Genetic basis of HIV-1 resistance and susceptibility: An approach to understand correlation between human genes and HIV-1 infection

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HIV infection is the serious medical and public health issue of present generation. By 2005, it has already infected a cumulative total of more than sixty million people worldwide and the number of HIV positive cases are rising day by day. India is currently estimated to have about 5.1 million infected persons with HIV-1 or AIDS (second only to South Africa) and this number could increase to 24 million in the next ten years. This pandemic situation of the AIDS stimulated a plethora of longitudinal cohort studies which are designed to document medical heterogeneity as well as to mitigate the factors that regulate the HIV-1 infection, disease progression and the immune defenses. In recent years these genetic studies have led to the discovery of various MHC and non MHC encoded genes, which directly or indirectly influence the susceptibility and resistance to HIV infection and AIDS.

These genes and their mutated forms and their products which play a major role in determining the susceptibility or resistance to HIV-1 infection and AIDS. These genes have been categorized into MHC or non MHC encoded genes. The MHC encoded genes which determine HIV resistance or susceptibility are HLA-B57, HLA-B58, HLA-B27, HLA-Bw4 and HLA-A11 in Southeast Asians. On the other hand, non MHC encoded genes are CCR5, CCR2, RANTES, CXCL12, CXCR6, CCL3L1, Interleukin-10 (IL-10), and interferon gamma. The site specific mutations in these genes determine the susceptibility or resistance to HIV-1 infection and AIDS. In future the study of host genes in relation to HIV-1 infection may provide the researchers to develop newer chemotherapeutic approaches to prevent or cure HIV-1 infection effectively.

Keywords: AIDS, HIV-1, HLA, MHC

The HIV infection has become prevalent world wide and is clearly the defining medical and public health issue of our generation ranks among the greatest infectious disease scourage in history¹. Since its discovery² ³ in 1981, the disease has progressively spread to various regions of the world. According to WHO December 2005 report, a total of more than 40.3 million people are living with HIV-1 infection and about 3.1 million people died due to HIV-1 infection in 2005 (Ref. 4). HIV and AIDS continue to have an enormous toll throughout the world, notably in sub-saharian Africa, and their incidence is increasing in some countries and regions, including China, India and parts of eastern Europe and Central Asia⁴.

It is estimated that about 40.3 million individuals are living globally with HIV or AIDS (WHO report, Dec.2005) and over 90% of them live in the developing world⁵. AIDS increasingly has a woman face; almost 60% of infected individuals with HIV-1 are women⁶. India is currently estimated to have 5.1 million infected persons with HIV-1 or AIDS (second only to South Africa), and this number could rise to 24 million in the next ten years⁷.

This pandemic situation of AIDS has stimulated a plethora of longitudinal cohort studies designed to document medical heterogeneity as well as to mitigate the factors that regulate HIV-1 infection, disease progression, and immune defences⁸. Recently, genetic association studies have enrolled AIDS cohorts to identify a dozen of AIDS restriction genes (ARGs).

Abbreviations
HIV-1–Human immunodeficiency virus-1; AIDS–Acquired immunodeficiency syndrome; ARG–AIDS Restriction gene; CCR5–Chemokine receptor 5; CCR2-V641–Chemokine receptor-2 variant 641; RANTES (CL5) –Regulated on activation normal T-cell expressed and secreted; CXCL12–Chemokine ligand 12; IL-10–Interleukine-10; IFNγ–Interferon γ; TNF-α–Tumor necrosis Factor-alpha; KIR–Killer immunolobulin like receptor; CTL–Cytotoxic T-Lymphocyte; Leu–Leucine, Met-Methionine; Val-Valine; KIR2–NK-killer inhibitor receptor; HEPS–Highly exposed to HIV-1 but remains persistently seronegative; and CCL3L1–Chemokine ligand 3 like-1.
Polymorphic human loci whose allele impact on the susceptibility and resistance of people to HIV-1 infection.

