Review Article

Indian J Med Res 138, November 2013, pp 663-681

Genomic architecture of HIV-1 infection: Current status & challenges

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Received August 2, 2013

Studies on host genomics have revealed the existence of identifiable HIV-1 specific protective factors among infected individuals who remain naturally resistant viraemia controllers with little or no evidence of virus replication. These factors are broadly grouped into those that are immune associated (MHC, chemokines, cytokines, CTLs and others), linked to viral entry (chemokine co-receptors and ligands), act as post-entry restriction elements (TRIM5a, APOBEC3) and those associated with viral replication (cytokines and others). These features have been identified through multiple experimental approaches ranging from candidate gene approaches, genome wide association studies (GWAS), expression analysis in conjunction with functional assays in humans to primate based models. Several studies have highlighted the individual and population level gross differences both in the viral clade sequences as well as host determined genetic associations. This review collates current information on studies involving major histocompatibility complex (MHC) as well as non MHC genes in the context of HIV-1 infection and AIDS involving varied ethnic groups. Special focus of the review is on the genetic studies carried out on the Indian population. Further challenges with regard to therapeutic interventions based on current knowledge have been discussed along with discussion on documented cases of stem cell therapy and very early highly active antiretroviral therapy (HAART) interventions.

Key words AIDS - chemokine - elite controllers - genes - HIV-1 - HLA - restriction - viraemia

Introduction

The human immunodeficiency virus (HIV-1) infection induces a wide range of immune responses in humans and depending on the level of immune resistance elicited, the host may or may not develop acquired immunodeficiency syndrome (AIDS). Only a few can resist virus spontaneously and contain its replication to undetectable levels without any therapy and these are classified as 'elite controllers'. However, most individuals tend to progress at either slow or fast rates (classified as 'slow' or 'fast progressors', respectively), if not treated with antiretroviral therapy (ART) to AIDS.

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The arena of host genetics has progressed immensely owing to the recent advancements in analytical approaches, development of high throughput next generation sequencing platforms, genome and proteome wide microarrays, expression profiling screens, highly sensitive and specific immunological assays and other tools for gene function readouts. Several international consortia studies have utilized multiline approaches based on candidate genes in case-controls studies involving large cohorts. Further, genome wide association studies (GWAS), siRNA/miRNA (small interfering/micro RNA) screenings, and their meta-analyses have been performed in different populations to understand the gross variability observed in genetic propensity towards HIV-1[1,2]. However, the genetic prototype of natural viraemia controllers that empowers antiviral resistance remains largely enigmatic. A more comprehensive analysis involving different ethnic groups could provide a better understanding of the mechanisms underlying host pathogen interaction.

Genomic architecture of HIV-1 infection relates to a complex network of genes and their cumulative influence on predilection (or resistance on the contrary) to HIV infection and its progression to AIDS. Multiple host genetic factors regulate individual variations in acquisition of HIV-1 infection and disease progression[2]. Investigations into the host determinant factors in individuals who can resist viral infection or delay the rate of disease progression could help identify putative 'antiviral resistance factors' which would eventually lead to more efficient anti-HIV therapeutic approaches.

Despite several achievements in research, therapy and management against HIV/AIDS during the last more than three decades (Fig. 1), attempts to generate an effective preventive or therapeutic vaccine have not been successful so far.

This review collates the essence of several studies on the role of host determined factors in the progression and transmission of HIV-1 infection, with a view to ascertain the genetic architecture of the disease based on studies on specific functional genes. These include *(i)* virus entry gatekeepers (CCR2, CCR5), *(ii)* their

