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REVIEW

HLA Genetic Polymorphisms: Role in HIV-1 Susceptibility, Disease Progression and Treatment Outcomes

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Abstract: The human leukocyte antigen (HLA) gene loci are key in human immunodeficiency virus (HIV) antigen presentation leading to an immune response to infection. The high genetic variation in these gene loci forms the basis of the host's ability to mount immune responses to different viral epitopes. Polymorphisms of the HLA will impact susceptibility to HIV infection, disease progression, and treatment. This review aims at giving an overview on the role of HLA gene polymorphisms on HIV acquisition, rate of disease progression, and treatment outcomes. Understanding the HIV epitope-HLA complexes during infection might provide insight into the design of multi-epitope HIV vaccine for different populations.

Keywords: HIV, HLA, HIV susceptibility, transmission, disease progression

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Introduction

The course of human immunodeficiency virus (HIV) infection varies among individuals, and is thought to be controlled by highly heterogeneous host factors, immunologic responses, and viral pathogenic factors.[1,2] Disease susceptibility, progression to clinical disease, and treatment outcomes are driven by host-virus genetics together with environmental factors. In practice, HIV infection is monitored by analyzing changes in $CD4^+$ T lymphocytes and plasma HIV RNA concentrations (viral load) together with clinical symptoms. Host genetic factors that determine these changes are often less well understood.[3,4] The evolution of both the host and the virus genomes provide a driving force for the selection of favorable or deleterious factors. The human genome is littered with remnants of retroviral genes from previous exposure and about 8% of the human sequence is derived from these remnants.[5] The presence of these remnants has revolutionized human immune responses to retroviruses, partly through development of new genetic loci critical for immune functioning.[6] Prior to the antiretroviral drugs era, control of HIV infection was solely based on host immune responses to control replication. However there is high genetic diversity in the proteins shaping the immune responses, an avenue needing exploitation in the development of potent HIV vaccines.[7]

The major histocompatibility complex (MHC), a large genetic complex with multiple loci, is located on the short arm of chromosome 6. It has highly polymorphic human leucocyte antigen (HLA) genes. Loci within the MHC encode two major classes of membrane bound glycoproteins: class I and class II HLA molecules. HLA class I molecules bind to endogenous antigenic epitopes and present them to $CD8^+$ T lymphocytes, while HLA class II molecules present antigenic peptides to $CD4^+$ T lymphocytes. The polymorphic nature of HLA genes allows the presentation of a wide range of peptides to the immune system, hence their influence on HIV disease recognition and/or progression. HLA gene polymorphism is highly linked to the rate of disease progression.[8] Cytotoxic T lymphocytes (CTLs) responses, key to the control of viral infections, are influenced by HLA presentation of antigens. $CD8^+$ CTLs have been shown to confer protection from viral infection through cytolysis and cytokine production. There are strong HIV-1 specific CTLs responses during the acute infection phase which are linked to control of viral replication, resulting in a decrease in viral load. Although some data bring into question the effectiveness of CTLs responses in the curtailment of viral replication during chronic HIV-1 infection,[9] CTLs are considered to represent an important arm of protective immunity in the early stage of infection. Indeed, maintenance of CTLs throughout the asymptomatic phase of HIV-1 infection has been directly visualized using peptide/MHC tetrameric complexes.[10–12] Individuals persistently exposed, but uninfected, are thought to mount protective CTLs responses.[13] HLA restricted viral escape of CTLs is based on mutations on or around the immunogenic epitopes (processed viral antigens presented by HLA class I alleles). It is possible to predict the CTLs escape based on the host HLA profile,[14] that is correlation between HLA alleles and HIV polymorphisms are used to identify sites of immune selection on the viral genome and pathways of escape.[15] This review aims to discuss the role of HLA gene polymorphism in HIV-1 susceptibility, transmission, disease progression, and treatment outcomes.