**AIDS restriction genes (ARGs)**

In the early 1980s, genetists at US National Cancer Institute initiated a program to search for AIDS restriction genes (ARGs; human genes with polymorphic variants that influence the outcome of HIV-1 exposure or infection)⁹⁻¹⁴. There are many rationales for identification of ARGs i.e., (i) Determining the effects ARGs in individuals with AIDS would connect laboratory-identified host factors to AIDS pathogenesis, particularly when a plausible functional or physiological mechanism has been found; (ii) The powerful antiretroviral therapy is not universally effective and also is not a true cure, genetic retardation of AIDS progression could implicate new cellular targets for anti-AIDS therapy that complement the currently available antiretroviral drugs¹⁵; and (iii) Ongoing clinical trials for new vaccines and anti AIDS drugs, like longitudinal cohort studies, show that these drugs elicit heterogenous responses from people with AIDS¹⁶. In some cases this heterogeneity may be attributable to the distribution of the ARG genotypes in the study population, a quantitative ARG score, a genetic propensity index (GPI) for individuals could be used to adjust (or subtract) the genetic noise in clinical trials based on each participant’s ARG genotype would be useful¹⁷.

Till date up to 15 ARGs have been identified, whose genetic influences differ in several ways, including mode of inheritance (dominant, recessive, co-dominant etc.), stage at which they act (infection, AIDS progression, the type of AIDS-defining pathogenic disease) and the interval of HIV-1 progression during which the influence is apparent. ARGs are polygenic or multifactorial (i.e. they must interact with environmental factors, such as HIV-1 exposure in order to be detected).

**Mode of action of ARGs**

CCR5Δ32 is a naturally occurring knockout deletion (2bp) variant, homozygote resistant to R5-HIV-1 infection (the principal infecting HIV-1 strain) lack the requisite HIV-1 entry co-receptor CCR5 on the lymphoid cells¹⁸, ¹⁹. CCR5Δ32 heterozygotes, whereas, express less than half the wild type levels of CCR5 receptor, which slows down HIV-1 replication, spread and pathogenesis²⁰,²¹. However, CCR5Δ32 deletion evolved in response to selection by pathogens other than HIV-1. CCR5Δ32 arose during the middle ages and bubonic plague and the smallpox era²²,²³. Whereas, the CCR5P1 allele which is a composite haplotype comprising 13 distinct SNP alleles in the upstream promoter region of the CCR5, confers recessive more rapid progression to AIDS²⁴,²⁵. Analysis of CCR5 promoter allele found no quantitative differences in luciferase transcription, HIV-1 binding or HIV-1 infectivity, although the alleles influence CCR5 abundance on lymphoid cells²⁶,²⁷.

CCR2-V641 variants mediate delay in AIDS progression indirectly, as it causes no allele specific quantitative differences in the amount of CCR2 produced, in the amount of alternative allelic products to bind HIV-1 or in signal transduction with CCR2 specific ligands²⁸,²⁹. One report has indicated that CCR2- 641 protein can preferentially dimerize with CXCR4 polypeptides (the HIV-1 coreceptor that replaces CCR5 as an entry receptor at later stages) whereas wild type CCR2 peptide do not³⁰. It is not confirmed, but this mechanism suggests that CCR2- V641 delays AIDS by limiting the transition from CCR5 to CXCR4 in infected individuals⁸.

**RANTES (CCL5)—**RANTES is a principal chemokine ligand for CCR5. Increased RANTES or CCL5 levels have been found in HIV-1 exposed people who do not develop AIDS and in individuals infected with HIV-1 who have late onset of AIDS³¹,³². One of the seven SNP variants found in CCL5 (encoding RANTES), In1.1c, is nested in an intronic regulatory sequence element that has differential allele affinity to nuclear binding proteins and whose transcription is down regulated by a factor of 4 (Ref. 33). A reduction in RANTES production in individuals carrying this allele leads to rapid AIDS progression, ostensibly by uncovering available CCR5 that facilitates the replication and spread of HIV-1.

**CXCL12 3’A—**The CXCL12 3’A variant is a G→A transition in the 3’ untranslated region of one of two alternatively spliced transcripts of CXCL12 (also called SDF1)³⁴. Stromal derived factor is the primary ligand for the late stage HIV-1 receptor CXCR1, and 3’A variant is 37bp downstream of two blocks whose sequence are 88 and 92% conserved, respectively in mouse and human transcripts³⁴,³⁵. The delay in onset of AIDS observed in CXCL12 3’A homozygous might result from over production of
SDF1 in certain tissue compartments postponing the CCR5-CXCR4 transition. A synergistic protective effect in individuals carrying CXCL12 3’A and CCR2V-641 would be consistent with this model.

CXCR6E3K—CXCR6E3K is associated with late state progression in individuals with AIDS and pneumocystis carinii pneumonia. One CCL2-CCL7-CCL11 haplotype, H7, which includes SNP variants in 31-kb region is associated with resistance to HIV-1 infection, based on comparison of highly exposed uninfected individuals with exposed infected individuals.

CCL3L1 and duplicated host defense genes
CCL3L1 duplicated host defense genes might have dosage effects that could contribute to the genetic susceptibility or AIDS pathogenesis. There is one hot spot for segmental duplication on human chromosome 17q, comprising the β-chemokine genes CC chemokine ligand 3-like 1 (CCL3L1) and CCL4L. CCL3L1 (also known as LD78β) is one of the isoforms of MIP-L alpha and the other is CCL3 (LD78α). One consequence of the duplication of CCL3 and CCL4 has been variation in the copy number of CCL3L1 and CCL4L1 among individuals. CCL3L1 is high affinity ligand for CCR5, in addition to other HIV-1 co-receptors like CCR3 and CCR1, and is the most potent natural chemokine inhibitor of HIV-1 binding and entry through CCR5R binding of gp-120. CCL3L1 is the highest affinity chemokine ligand for CCR5 and the best inhibitory chemokine of HIV-1 entry. CCL3L1 also affect CCR5 expression. There is an inverse relationship between CCL3L1 copy no. and CCR5 expression by T-cells, at least in vitro, suggesting that CCR5 signaling in response to copious CCL3L1 causes receptor internalization. Thus, this downregulation of CCR5 on T-cell may also play a role in HIV infection resistant.

IL-10 and IFNγ; AIDS resistance genes
The two other AIDS resistance genes are interleukin10 (IL-10) and interferon gamma (IFNγ) which encode the two powerful cytokines IL-10 and IFNγ that inhibit HIV-1 replication. The IL-10 5′A SNP variant involves a promoter region alteration that reduces IL-10 transcription by a factor of 2-4 (ref.43). The individuals which are heterozygous or homozygous to IL10 5′A allele are fast progressors of HIV-1 infection as compared to individuals not having this allele. This is probably because these individuals have decreased inhibitory action of IL-10 cytokine. IFNγ has a polymorphic promoter region, one allele of which (-179T) is inducible by tumor necrosis factor (TNF-α), whereas the wild-type allele (-179G) is not. In African Americans, among whom the IFNG-179T allele has 4% frequency (<1% in European Americans), individuals infected with HIV-1 who are heterozygous with respect to IFNγ-179T progress to AIDS more rapidly than IFNγ-179G/G homozygous, indicating that allele-specific inducibility confers a risk of rapid AIDS progression (Table 1).
Beside these non MHC AIDS restriction genes various laboratories have identified many MHC genes which play an important role in the resistance or susceptibility of an individual to HIV-1 infection.

Phylogenetic analysis of HIV-1 diversity has defined a main or M group of viruses, comprising a variety of subtypes or clades (A, B, C, D, F1, F2, G, H, J and K), all of which circulate in the African population. HIV-1 subtype B has also spread extensively into the Caucasoid populations of Europe, the Americas and the Antipodes, as well as some oriental population in far East. By contrast, HIV-1 subtype C predominates in South Asia whereas, inter subtype (B and C, or B/C) circulating recombinant forms (CRFO1 and AE) are largely responsible for the current AIDS epidemic in the population of mainland Southeast Asia.

**MHC polymorphism and AIDS resistance/susceptibility**

MHC contains two clusters loci encoding cell surface molecules that have a crucial role in initiating adaptive immune responses. In humans, these loci are designated as HLA-A, -B,-C,-F,-G (class1MHC) and DP, DQ, DR (class II MHC) and they encode molecules with peptide binding sites. CD8+ cytotoxic T cells recognize MHC-1 molecules with pathogen-derived peptides as foreign and result in the lysis of the infected cells. Some viruses try to evade the immune recognition by interfering with MHC-1 transcription and expression pathway. For example, HIV-1 Nef protein selectively downregulates cell surface expression of HLA-A and HLA-B molecules, whereas expression of HLA-C and –E molecules important for NK-cell recognition, is not significantly affected.

MHC of different primate species share many highly related loci. Distinct MHC alotypes select different peptides for activation of an immune response, and as a consequence particular MHC molecules can be associated with either susceptibility or resistance in contracting disease. Consistent with

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**Table 1** — Summaries non MHC encoded AIDS restriction genes (ARGS), chromosomal location, mode of inheritance and their effect on HIV-1 infection

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alleles</th>
<th>Chromosome no.</th>
<th>Inheritance mode</th>
<th>Effect</th>
<th>Mode of action</th>
<th>Mode of action</th>
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<tr>
<td>CCR5</td>
<td>Δ32</td>
<td>3p21.31</td>
<td>DOM</td>
<td>Delays onset of AIDS</td>
<td>↓ Availability of CCR5</td>
<td></td>
</tr>
<tr>
<td>CCR5</td>
<td>P1</td>
<td>3p21.31</td>
<td>REC</td>
<td>Accelerates AIDS in early infection</td>
<td>↑ CCR5 Expression</td>
<td></td>
</tr>
<tr>
<td>CCR2</td>
<td>641</td>
<td>3p21.31</td>
<td>DOM</td>
<td>Delays AIDS</td>
<td></td>
<td>Interacts with CXCR4 and reduces free CXCR4 for virus binding</td>
</tr>
<tr>
<td>CCL5 (RANTES)</td>
<td>In1.1c</td>
<td>17q</td>
<td>DOM</td>
<td>Accelerates AIDS</td>
<td>↓ RANTES Expression</td>
<td></td>
</tr>
<tr>
<td>CXCL12 (SDF1)</td>
<td>3’A</td>
<td>10q11.1,</td>
<td>REC</td>
<td>Delays AIDS by acting late in AIDS progression</td>
<td>Impede CCR5-CXCR4 transition</td>
<td></td>
</tr>
<tr>
<td>CXCR6</td>
<td>E3K</td>
<td>3p21.31</td>
<td>DOM</td>
<td>Accelerate PCP(L) Pneumocystis carinii) pneumonia</td>
<td>Alter T-cell activation</td>
<td></td>
</tr>
<tr>
<td>CCL2(mcp1)</td>
<td>H7</td>
<td>17q11.2</td>
<td>DOM</td>
<td>Enhance Infection</td>
<td>Stimulate Immune Response</td>
<td></td>
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<tr>
<td>CCL7(mcp3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL11(eotaxin)</td>
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<td></td>
</tr>
<tr>
<td>CX3CR1</td>
<td></td>
<td>3p21.33</td>
<td>Homozygous variation</td>
<td>Rapid Progression of AIDS</td>
<td>Compromised Recruitment of antiviral cytotoxic CD8+T cells.</td>
<td></td>
</tr>
<tr>
<td>IL10</td>
<td>5’A</td>
<td>1</td>
<td>DOM</td>
<td>Limit infection</td>
<td>↓IL10 Expression</td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>179T</td>
<td>12q.241</td>
<td>DOM</td>
<td>Accelerated AIDS in early infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIR3DS1</td>
<td>3DS1</td>
<td>12</td>
<td>Epistatic with HLA –Bw4</td>
<td>Delays AIDS</td>
<td></td>
<td>Clear HIV-1 Positive HLA-Cells</td>
</tr>
</tbody>
</table>
these observations, HLA heterozygosity might represent a selective advantage in infectious diseases, like AIDS. A benefit of MHC polymorphism is that individual variation reduces the chance that a particular pathogen can exterminate an entire population.

Human HLA class I molecules are highly polymorphic and are center of many recent studies in different laboratories involved in identifying the factors involved in resistance or susceptibility to HIV and AIDS. Extensive HLA class I and class II allelic variation occurs both within and between different ethnic groups. Similarly, linkage disequilibrium between HLA loci has generated stable combinations of HLA I and II alleles or haplotypes, which also vary in composition and frequency between ethnic groups.