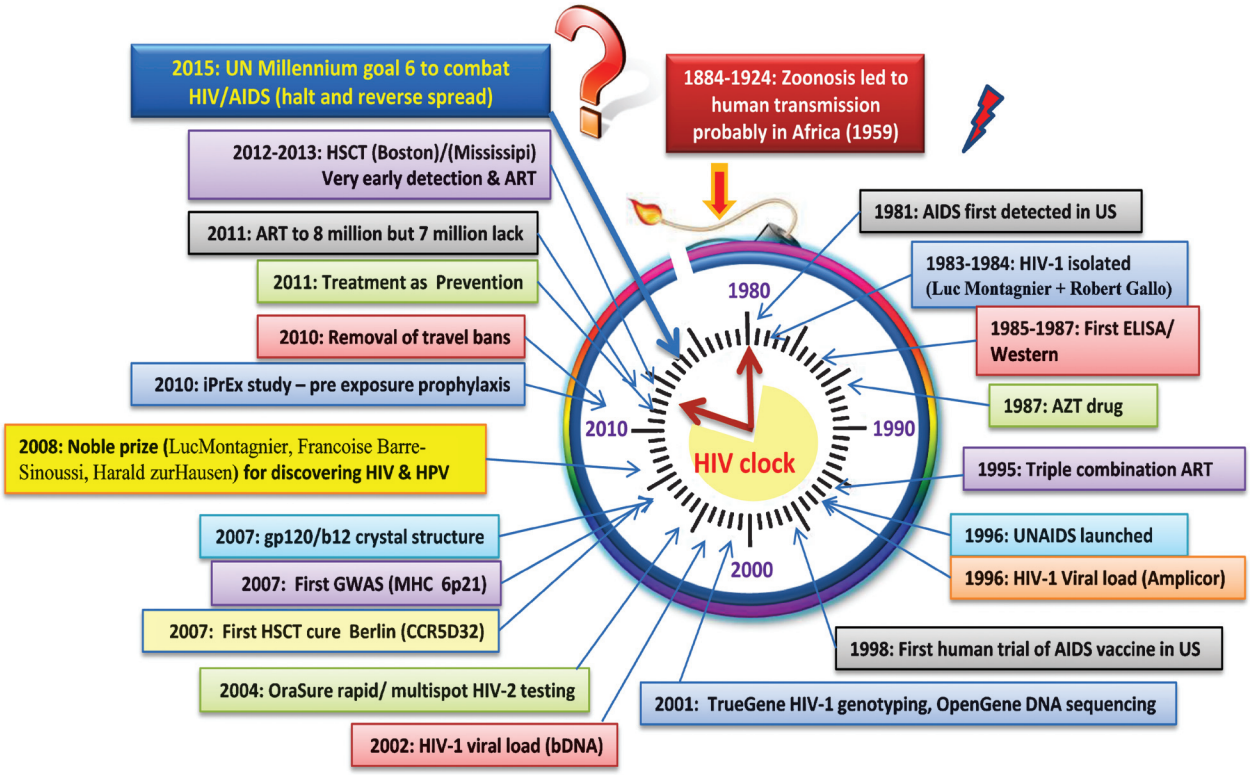


Fig. 1. 'HIV clock' showing major landmarks in research and therapy relating HIV/AIDS pandemic since its inception apparently in early 1980s'. ART, antiretroviral therapy; HSCT, hematopoietic stem cell transplantation; GWAS, genome-wide association studies; HPV, human papilloma virus.

ligands (SDF-1, RANTES, MIP1a), *(iii)* post-entry restriction factors (TRIM5a, APOBEC3), and *(iv)* immune response genes of the major histocompatibility complex (MHC), cytokines and others that synchronize an effective immune response. A later section describes evolutional medicine lessons from primate studies and concludes with an overview of the genomic portrait of HIV-1 infected individuals from different geographical regions of India.

Variability of host responses

All individuals are not equally susceptible to HIV infection and they exhibit gross variability in terms of their viral load set-points and course of chronic progression to AIDS[2-4]. Depending upon the variability in their CD4 T cell counts following seroconversion, levels of viraemia and symptoms manifested, HIV-1 infected individuals can be categorized into different progression phenotypes[3,4] as summarized in Table I.

Most individuals when infected with the virus, if untreated, tend to progress towards fatal AIDS and are referred to as 'progressors' or 'viraemia non-controllers'. However, the rates of progression could either be rapid (development of AIDS within 2-3 years) or slow (takes more than 3 years to develop AIDS) and this is reflective of host determined factors. Most of the latter group of individuals turn aviraemic on treatment with antiretroviral therapy (ART) and can suppress their viraemia levels to <75 copies/ml[3,4].

A privileged small subset of naturally resistant individuals is known to exist who possess effective immune surveillance against HIV-1. They can remain aviraemic for periods beyond 10 years without the aid of antiretroviral therapy and are referred to as long term non progressors (LTNPs). A minor group of LTNPs (~1%) can retain viral loads to below detectable levels (<50 copies/ml) and these are referred to as 'elite controllers'. Similarly, individuals who are

Table I. Definition of HIV-1 infected progression phenotype groups

	Group	Symptoms	ART	CD4 counts/ml	Plasma VL RNA copies/ml	Viraemia episodes RNA copies/ml
Potential LTNP	Viraemia Controllers	Asymptomatic for >10 years after sero-conversion	None	> 400	< 2000	Rare, non consecutive, > 2000
	Elite Controllers	Asymptomatic for >10 years after sero-conversion	None	> 400	Undetectable (<50) for > 1 yr	Rare, non consecutive, up to 1000
Viraemia Non-controllers	Chronic progressors	Symptomatic chronic phase leading to AIDS	Yes	<350	> 2000 in > 50% samples	Common > 2000
	Rapid progressors	Symptomatic ; development of AIDS within 3 yr (*e.g.*, Women married < 5 yr; Men with sero-conversion <5 yr)	Within < 3 yr	< 350 at least twice	>2000	Frequent > 2000
HEPS	Exposed Uninfected (EUs) Discordant couples	Asymptomatic for >1 yr (Donor partner is symptomatic with CD4 < 350 copies/ml)	None	> 400	< 2000	Less common
	Exposed Uninfected (EUs) CSWs/IDUs	Asymptomatic for >1 yr despite being in profession for > 3 yr	None	> 400	< 2000	Less common

HEPS, highly exposed persistently seronegative; ART, antiretroviral therapy; LTNPs, long term non progressors; CSWs, commercial sex workers; IDUs, intravenous drug users; VL, viral load
Source: Refs 3, 4

'intermediate viraemia controllers' can maintain viral loads up to <2000 copies/ml despite no ART[3,4].

Another group of naturally resistant individuals are those who encounter virus repeatedly but do not develop AIDS despite lack of any therapeutic intervention for several years and remain naturally resistant. Such 'highly exposed persistently seronegative (HEPS)' or 'exposed uninfected' (EUs) individuals include discordant couples, commercial sex workers and intravenous drug users and these have been widely studied in different populations[1-4].

An in depth understanding of the immunoprotective mechanisms among resistant individuals who are genetically programmed to be 'viraemia controllers' offers a prudent approach to identify and grade genes that could serve as 'guardians' against the virus. To that extent, an International Viremia Controllers Consortium has recently been established with the primary aim of determining the immunogenetic mechanisms that underlie natural resistance to HIV-1 infection [5]. Indeed a better understanding of the various host genes that confer protection against HIV infection is of immense translational value in disease management, control of viraemia and finally towards a more robust vaccine design. Role of important gene families representing viral entry mediators or restriction factors, or those involved in innate/acquired antiviral immune responses are dealt with in details in the following sections.

Immune response genes of the MHC

The major histocompatibility complex (MHC) represents a highly polymorphic, gene dense component of the human genome, located on chromosome 6 (6p21.3) whose major function is antigen presentation. By presenting specific viral epitopes, the human leukocyte antigen (HLA) class I genes instruct cytotoxic T lymphocyte (CTL) mediated immune pressure against the virus and thus has an important impact on the consequences of viral adaptive evolution. Conversely, the virus tends to evolve in an attempt to escape HLA peptide binding signatures of the CTLs, although it may or may not be conducive to viral fitness. Studies focused on comparative evolution have suggested that the non human primates like chimpanzees experienced a selective sweep of certain MHC class I repertoire to survive through the historic SIV/HIV-1 (Simian/human immunodeficiency virus) like retroviral epidemic in the past[6,7].

A number of HLA class I and class II alleles and haplotype associations have been reported in relation to genetic susceptibility to HIV-1 infection, transmission and disease progression in different population groups[8-10]. