance, and its main function appears to be to protect the fetus from maternal CTLs and natural killer (NK) cells (Hunt, Petroff et al. 2000). Because of its presence in the placenta, it is logical to suggest that HLA-G helps to determine vertical transmission of HIV-1, and that certain allelic mutations in the HLA-G gene increase or decrease protection of infants against *in utero* transmission. Indeed, a correlation between HLA-G variants and mother-to-child transmission was found in a study by Aikhionbare et al. (Aikhionbare et al., 2001). Discordance between mother and child for a mutation in exon 2 of HLA-G was significantly more common among non-transmitting than transmitting mother-child pairs. This suggests that mother-child pairs in which both carry the same mutation in HLA-G exon 2 may be at higher risk of vertical transmission of HIV-1. Nevertheless, another study with a bigger cohort of mother-child pairs in Zimbabwe did not find any relation between mother-child HLA-G concordance/discordance and either intrauterine or peripartum transmission (Matte et al., 2002). Moreover, the mutation in exon 2 of HLA-G (at codon 57) does not change the amino acid composition of the protein (silent mutation), so it is difficult to envisage how a silent mutation could have a direct influence on mother-child transmission of HIV-1. The significant association reported in the first study (Aikhionbare et al., 2001) may be attributed to their relatively small sample size. However, in more recent work, Aikhionbare et al. argued that the differences between the studies may be due to the homogeneous population in the Zimbabwe study, where 90% of the mother-child pairs belonged to the Shona ethnicity. They suggested that in such a homogeneous group, certain mutations may not play a role in disease protection, whereas they do in mixed populations. In addition, they identified several polymorphisms in HLA-G that may be associated with decreased risk of vertical transmission of HIV-1 (Aikhionbare et al., 2006).

An important milestone is the so-called "pattern of inheritance theory," based on the premise that HLA concordance between a mother and her infant can be a determinant of vertical transmission. A study showed that HLA class I antigen concordance between a mother and her child is associated with an increased risk of intrauterine HIV-1 transmission, whereas maternal-child HLA discordance results in protection against vertical transmission (MacDonald et al., 1998). This was confirmed in another study showing the association with HLA class I concordance, but not with HLA class II (Polycarpou et al., 2002). This was also shown in other studies where children who inherited one or more alleles associated with short-term disease progression progressed more rapidly to AIDS if they inherited the alleles from their fathers, but not if they inherited them from their mothers. The opposite situation also occurs: a protective allele may be effective in children only when it comes from the father and not from the mother (Kuhn et al., 2004). It has been proposed that fetal alloimmune responses directed against maternal HIV-infected cells or free virus bearing maternal MHC determinants may account for protection in some children (Mittleman and Shearer, 1996). Maternally derived cells carry HLA molecules on their surface, as well as infectious viral particles. Fetal cord blood leukocytes are able to recognize foreign maternal HLA and mount a strong immune response. Nevertheless, in cases in which maternal HLA antigens are similar or identical to fetal HLA, the fetal immune response is probably less potent or nonexistent (Mittleman and Shearer, 1996). This may explain why HLA

concordance between a mother and her child is associated with an increased risk of intrauterine HIV transmission. A recent study of mother-child pairs in Spain suggests that HLA-B35 increases transmission risk, a finding that is also consistent with the pattern of inheritance theory (Arnaiz-Villena et al., 2009).

## 5. Other MHC-related factors that influence HIV transmission

### 5.1 Innate immune response

Although the innate immune response is an essential part of anti-viral responses, its role in HIV infection remains obscure (Biasin et al., 2010). Viruses are recognized by the immune system through receptors named "pattern recognition receptors" (PRRs) that bind to "pathogen-associated molecular patterns" (PAMPs), which are small pieces of the virus with a conserved "viral tag" that host cells identify as foreign. Viral proteins are recognized by Toll-like receptors (TLR) 2 and 4 in the plasma membrane, while viral nucleic acids are recognized by TLR 3, 7, 8 and 9, which are located in endosomal membranes. In this latter group, TLR7 and 8 recognize single-stranded viral RNA (v-ssRNA) from HIV. Studies on TLR signalling during HIV infection are scarce, even though it has been proposed that exposed but non-infected individuals mount stronger responses through TLR-initiated signalling (Biasin et al., 2010).