HIV Susceptibility and Transmission

Advances in molecular techniques have allowed the elucidation of HIV susceptibility gene loci.[16] Carrington et al showed that heterozygosity of the HLA class I loci (HLA A, B and C) was associated with slow HIV disease progression whilst homozygosity was associated with slower disease progression.[17] This can be attributed to the fact that heterozygosity allows a diverse number of viral antigens to be presented to effector cells and hence allowing a higher chance of controlling HIV replication. Sharing of HLA alleles between or among individuals influences HIV-1 transmission amongst these people.[16,18] Dorak et al used cohabiting Zambian heterosexual couples to show that HLA B allele sharing amongst these couples was independent of intracouple transmissibility of HIV-1.[18] There is a high chance of HIV-1 transmission between HLA concordant virus donor and recipient. The mechanisms of immune evasion in these individuals are generally similar, when taking into consideration the high genetic diversity of the virus itself.[16,19] In mother to child HIV-1 transmission, the virus easily adapts in the

new host if the mother-infant pair is haploidentical. The infected mothers may transmit the virus to their infants in utero, intrapartum, or postpartum, through breastfeeding.[20,21] Free floating HIV particles and HIV-infected cells from the mother display maternal MHC and hence activate fetal/newborn anti-MHC antibodies or alloreactive T cell responses. There is an increased risk of intrauterine, intrapartum, or early breast milk HIV transmission if there is concordance in HLA class I between the mother and child. The relative HIV protection associated with HLA discordance in mother-infant pairs can be attributed to allogeneic immune responses.[22] A study by Goulder et al reported that HLA B*27$^+$ infants born to HLA B*27$^+$ mothers were not clinically fit despite the protective role of the HLA genotype.[23] In this study, children who inherited the B*27$^+$ allele from their father were slow progressors. The discrepancy was attributed to infection by mutated virus strains, ascertaining the collective role of host-pathogen molecular genetics in fashioning HIV transmission.[23] Schneidewind et al found that HLA B*57$^+$ infants born to B*57$^+$ mothers controlled viremia, whilst B*57$^-$ infants born to B*57$^+$ mothers rapidly progressed to clinical AIDS.[24] This suggests that the B*57 gene variant controls HIV fitness, not CTLs advantage. HLA footprints can be traced in viral genomes, and may be useful in predicting viral immune evasion.[16,24]

HLA gene variants in patients with autoimmune diseases have also been linked to control of HIV infection. Chen et al described the association of HLA gene variants in psoriasis (a common autoimmune disease) patients and HIV control compared to healthy individuals. HLA B*27 and HLA B*57 were the most dominant gene variants seen in psoriasis patients[25] and are known to play a protective role against HIV acquisition. The presence of HIV protective HLA gene variants in Chen et al's study was unique to psoriasis as compared to other autoimmune conditions such as Crohn's disease, rheumatoid disease, coronary heart disease, and diabetes (both types I and II). Results from this study were suggestive of activation of antiviral immunity as a result of excessive skin inflammation (psoriasis).[25] It is important to note that results from Chen et al's study suggest that the association of HLA gene variants in psoriasis and HIV control may be attributed to linkage disequilibrium rather than structural similarities of HLA molecules. The fact that there is shared amino acid homology between psoriasis and HIV antigens that bind to the HLA B groove cannot be ascertained.[25,26]

Most HIV transmission is through the mucosal epithelium. Thibodeau et al reported no association between soluble HLA G (sHLA G), a non-classical HLA class I molecule, and an increased risk of HIV transmission in commercial sex workers in Benin. The presence of sHLA G in genital mucosa was also not associated with bacterial vaginosis in this study.[27] Non-classical HLA I molecules (HLA E*0103 and HLA G*0105) have a potentially low affinity for inhibitory natural killer (NK) cell receptors associated with a low risk of HIV acquisition. These rare alleles have been shown to have both an independent and synergistic effect on HIV susceptibility and acquisition in a Zimbabwean population.[28] HLA G has been shown to inhibit NK cells and CD8 CTL function[29–33] and CD4 proliferation.[34] This non classical HLA molecule is associated with heterosexual transmission of HIV.[27] A recent study in ART naïve Kenyan women, showed less likelihood of perinatal HIV transmission in HLA G*01:03$^+$ mothers compared to those with HLA G*01:03$^-$ genotype. There was no association between transmission rate and mother-child HLA G concordance in this study.[35]

HLA class II molecules influence virus specific CD4 responses and HIV-specific CD8 CTL.[36,37] There is limited information as to how class II HLA molecules influence susceptibility and transmission of HIV. HLA DR1*01 was associated with protection to HIV infection in high risk population (commercial sex workers) in Kenya. This allele is associated with efficient viral antigen presentation to CD4 T lymphocytes, which target HIV p24 leading to decreased virus load.[22]

Rare HLA alleles may confer selective advantage to individuals, coupled with control of viral replication. The virus is forced to evolve to these rare alleles thereby compromising viral fitness. It is important to note that HIV escape mutants correlate with the prevalence of restrictive HLA alleles[38] and hence the virus adapts to these alleles over time, especially in populations with high frequencies of these restrictive alleles. The protective role of HLA B*57 and B*27 may decline with time as HIV adapts to these alleles.[16] Generally, there might be hope in using the anti-HLA vaccine strategy against HIV in reducing virus transmission.

Disease Progression

HIV disease progression is clinically monitored as a change in $CD4^+$ T lymphocyte counts and viral load with time, clinical symptom manifestation, and appearance of opportunistic infection or neoplasm among HIV-infected individuals. In resource rich countries, plasma viral load and $CD4^+$ T lymphocyte counts are routinely measured during clinical follow-up and are thus widely available for large numbers of patients. These markers have been shown to be independent predictors of HIV disease progression to severe immunodeficiency. Viral set point is determined by the equilibrium between HIV-1 replication and host immune responses[39] and is an indicator of disease progression.[40] For analysis, $\log_{10}$ copies per mL are used instead of absolute values as the fluctuations with time are not clinically significant. HLA A and HLA B present viral epitopes to T lymphocytes, which may lead to control of viral replication. HLA C on the other hand can present viral epitopes as well as bind self-peptides and interact with NK cells. Since HIV Nef down regulates HLA A and B expression but not HLA C, it is possible that HLA C forms the basis of HIV control.[14,41,42] Rajapaska et al showed better HIV control by HLA B restricted CTLs as compared to HLA A restricted CTLs. This same study showed high interferon gamma (IFNγ) responses in HLA B restricted CTL clones in comparison to HLA A clones, supporting the polyfunctionality of HLA B CTLs.[43] Variation amongst individuals in the viral set point is approximately 4–5 $\log_{10}$ copies per mL. Single nucleotide polymorphisms (SNPs) on the HLA B and C loci were identified to have an independent effect on variation in the viral set point amongst individuals.[44] Fellay et al identified a 9.6% and 6.5% variation in total viral set point being contributed by SNPs on HLA B and C loci, respectively. They also attributed 5.8% of total variation to a gene coding for RNA polymerase 1 subunit upstream of MHC.

With advances in molecular biology, host factors that contribute to HIV viral load and disease progression have been determined at the genomic level.[44] Silva et al noted an association between HLA Bw4-HLA B*57 and HLA Cw*18 with low HIV viral load in Brazilian patients.[45] A related study by Lazaryan et al demonstrated an association of low virus load and the presence of Cw*18 allele regardless of the presence or absence of the protective B*5703 allele in a Zambian subtype C HIV infected cohort.[46] HLA Bw4 and HLA C are ligands for NK cell receptors (KIRs) that stimulate cytotoxic activity of these effector cells. The B*5703 allele is associated with low viremia and selection of multiple HIV escape mutations. Mutations in this allele are associated with a decreased replicative capacity of HIV.[47,48] However, patients with this allele still progress to clinical AIDS suggesting that an impaired replicative capacity due to B*5703 is not enough to confer long term protection.[47,48] In a related study, Yager et al showed that HLA B*5101 restricted LI9 (an epitope in the N terminal of the HIV integrase which strong binds to HLA B*5101) variants evade CTL recognition. Although the HLA B*5101 selects for a number of LI9 variants that escape the CTL, there is a reduced replication capacity of these viruses.[49]