Polymorphism generates structural changes in a series of pockets in HLA class I extra cellular protein domains, which accommodate certain amino acid residues of antigenic peptides. This affects the biological function of HLA class I molecules to bind and present microbial peptides to the antigen-specific receptors of CD8+ T cells. Nevertheless, there is evidence for groups of HLA-A and HLA-B class I alleles called ‘Supertypes’ that share specific binding preferences for short antigenic peptides or supermotifs with a similar size, charge and amino acid composition. These alleles share a preference for antigen supermotifs with small aliphatic residues (A, S, T) in position 2, and aromatic (F, W, Y) or hydrophobic (U,V) residues at the C-terminus of their peptide ligands. The B58 supertype alleles have combined phenotypic frequency of some 10-25% in Caucasoid, Africans and Oriental populations. The carriers of HLA-B57 allele have relatively slow HIV-1 disease progression. In these persons, immune responses restricted by HLA-B57 consistently exceed the magnitude of immune responses restricted by the five remaining HLA alleles together. The acute HIV-1 infection syndrome in these HLA-B57-positive individuals is relatively mild and most individuals are able to control viral replication at low levels without antiretroviral therapy for several years of follow up, although the spontaneous clearance of virus is never observed. These data suggest that certain HLA class I alleles, such as HLA-B57, which are associated with slow HIV infection progression, can restrict immunodominant CD8+ T cell epitopes in acute infection and by this mechanism might enable a rapid control of viral replication.

Role of various HLAs in HIV-1 infection

The most reproducible HLA class I association with low HIV-1 viraemia and prolonged AIDS survival has been observed with HLA-B57 and related alleles. These associations are likely to be with the HLA-B57 allele per se and not secondary to linked allele, as Caucasoid and Africans vary in composition of their HLA-B57-containing haplotypes. At the molecular level, there are 9 allelic variants of HLA-B57 (B*5701-9). Nearly all HLA-B57 alleles are characterized by a unique valine at position 97, which contributes to the formation of the C-pocket of the class I antigen binding cleft. In Caucasoid, HLA-B57 forms a stable haplotype with the allelic products of at least 3 other class II gene loci, DRB1* 0701, DRB1*0301N, and DQB1*030258. DRB4*0301N is defective class II gene allele with complete abrogation of gene product (DR53 null) expression. HLA-B57 also belongs to the B58 supertypes structurally and functionally related alleles (B*57, B*58, B*1516 and B*1517)59. These alleles share a preference for antigen supermotifs with small aliphatic residues (A, S, T) in position 2, and aromatic (F, W, Y) or hydrophobic (U,V) residues at the C-terminus of their peptide ligands. The B58 supertype alleles have combined phenotypic frequency of some 10-25% in Caucasoid, Africans and Oriental populations. The carriers of HLA-B57 allele have relatively slow HIV-1 disease progression. In these persons, immune responses restricted by HLA-B57 consistently exceed the magnitude of immune responses restricted by the five remaining HLA alleles together. The acute HIV-1 infection syndrome in these HLA-B57-positive individuals is relatively mild and most individuals are able to control viral replication at low levels without antiretroviral therapy for several years of follow up, although the spontaneous clearance of virus is never observed. These data suggest that certain HLA class I alleles, such as HLA-B57, which are associated with slow HIV infection progression, can restrict immunodominant CD8+ T cell epitopes in acute infection and by this mechanism might enable a rapid control of viral replication.

HIV-1 subtype B and C cross clade, CD8 reactivity, restricted by B5701 in Caucasoid and by B*5703 in Africans, has been described for a variety of conserved immunodominant epitopes. Mutation at specific position of certain HIV-1 gag-encoded peptides occur uniquely and frequently in HLA-B57+ and B58+ patients, infected with either HIV-1 Clades B or C. The gradual accumulation of mutations within an immunodominant HIV-1 gag peptide designated TW10(TSTQE-QIAW, residue240-249) can result in
functional loss of T-cell recognition, indicating that positive selection for these mutation is being driven by HLA-B57 or B58 restricted CTLs. Mutations specifically occur in residue 242 of the HIV-1 gag TW10 peptide. However, if mutant HIV-1 is transmitted to individuals not carrying the HLA-B57 or B58 alleles, the mutation at residue 242 reverts to wild type. Viral reversion to wild type in the absence of HLA-B57 or B58 mediated T-cell responses indicates a loss of fitness or replicative ability in some HIV-1 mutants. Thus, HIV-1 clade B-viruses could be partially attenuated in some HLA-B57 or B58 patients, which might account for their long term survival occurring with low level of viraemia even in the absence of CTL recognition of mutations.

But long term survival of HIV-1 infected patients carrying HLA-B57, have complication of receiving antiretroviral therapies. Hypersensitivity to certain RT-inhibitors has been associated with patients carrying the extended HLA haplotype, HLA-B57, DR7-DQ3, which is also likely to carry the defective null allele, DRB4*0301 MHC restriction of drug metabolites driving detrimental T-cell activation has been proposed as a possible explanation for this association.

**HLA-B27**—Like HLA-B-57, the HLA-B27 has been consistently associated with low viraemia and late onset of AIDS in HIV-1 clade B infected Caucasoid, but not in Africans. HLA-B27 is present in Caucasoid, African and Asian population, with observed alleles frequency as higher as 15%. There are numerous molecularly defined HLA-B27 related alleles (B*2701-25) out of which some HLA-B27 alleles are highly associated with spondenogative spondyloarthropathies, like ankylosing spondylitis, in different ethnic groups. HLA-B27 molecules also have some unique structural and functional features. For example, unusual alpha or heavy chain homodimers of HLA-B27 without β2 microglobulin have been identified. HLA-B27 can also act like an HLA class 2 molecule and present antigenic peptides to CD4+ T-cells.

HLA-B27 restricted CTL responses to immunodominant HIV-1 antigenic peptides have been carefully monitored during the course of infection in Caucasoid patients. With inevitable erring, HIV-1 mutant emerge, which escape HLA-B27 restricted CTL responses and correlated with disease progression. However, HIV-1 escape mutants emerging in HLA-B27 patients appears to be replication competent and rarely revert back to wild type in the presence of weaning or abrogated HLA–B27 driven CTL response.

Beside these above mentioned HLA molecules HLA–B7 subtype (B*0702-5, *1508,*3501-31,5101,5301,5401,5501-2,5602,6702,7801) is associated with high viraemia relatively poor CTL responses and fast progression to AIDS in Caucasoid and African-American infected predominantly with HIV-1 subtype B, but not in Africans infected with HIV subtype C. Alleles of the HLA-B7 super type are relatively common in most population. Some of the HLA-B7 supertype alleles (namely* 3502, 3503, 3804 and 5301) tend to engage permissibly with antigenic supermotifs with certain residues (Leu, Val, Met) at their C terminal associate with fast progression to AIDS. By contrast, other alleles of the HLA-B7 super types (B*3801, 2*3508) preferred to engage supereencies with just a tyrosine at the C’ terminal and do not associate with fast progression to AIDS.

**HLA-Bw4**—Recently, new reports on AIDS progression have discovered a group of people “homozygous” for the HLA-Bw4 molecular epitope (a seven amino acid motif in alpha-1 domain shared by about 40% of HLA-B allele plus several HLA-A alleles) of HLA class 1 alleles which delays the HIV-1 spread and AIDS pathogenesis. HLA–Bw4 epitope by epitopic association with NK-cell inhibitor receptor (KIR) known as KIR3DS1 acts as its ligand and blocks the inhibition of NK lysis, leading to increased NK lysis of infected cells contributing to slowing of virus spread and AIDS progression. Thus HLA class 1 molecule have pivotal role in range of immunological responses that control or influence HIV-viraemia.

**HIV-Nef and HLA-A11 in Southeast Asians**—HIV-1 Nef protein acts as an early infectivity factor and down regulates HLA expression on HIV-1 infected cells. CTL responses against HIV Nef are common and have been described in a group of ethnic Thais that have been described in highly exposed to HIV-1 but remain persistently seronegative (HEPS) and uninfected. In this group, an immunodominant HIV-1 Nef derived peptide (QVPLR, PMTYK, positions 73-82) stimulates in vitro HLA-A11 restricted CTL activity in HEPS individuals. The HIV-1 Nef 73-82 motif has an anchor site at positions 74 (val), 79 (met) and 82 (lys), which bind to the B, E and F pockets of A*1101. This interaction of HLA-A2 with Nef protein creates a “double hump” in the
bound peptide. This effect could have an impact on T-cell recognition and function.

Recent functional analysis of dominant CTL responses against HIV-1 in Caucasoid, Hispanic, African and American, Caribbean and Chinese population has confirmed an importance of this region in Nef, which might be relevant to the design of future vaccines.

Role of natural killer cell inhibitory receptors and HLA-As—The KIR-3DL2 gene locus is located on chromosome 12 and encodes an inhibitory NK receptor which only recognizes the HLA-A3 subtype of class 1 alleles, along with HLA-A11. Under normal conditions, if KIR-3DL2 receptor is engaged with HLA-A2 on the target cell, it transmits an inhibitory signal to NK cell and prevents the lysis of the target cell. But there are accumulating evidences which show that if HLA-A11 is loaded with viral peptides invites the inhibitory signal leads to NK lyses of target cells occur. The KIR-3DL2 gene locus is detected in all individuals including ethnic Thais, and is most polymorphic of the KIR receptor loci (Table 2).

At present, the biological relevance of NK KIR polymorphism is unclear, there are variations of KIR alleles frequencies between different ethnic groups, which might correlate with reported differences in NK activity in HIV-1 infected Caucasoid and Ethnic Thais or the enhanced NK activity in HIV-1 exposed but uninfected Vietnamese.

Allogenic priming, heterozygote advantage and other HLA association

HIV-1 can hijack infected cell protein including HLA molecules, and incorporate these host molecules into its viral envelope. Host reactivity to allogenic HLA molecule carried by HIV–1 responsible for the apparent resistance to horizontal and vertical transmission in some highly exposed Caucasoid and Africans. HIV-1 infected patients that are fully heterozygous for HLA class 1 alleles have a clear survival advantage against developing AIDS. This is due to increased diversity of immunodominant peptides presented to T-cells in these patients. Comparisons of dizygotic combination of HIV and AIDS (high risk; HLA-B7 supertype) and (low risk: HLA-B58 supertype) alleles profiles indicate that the patient with heterozygous combination of at risk supertype have intermediate HIV-1 viral loads.

The most common HLA class 1 alleles in HIV-1 exposed cohorts are reported to associate with a faster onset of AIDS and influence the diversity of the HIV-1 viruses circulating in Caucasoid population. By contrast, HLA alleles that are less common in Caucasoid might be advantageous in driving CTL response against HIV-1 epitopes that have been under enhanced immunological pressure. Similarly, transmission of HIV-1 is reduced in HLA-B discordant African heterosexual couples.

Conclusion

AIDS is the most serious medical as well as public health issue of our generation. Its epidemic spread has led to the intense research in the field of virology, immunology, vaccine development, and antiretroviral drug development and also in health education. In this review we have tried to highlight the both MHC and non MHC genes that influence this complex and multifactorial disease with the aim of applying these discoveries to further defining the regulatory components of an infected individual’s cell physiology in AIDS progression and pathogenesis.

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<td>HLA-B*2705</td>
<td>6p</td>
<td>CODOM</td>
<td>Delays AIDS</td>
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<td>HLA-B*5701</td>
<td>6p</td>
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Table 2—Role of different MHC encoded genes and their alleles in HIV-1 infection

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<tr>
<th>KIR-3DL2</th>
<th>3DL2</th>
<th>12</th>
<th>Delays AIDS</th>
<th>Enhanced NK-activity</th>
</tr>
</thead>
</table>

Currently available anti-HIV-1 drugs mainly target two enzymes encoded by HIV-1 genome—(1) Reverse transcriptase; and (2) Protease. Recent drug formulations that allow single daily doses have improved compliance prognosis, but there is still a pressing need for better, safer, cheaper and more effective anti-AIDS drugs.

Discovery of certain ARGs has solved this problem to some extent this is because the mechanism of AIDS restriction by natural genetic variants has encouraged the development of new class of anti-HIV drugs, which block HIV-1 binding to its cellular receptors and membrane fusion e.g. Enfuvirtide (T-20) or Fuzeon, a fusion inhibitor which was approved by US FDA on March 2003. The discovery of these AIDS restriction genes (ARGs) in particular community will encourage researchers and scientists to conduct clinical trial of the new drugs or vaccines development for AIDS patients.

For all of the abovementioned applications, the ARGs fulfill some but not all of the expectations, thus we need to identify further other genes which will be implicated in the determination of susceptibility or resistance to HIV-1 infection. In future, the identification of ARGs offer hope that additional genes not yet known will be discovered not only among known candidate genes, but also by SNP haplotype-based association in high density genome scans of clinically well described epidemiological cohorts. The consequences of discovery and identification of these ARGs will be beneficial to mankind if their translational benefits can be used in future for improved early diagnostics and better drug therapy for HIV-1 infection (AIDS).

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