There are also cytoplasmic receptors such as RIG-I-like (RLR) and nucleotide-binding domain, leucine-rich receptors (NLRs) that have been implicated in the recognition of viruses. Signals from these receptors activate the cells that express them and initiate the production of interferons and inflammatory cytokines, including IL-1 $\beta$  and IL-18, which determine important aspects of the adaptive immune response, such as the CTL response. HIV is able to disrupt both TLR and RIG-1 signalling by depleting IRF3 interferon regulatory factor 3 (IRF-3) (Doehle et al., 2009). Type I interferons (IFN  $\alpha/\beta$ ) are especially crucial in early stages of viral infections. They promote an "antiviral state" by inducing the expression of hundreds of target genes, so-called interferon-stimulated genes (ISGs) (Baum and Garcia-Sastre, 2010). Plasmacytoid dendritic cells (pDCs) are the main natural IFN $\alpha$  producers *in vivo*. This subpopulation appears to be depleted in chronic HIV infection (Soumelis et al., 2001).

### 5.2 NK responses

NKs are CD3<sup>+</sup> lymphocytes and they are divided into two major subgroups, NK regulatory or NK effector cells, depending on the levels of expression of CD56 and CD16. These cells play a prominent role during viral infections because they mediate early, non-adaptive responses against virus, and they modulate the activity of other effector cells of the innate and adaptive immune system. NKs exhibit cytolytic activity against cells infected with viruses and they secrete anti-viral products. Their cytolytic activity appears to involve receptors that bind MHC class I molecules. HIV-exposed but uninfected subjects have been reported to have enhanced NK functions and increased IFN- $\gamma$  and TNF- $\alpha$  levels. During chronic HIV infection, NK cell cytotoxicity is reduced (Ahmad et al., 2001).

The ability of NKs to kill virally infected cells depends on a fine balance in the relative expression of inactivating and activating NK receptors (NKR). Several studies have addressed the relationship between NK receptors that bind to MHC molecules, and viral load and NK activity during HIV infection (Ahmad et al., 2001; Gaudieri et al., 2005).

HLA-B molecules can be classified according to the presence of the mutually exclusive public epitopes Bw4 or Bw6 that are shared by various MHC molecules. However, only Bw4 is a ligand for KIRs, which are type I integral membrane glycoproteins. To date, 14 distinct KIR genes have been described (<http://www.ebi.ac.uk/kir>) (Paximadis et al., 2011). KIRs can have either activating or inhibitory functions. It has been shown that suppression of HIV-1 viremia is associated with homozygosity for HLA-Bw4. Furthermore, the Bw4-80I group, which has isoleucine at position 80, includes two alleles (B\*57 and B\*27) that are considered protective, as previously mentioned. KIR allele KIR3DS1, which is an activating receptor, binds HLA-B Bw4-80I molecules, and this binding was shown to delay progression to AIDS. Furthermore, coexpression of both alleles in the same individual reduces the risk of both infection and progression (Lopez-Vazquez et al., 2005; Boulet and Bernard 2008; Boulet et al., 2008).

The involvement of HLA-B Bw4/6 epitopes in transmission from infected men to their female sex partners was analyzed. Compared with men who were homozygous for Bw6, men who carried Bw4 were about half as likely to transmit HIV-1 to their female partner (Welzel et al., 2007). However, a more recent study that compared men homozygous for HLA-Cw1 or HLA-Cw2 attributed functional differences in human NK cell activity to distinct KIR/HLA genotypes, independently of KIR3DL1/HLA-Bw4 interactions (Ahlenstiel et al., 2008). It turns out that HLA-E and HLA-G are also important in the regulation of NK cell responses (Tripathi and Agrawal, 2007).

The simultaneous presence of the HLA-Bw4 epitope and both the HLA-B\*57 and HLA-Cw\*18 alleles correlated with low levels of viremia in 147 HIV-infected individuals in Brazil. The protective effect of HLA-Bw4 depended on the presence of HLA-B\*57. In contrast to previous studies, the HLA-Bw4 epitope bearing isoleucine at position 80 did not confer a protective effect in the presence of the activating KIR3DS1 allele (Da Silva et al., 2011).

The associations most consistently observed between KIRs and HIV progression involves KIR3DS1 and KIR3DL. KIR and HLA class I alleles were studied in 224 South African mothers and their 222 infants, of whom 72 were infected and 150 uninfected (Paximadis et al., 2011). The frequencies of KIR2DL1 and KIR2DL3 were lower in intrapartum-transmitting (IP-T) mothers than in non-transmitting (NT) mothers. Homozygosity for KIR2DL3, alone or in combination with HLA-C heterozygosity (Cw1/Cw2), was more frequent in IP-T mothers than in NT ones. The combination of the KIR2DL3 allele and its ligand, HLA-Cw1 occurred less frequently in infected infants, as did homozygosity for KIR2DL3 in combination with HLA-Cw1/Cw2. It is noteworthy that these effects of genotype were more readily detectable after stratifying the sample based on low or high maternal viral load.

### 5.3 Chemokines

Since the discovery of CCR5 as an HIV entry cofactor (Dean et al., 1996), researchers have focused on chemokines as possible restriction/susceptibility factors (Alkhatib et al., 1996). Thus variants or haplotypes of CCL5, CCL2-CCL7-CCL1 and CCL3 have been consistently associated with differential susceptibility to infection or transmission (Telenti and McLaren, 2010). Polymorphism of chemokine receptors has, in turn, been linked to specific HLA alleles, such as CCR2 and HLA-B58; the latter is present in long-term survival women from Nairobi (Fang et al., 2004)

#### 5.4 Other factors

CTL-associated antigen 4 (CTLA4) is a member of the immunoglobulin superfamily, and is expressed mainly on helper and regulatory T cells. After ligand binding it transmits an inhibitory signal to the cell. Single-nucleotide polymorphisms in the promoter region of the CTLA4 gene were analyzed in relationship to viral load and time to AIDS, but no clear association was established (Shao et al., 2006).

### 6. Contribution of HLA selection of CTL responses to HIV susceptibility or protection

Here we provide an overview of an important subject that is central to the struggle to develop a successful CTL-based HIV vaccine (Bangham et al., 2009). CTLs, also known as CD8+ T cells, eliminate HIV-infected cells through the recognition of antigenic peptides displayed by HLA class I molecules on the infected cell surface. HIV can evade T cell responses by mutating epitopes that are recognized by CTLs (Phillips et al., 1991) and then those HIV variants or “escape mutations” are selected if they maintain the fitness of the virus. This is called “fixation” of the mutation and it implies that the mutation confers some advantage for the virus against the CTL response. Significant efforts have been made to obtain a complete map of HIV epitopes recognized by CTLs and antibody-producing cells (<http://www.hiv.lanl.gov>), since this mapping is essential for vaccine development.

In general it is thought that most mutations occur in the initial phase of the infection when the virus is rapidly replicating and therefore is more likely to mutate. However, it appears that the mutations in some delayed escape variants occur later in the viral life cycle. One of the best documented examples of an HIV escape variant is a “gag epitope” recognized by the HLA-B27 molecule. Patients with HLA-B27 progress more slowly to AIDS than does the general HIV-infected population. Peptides that bind HLA-B27 very frequently have an arginine (R) at the second position. The HIV gag epitope<sup>263-272</sup> contains such arginine that when mutated, is no longer recognized by T cells. This escape mutation occurs in approximately 50% of HLA-B27-infected individuals after several years of infection. Why does it not appear at the beginning of the infection? Because the escape mutation R264K must be preceded by a first mutation, and then it subsequently appears together with a third. The mutation R264K has a fitness cost and thus the mutant virus tends to revert to the wild-type (WT) sequence in the absence of selection (i.e. HLA-B27). This was demonstrated by studying HLA-B27-negative babies born to HLA-B27-positive mothers infected with virus carrying the R264K mutation (Goulder et al., 2001); this study found that “HLA-mediated selective pressures on the virus in a transmitting mother-infant pair may undermine future HLA-mediated viral control in the child”. Later the fitness cost was shown to be compensated by a third mutation in a position that binds an inhibitory receptor on dendritic cells (DCs). This example illustrates that escape mutations can be very complicated events, which may explain their late appearance in the course of the infection (McMichael et al., 2007).

There are well established examples of associations between expression of an HLA class I molecule and deviation from the consensus HIV sequence (“escape mutations”). The converse situation also exists, namely, association of certain HLAs with the WT or “preserved” sequence (Leslie et al., 2005). Therefore it was proposed that HIV-1 is adapting to HLA-restricted responses as a consequence of selection pressure (Moore et al., 2002; John et al., 2005). However, CTL escape mutants that revert following transmission to individuals

lacking the selecting MHC alleles have been identified. The obvious implication of these data is that some CTL responses can be evaded only by escape mutations that paradoxically reduce the replicative fitness of the virus (Leslie and Goulder, 2006). Study of the impact of HLA on HIV molecular evolution is further complicated by the “founder effect” of HIV strains (Bhattacharya et al., 2007; Klenerman and McMichael, 2007).