A minor amino acid difference in HLA-peptide recognition region might have a major impact on epitope recognition and control of HIV replication. Ngumbela et al showed that patients with B*5802 had higher virus load and lower $CD4^+$ counts when this allele contributed to overall $CD8^+$ responses in comparison to those patients with the B*5801. These two HLA alleles only differ by three amino acid residues.[50] Klϕverpris et al demonstrated a better control of HIV by HLA B*4201 individuals (measured by viral load) when compared to HLA B*4202 individuals in a HIV subtype C infected population.[51] These two genotypes only differ by one amino acid (Tyr in HLA B*4201 and His in HLA B*4202). This study had minimal confounding effect of other HLA alleles since both HLA B*4201 and HLA B*4202 are in strong linkage disequilibrium with the same HLA A and C alleles.[51] In a related study, Grifoni et al showed that the Val polymorphism in position 194 of the α-3 domain (outside of the peptide binding domain) of HLA B locus was associated with long term non progression of HIV. This single amino acid polymorphism was shown not to be in linkage disequilibrium with HLA Bw4/6, suggesting an independent protective role.[52]

Feeney et al[53] and Oxenius et al[54] reported an association between selection of escape mutants and inability to control HIV virus load together with disease progression. It is important to note, however, that this observed association does not cut across all the known HIV epitopes.[55,56] Two study findings by Moore et al[57] and Brumme et al[58] suggest that HLA

associated polymorphisms interacting with the HIV reverse transcriptase predicted high levels of plasma virus load. These two studies contradict the results by Iversen et al that suggested higher virus load in patients with efficient CTL selection.[55] It should be noted, though, that Iversen's study investigated escape to a single HLA restricted epitope when compared to the other studies that looked at HLA associated polymorphisms to several HIV epitopes.[55,57,58]

Several HLA class I alleles have been associated with HIV disease progression. HLA alleles linked to slow disease progression are: HLA A*02,[22,59] HLA A*11,[60] HLA B*27,[59,61–63] HLA B*51,[61,64,65] and HLA B*57.[61,66] Alleles associated with rapid disease progression include; HLA A*24,[59] HLA B*40,[60] HLA B*35, and HLA B*53.[67,68]

HLA B*57 and B*27 have been shown to be protective in Caucasians[69,70] whilst B85801 and B*8101 have been reported to protect subtype C HIV infected South African patients.[41] HLA G, a non-classical HLA molecule, has also been associated with HIV disease progression in ART naïve population.[71] In a recent study, Larsen et al showed that HLA G rs16375, a 14 base pair polymorphism, was associated with high viral load, low CD4, and increased mortality in a four year follow up study in a Zimbabwean cohort.[71]

Although the exact mechanisms are poorly known, the interplay of HLA class I imposed selection pressure escape mutants and viral fitness might contribute to the rate of disease progression.[72] Late stage HIV infection is characterized by low $CD4^+$, with $CD8^+$ T cells exhibiting less avidity, less polyfunctionality, and very minimal differentiation,[72,73] Interestingly, $CD8^+$ CTL predominantly target the genetically diverse *env,* instead of the *gag* region, during late clinical stages of AIDS. Reversion of mutant viral strains to wild type in late stages of HIV infection might explain the restoration of viral fitness coupled with elevated viremia.[72,74]

Heterozygosity of the HLA loci offers advantage in delaying disease progression. Homozygosity was linked to more rapid disease progression in both Caucasians and Afro-Americans.[17] HLA B locus homozygosity was strongly associated with disease progression in Dutch men who have sex with men and Rwandan patients, with no strong association with HLA C locus.[69,75] It is logical to attribute the protective role of heterozygosity of HLA loci to an enhanced ability to present several HIV epitopes to effector cells. Ignoring the high mutational rate of HIV-1, heterozygosity might contribute in the delay of escape mutants during the course of infection.

Most individuals with documented protective HLA alleles still progress to clinical AIDS.[76,77] A recent study compared $CD8^+$ T cell responses to immunodominant HIV epitopes in treatment naïve elite controllers and chronic progressors.[76] This study only included wild type sequences to assess T cell responses to limit the confounding effect of viral mutation to specific epitopes. In this study, $CD8^+$ responses of elite controllers were found to be more efficient in inhibiting viral replication compared to those of chronic progressors. However, these observations were augmented by the ability of dominant T cell receptor (TCR) clonotypes in up-regulating perforins and granzyme B molecules responsible for cell lysis. Results from this recent study suggest a link between antiviral efficacy, shown by protective HLA alleles and $CD8^+$ T cell clonotypes selected during the course of HIV infection.[76] Despite the small sample size of 5 controller and 5 progressors, this study indicates that TCR rearrangement drives the protective role of HLA alleles and influences disease progression.[76]

Treatment Outcomes

With the advent of combination antiretroviral therapy (cART), mortality for many has been reduced and the lives of many HIV infected patients have been prolonged.[78] However, prolonged survival may be associated with drug resistance[79] and adverse drug reactions (ADRs).[80] Host immunogenetic factors (including HLA polymorphisms) and other genetic variations may directly or indirectly influence response to cART and development of ADRs. The cART associated ADRs have varying severity, frequency, and clinical symptoms attributed to the different antiretrovirals in the regimen.[80] A few studies, involving predominantly subtype B HIV infected individuals, have reported an association of abacavir (ABC) hypersensitivity syndrome with HLA-B57*01.[16,81,82] Hypersensitivity is a result of modulation of specific B*5701 restricted $CD8^+$ T cell responses,[83] with the ABC recognition site within the 'pocket F' of B85701 binding region. A study by Ahuja et al, which evaluated the association of genetic variation and HLA alleles with sensitivity to cART

in two United States of America cohorts (predominantly subtype B HIV infected patients), reported that CCL31-CCR5 genetic risk status, but not HLA-B*57, is apparently a good predictor of the recovery rate of $CD4^+$ T lymphocytes during cART.[84] Other HLA alleles associated with treatment outcomes of HIV infection include DRB1*0101 and Cw*8 associated with nevirapine hypersensitivity.[85]

Concluding Remarks

Advances in molecular biology enable the understanding of the genetic basis of variability in HIV susceptibility, transmission, disease progression, and treatment outcomes. This field requires additional research that is integrated with the highly variable HIV genome. The studies on the interplay of host-pathogen genetics which have largely been focused on subtype B HIV infection should be further explored to understand the role of HLA polymorphisms in subtype C HIV-1 (responsible for the majority of HIV infections globally) susceptibility, transmission, and treatment outcomes. Identification of viral epitope-HLA complexes associated with disease progression may be useful as a basis for formulating a multi-epitope vaccine for HIV. Stable epitope-HLA complexes are associated with an increased immunogenicity coupled with virus control.[86–88] It is thus critical to elucidate the host-pathogen molecular interaction with the view of protective immunity in all major ethnic and distinguished populations to concert the HIV vaccine initiative.

Author Contributions

Conceived and designed the experiments: MT, GDM. Analyzed the data: MT, GDM, LSZ. Wrote the first draft of the manuscript: MT. Contributed to the writing of the manuscript: GDM, LSZ. Agree with manuscript results and conclusions: MT, GDM, LSZ. Jointly developed the structure and arguments for the paper: MT, GDM, LSZ. Made critical revisions and approved final version: GDM, LSZ. All authors reviewed and approved of the final manuscript.

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Competing Interests

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