The question at the moment is to what extent is HIV adapting to HLA class I molecules? This issue was directly addressed in an international multi-cohort study, in which nine cohorts from 5 different continents were pooled, allowing the analysis of more than 2,800 subjects. They studied the HLA-B\*51-restricted epitope TAFTIPSI, corresponding to residues 128-135 of reverse transcriptase, and they showed a strong correlation between the frequency of the escape mutation I135X and HLA-B\*51 prevalence. Similarly, the frequencies of other well-defined CD8+ T-cell epitopes restricted by HLA-B\*57 and HLA-B\*27 correlated with the prevalence of the restricting HLA allele in the different cohorts, demonstrating strong evidence of HIV adaptation to HLA at the population level (Kawashima et al., 2009).

## **7. Summary: HLA molecules confer protection or susceptibility to HIV infection**

The best way to identify protection or susceptibility factors is to study exposed but seronegative (ESN) individuals and HIV-infected LTNPs (Miyazawa et al., 2009). There are several possible factors that may determine how HLA molecules condition the anti-HIV immune response (Fig. 2). One obvious factor is the differences in peptide-binding repertoires among HLA molecules, which is the logic behind grouping the alleles in clusters or supertypes. Another factor is that HLA-DR polymorphism affects interaction with CD4 (Fleury et al., 1995), which implies that some HLA-DR molecules bind CD4+ lymphocytes more than others. Similarly, particular HLA molecules, such as HLA-B\*27, HLA-B57, HLA-B\*5701 (in Caucasians) and HLA-B\*5703 (in Africans), are more likely to mediate successful control of HIV infection by activating CTL responses (den Uyl et al., 2004). HLA B\*5701 was found to be a clear protective factor, but the protection could not be attributed to any quantitative differences in the total HIV-specific CD8+ T cell response (Migueles et al., 2000). In the case of HLA-B27, there are reports of CTL-protective response against p24 HIV protein, which has a relatively low rate of mutation (den Uyl et al., 2004). HIV-infected chimpanzees do not develop AIDS and therefore they have been used as a model to understand the influence of MHC on HIV disease. The peptide-binding groove of frequent chimpanzee MHC class I molecules, similarly to HLA-B\*27/B\*57, target similar conserved areas of HIV-1/SIV(cpz) (de Groot et al., 2010). Interestingly HLA-B\*5701 is one of the major alleles responsible for hypersensitivity to the reverse transcriptase inhibitor abacavir (Mallal et al., 2002).

Various factors, including HLA that might confer protection or susceptibility, have been studied in a cohort of 30 LTNPs from Spain (Salgado et al., 2011b). For example, these investigators studied CCR5 and the *CCL3L1* gene, which encodes the MIP1a protein, an inhibitory CCR5 ligand. They found the B27 and B58 supertypes, as well as certain class I alleles, to be protective; the B7 supertype and other class I alleles were non-protective. No significant association with CCR5-Delta32 was found, probably because this mutation is rare among Spaniards. Similarly, *CCL3K1* copy number did not influence the rate of progression.

Protective HLA-B and -C alleles were more frequent in LTNPs, though such an association was not observed with HLA-A alleles. In addition to HLA-B\*5701 and -B\*2705, the investigators found HLA-Cw0102, -Cw0602 and -Cw1203. The presence of allele combinations such as HLA B\*5701-Cw0602, HLA B\*2705-Cw0102, and HLA B\*3801-Cw1203 showed the strongest association with non-progression.

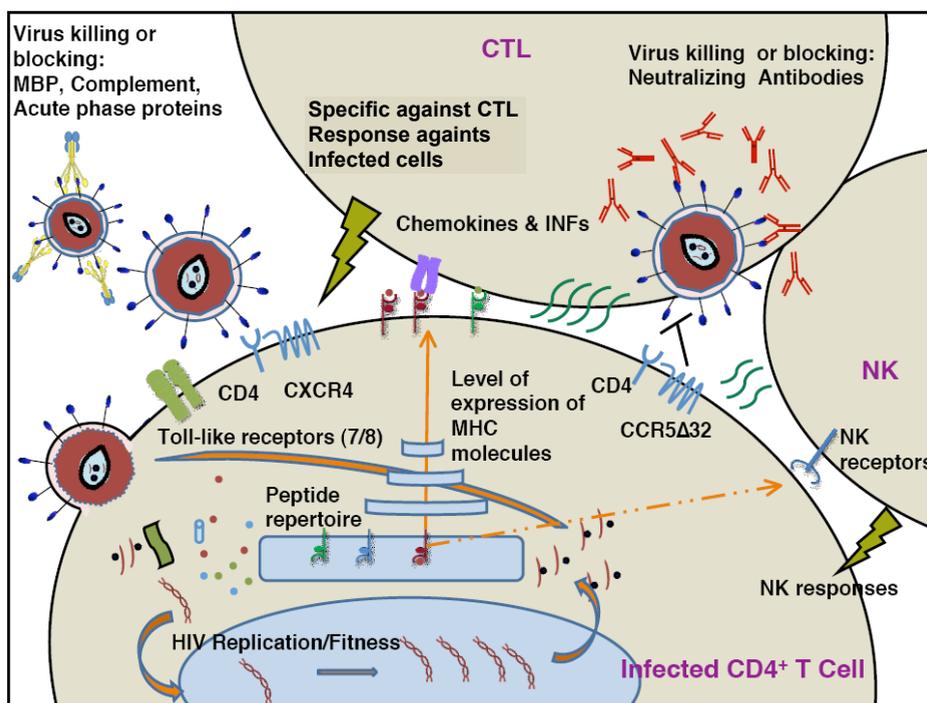


Fig. 2. Points where genetics influences HIV infection and its progression.

Although chimpanzees are susceptible to infection with HIV-1, they do not develop AIDS. A similar situation occurs when they are infected with the chimpanzee simian immunodeficiency virus (SIVcpz). Chimpanzee class I molecules are designated Patr-A, -B and -C, and like those of humans, they are polymorphic. However it has been proposed that their repertoire has been skewed by strong selective pressure exerted by HIV or an ancestral retrovirus of HIV. Therefore the chimpanzee has been used as a model system to understand resistance to progression to AIDS. Thus, the Patr peptide-binding repertoire has been analyzed and compared to the binding repertoire of human HLA-B\*27 and B\*57, two HLA molecules correlated with resistance in humans (Groot et al., 2010). This work showed that at least one Patr molecule in the study population recognizes conserved areas of the Gag protein that are also recognized by B\*27 and B\*57.

The mechanism of the protective effect exerted by HLA-B\*58:01 was studied in South African individuals infected with HIV subtype-C (Chopera et al., 2011). One of the major conclusions of this work is that HLA-B\*58:01 patients whose CTLs target the TW10 in the p24Gag viral epitope maintain higher CD4+ T cell numbers than those whose CTLs do not target that part of the epitope. However, escape mutations were detected early, as soon as two

weeks after infection. In addition, the escape mutations were accompanied in some cases by compensatory mutations that may limit the protective effect of the HLA-B\*58:01 allele.

A correlation was found between the HLA peptide-binding affinities of 95 HLA class I alleles and sequence conservation of targeted viral regions in 52 human viruses, including HIV (Hertz et al., 2011). This analysis indicates that HLA-A alleles and those HLA-B alleles most closely related to chimpanzee alleles preferentially target peptides from DNA viruses, while other HLA-B alleles generally target peptides derived from RNA viruses. This is an important conclusion that may at least partially explain why it is primarily HLA-B alleles that determine susceptibility and progression of HIV infection.

### 7.1 Susceptibility conferred by HLA-B35 alleles

Individuals positive for HLA-B35 have a greater chance of becoming infected and show accelerated HIV-1 disease progression. In the late 1990s, numerous HIV mutations in HLA-B35-restricted epitopes were found (Kawana et al., 1999). Hence initial studies of susceptibility conferred by HLA-B35 focused on CTL responses (Jin et al., 2002). Later work showed that the increased risk was associated with the subset of HLA-B35 alleles known as B\*35-Px molecules (Jin et al., 2002). Interestingly, some alleles in the alternative set of B\*35 subtypes, B\*35-PY, present HIV-1 epitopes identical to those of B\*35-Px molecules, yet have no detectable impact on HIV-1 disease outcomes. In other words, both HLA-B35 subtypes recognize the same HIV epitopes, implying a similar CTL response. If that is true, how can we explain the differences in responses in these two HLA-B35 subsets? Differences in innate immunity could be the underlying cause: the B\*35-PY molecule B\*3501 and the B\*35-Px molecule B\*3503 differ by only one amino acid and present identical HIV-1 epitopes, yet the B\*35-Px molecule binds with greater affinity to immunoglobulin-like transcript 4 (ILT4), an inhibitory MHC class I receptor expressed on DCs. This binding to ILT4 is associated with significantly stronger DC dysfunction during *in vitro* functional assays (Huang et al., 2009). That study concludes that differential interactions between HLA class I allele subtypes and immune regulatory MHC class I receptors on DCs is an important determinant of the immune response to the HIV virus.

Lazaryan et al. (2011) compared the effects of class I alleles in African-Americans infected with subtype B with those in Africans infected with subtype C. Among African-Americans, HLA alleles A\*32, A\*74, B\*14 and B\*45 were strongly associated with control of HIV infection. Furthermore, infrequent HLA-B alleles were associated with better disease outcome. This was consistent with a previous study by the same investigators, in which they found that relatively infrequent supertypes in African-Americans correlated with a better immunological profile. When the researchers took into account the known linkage disequilibrium among A, B and C alleles in their cohort, they detected that HLA-A\*32 and A\*74 were associated with favourable outcome. The protective effect of HLA-B\*57 was also confirmed in this population, while B35 and B53 alleles were associated with poor outcome. These results are inconsistent with the previously described PX/PY theory (Huang et al., 2009) (section 7.1). Lazaryan et al. (2011) found that both B\*5301 (PX) and B\*3501 (PY), the most frequent alleles in their groups, were equally disadvantageous.

## 8. Hypersensitivity to anti-HIV drug treatment

The occurrence of hypersensitivity reactions to drugs used to treat HIV infection has complicated HIV treatment management. Antiretroviral drugs are currently grouped into 6 major classes:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Entry inhibitors, further subdivided into fusion inhibitors and CCR5 inhibitors
- Integrase inhibitors

Most HIV patients receive therapy that combines various drugs, known as HAART. This complicates the diagnosis of drug hypersensitivity. In addition, allergic reactions to anti-HIV drugs usually occur with a delay of 1 to 6 weeks. Skin reactions are the most common manifestations, and they can vary from exanthema to systemic symptoms or syndromes that have received various names, such as drug-induced hypersensitivity syndrome (DIHS). Most of the drugs used to treat HIV infection produce hypersensitivity in a percentage of patients. We recommend to our readers an excellent recent review on the subject (Chaponda et al., 2011).

Genetic factors have been shown to play a role in some of the adverse effects of these drugs, especially in the case of **abacavir**. This NRTI induces hypersensitivity that is strongly associated with the MHC class I HLA\*5701 allele (Mallal et al., 2002), implying a significant genetic component. Screening for HLAB\*5701 has now become part of HIV treatment involving abacavir and has helped prevent adverse reactions.

## 9. New technologies

Historically, studies of HLA association with HIV infection have evolved in parallel with advances in technology. Initially HLA determinations were performed by serology, which has gradually been replaced by molecular techniques. We are now in the so-called "-omics" era: genomics and proteomic technologies, including microarrays, next-generation DNA sequencing and mass spectrometry, are important for identifying molecular markers in complex traits (Sharon et al., 2010), such as in HIV infection. The genetics of HIV susceptibility will most probably include frequent and rare variants, with each type of variant making different contributions to the specific aspect of the disease analyzed. This implies that the design of the study itself is a key factor that affects the consistency of the results. Therefore a large number of subjects is recommended in some instances (>1000 patients and >1000 controls) (Telenti and McLaren, 2010).

A whole-genome association study (WGAS) was performed to uncover the genetic factors that govern variations in viral load among individuals during the asymptomatic period of infection. Two polymorphisms were found, one located in an endogenous retroviral element occurring within the HLA-B57\*01 allele, and another near the HLA-C gene (Fellay et al., 2007). More recently, a WGAS of a cohort of 2,554 HIV-infected Caucasian individuals excluded a role for any gene polymorphism outside the MHC complex, including the chemokine receptor gene cluster on chromosome 3 (Fellay et al., 2011). Viral control was associated with genetic variants that map near the HLA-B and -C loci, though variants also exist in the MHC region. The study detected in this cohort two previously described SNPs (Fellay et al., 2007) and found them to be associated with HLA-B\*5701 and HLA-C (Fellay et al., 2011).

In a study of the association of HLA-C with HIV control, Kulkarni et al., (2011) reexamined the SNP -35, which lies 35 kb upstream of HLA-C (Fellay et al., 2007). This SNP was found to be in fact a marker of another polymorphism in the 3'-untranslated region (3'-UTR) of HLA-C. This polymorphism regulates the binding of a microRNA (miRNA), has-miR-148, to

the 3'-UTR. This binding results in relatively low surface expression of HLA-C. MicroRNAs are RNAs that bind to the 3'-UTR to cause post-transcriptional repression, cleavage or destabilization. Even more, the 3'-UTR polymorphism of HLA-C that regulates binding by has-miR-148 is associated with HIV control.

Recently, the International HIV Controllers Study Group (Pereyra et al., 2010) analyzed a large cohort from multiple populations, comprising 974 controllers and 2,648 progressors. The study yielded 1,384,048 single-nucleotide polymorphisms (SNPs). In the largest group of 1,712 individuals of European ancestry, all SNPs that reached statistical significance were located in the MHC region, around class I genes. A similar clustering of SNPs occurred in other ethnic groups and across the entire sample population. When the HLA typing and the SNPs were considered together, through a process of "imputation" in which HLA type was inferred from a previous WGAS on diabetes, HLA B\*57:01, B\*27:05, B\*14/Cw\*08:02, B\*52, and A\*25 were identified as protective alleles, and B\*35 and Cw\*07 as risk alleles. These results are consistent with previous HLA association studies. The HIV Controllers study went a step further and analyzed whether the observed associations might be explained by the presence of specific AAs within the polymorphic positions on HLA molecules. Among a total of 372 polymorphic AA positions in class I and II, 286 were biallelic, accommodating two possible AAs, while the remaining 86 could accommodate more than two AAs. Interestingly position 97 was detected as the most polymorphic, with 6 alternatives. In fact, position 97 in HLA-B was more significant than any single SNP, and positions 67, 70 and 97, located in the binding groove, were better markers than any single classical HLA allele. Position 97 is located at the base of the binding groove and has an important contribution to peptide binding. Arginine is present at position 97 in HLA-B\*35, a "risk molecule", while protective HLA molecules, such as B\*5701, B\*27:05 and B\*14 possess valine, asparagine and tryptophan, respectively. A similar analysis performed on HLA-A showed a small but significant contribution of position 77, while for HLA-C the results were more difficult to interpret. This WGAS corroborated the importance of HLA-B peptide presentation for HIV susceptibility (Pereyra et al., 2010).

Novel genetic factors influencing plasma levels of HIV-RNA and cellular HIV-DNA in 605 HIV-1-infected individuals were investigated. Most of the SNPs were located in the 6p21 MHC region, near class I and II genes, except for two outside this region. One of them was located within the syndecan 2 gene (Dalmaso et al., 2008). Intriguingly, increased expression of syndecan isoform 1 -but not of isoform 2- has been implicated in microbial translocation in the gut that is associated with chronic stimulation of the immune system (Smith et al., 2010).

DNA microarrays were used to analyze gene expression patterns in CD3+ T cells from LTNPs and controls. They found that most up-regulated genes in rapid progressors localized to cellular organelles and were implicated in the regulation of DNA replication, cell cycle progression and DNA damage response. In contrast, most genes up-regulated in LTNPs were located at the plasma membrane and were involved in cytokine-cytokine receptor interaction, negative control of apoptosis and regulation of the actin cytoskeleton. This suggests that progressors mainly up-regulate markers of viral replication, while non-progressors do not (Salgado et al., 2010a).

Proteomics is now also being used to study host genetic factors in HIV response, though mostly in relation to specific aspects of the disease, such as neurological damage (reviewed by (Zhang et al., 2010)).

We would like to end this chapter by mentioning new trends in research on the genetics of HIV disease by mentioning the role of autophagy (Blanchet et al., 2010), and the cell skeleton or cytoskeleton (Harmon et al., 2010) during HIV infection and replication within the cells. A very recent and interesting report showed that a known tumour suppressor protein, the cyclin-dependent kinase inhibitor p21, has an important role in inhibiting various steps of HIV transcription in CD4<sup>+</sup> T cells. Elite controllers showed increased expression of p21, which should effectively down-regulate HIV replication. Future studies should determine whether individuals expressing protective alleles such as HLA-B\*57 express high levels of p21. These studies are necessary in light of the fact that the locus of the CDKN1A gene, which encodes p21, is located near the MHC class I genes (Chen et al., 2010). We are certain that genetic factors involved in these processes will be identified as susceptibility or protective factors in the near future.

Factor	Role in HIV infection	Reference (s)
<b>HLA class I</b>	Concordance between mother and child is associated with increased risk of HIV transmission. "Pattern of inheritance theory". Importance of AAs at position 97 in HLA-B and 77 in HLA-A molecules. HLA-B preferentially targets peptides derived from RNA viruses	MacDonald, et al., 1998; Polycarpou et al., 2002; Kuhn et al., 2004; Pereyra et al., 2010; Hertz et al., 2011
<b>A25</b>	Protection in disease progression	Pereyra et al., 2010
<b>B27</b>	Protection. Slow disease progression. Lower risk of infection and slow progression in vertical transmission. "Pattern of inheritance theory". CTL responses associated with HIV control	Kaslow et al., 1996, McNeil et al., 1996; Yap et al., 1996; Goulder et al., 2001; den Uyl et al., 2004; Groot et al., 2010 ; Pereyra et al., 2010 ; Salgado et al., 2011b
<b>B35</b>	Increase risk of infection and disease progression. Increased risk of vertical transmission. "Pattern of inheritance theory". Decreased number of CD4 <sup>+</sup> T lymphocytes. CTL responses associated with lack of HIV control. DC dysfunction	Klein et al., 1994; Carrington et al., 1999; Kawana et al., 1999; Jin et al., 2002; Flores-Villanueva et al., 2003; Liu et al., 2003; Arnaiz-Villena et al., 2009; Huang et al., 2009 ; Pereyra et al., 2010
<b>B*51</b>	CTL responses that control HIV replication. Viral mutations allow HIV escape	Kawashima et al., 2009
<b>B*52</b>	Protection in disease progression	Pereyra et al., 2010
<b>B57</b>	Protection. Slow disease progression. B*5701 in Caucasians and HLA-B*5703 in Africans, are more likely to mediate successful control of HIV infection by activating CTL responses	Kaslow et al., 1996; den Uyl et al., 2004; Fellay et al., 2007; Groot et al., 2010 ; Pereyra et al., 2010 ; Salgado et al., 2011b
<b>B57*01</b>	Hypersensitivity to <i>abacavir</i> .	Mallal et al., 2002

Factor	Role in HIV infection	Reference (s)
<b>B58 and B58*01</b>	Long survival in women in Nairobi. Protection against HIV infection. CTL responses	Fang et al., 2004 ; Chopera et al., 2011
<b>Bw4</b>	Protection in infection and disease progression. Suppression of viremia in homozygosis. Receptor for KIR (NK cells)	Lopez-Vazquez et al., 2005; Welzel et al., 2007; Boulet & Bernard, 2008; Boulet et al., 2008
<b>HLA-C</b>	Variation of viral load during asymptomatic period. Polymorphism at 3'UT region that binds microRNA decreasing its level of expression	Fellay et al., 2007; Kulkarni et al., 2011
<b>Cw*04</b>	Disease progression in Caucasian	Carrington et al., 1999
<b>Cw*07</b>	Risk of progression	Pereyra et al., 2010
<b>DQB1*0201</b>	Severe clinical outcome in children	Just et al., 1996
<b>DR1</b>	Kaposi's sarcoma	Klein et al., 1994
<b>DR3, DRB1*0301</b>	Opportunistic infections. Risk of infection in American Caucasian children.	Klein et al., 1994; Winchester et al., 1995
<b>DR13, DRB1*130101, *1302, *1303</b>	Protection in vertical transmission. DRB1*1303 associates with reduced viral loads	Greggio et al., 1993; Winchester et al., 1995; Julg et al., 2010
<b>HLA-E</b>	Implicated in NK cells responses	Tripathi & Agrawal, 2007
<b>HLA-G</b>	Discordance between mother and child for mutation in exon 2 has a higher frequency among non-transmitting mother-child pairs. Controversial role in vertical transmission. Implicated in NK cells responses	Aikhionbare et al., 2001; Matte et al., 2002; Aikhionbare et al., 2006; Tripathi et al., 2007; Fainardi et al., 2011
<b>A3-B7-DR2</b>	Protection in vertical transmission	Kilpatrick et al., 1991
<b>A1-B8-DR3</b>	Increased risk of vertical transmission	Kilpatrick et al., 1991
<b>KIR2DL1, KIR2DL3</b>	Lower frequencies in intrapartum-transmitting (IP-T) mothers than in non-transmitting (NT) mothers	Paximadis et al., 2011
<b>CCR5 (delta32), CCR2-64I</b>	Correceptor for HIV, reduced risk of infection. CCR2-64-I allele was shown to confer long-term protection in adults	Dean et al., 1996; Liu et al., 1996; Samson et al., 1996 ; McNicholl et al., 1997; Smith et al., 1997

Table 2. Major factors associated with HIV infection and progression.

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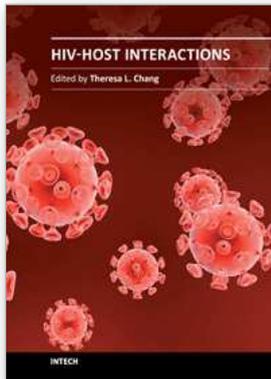
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## **HIV-Host Interactions**

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and *Trichomonas vaginalis* on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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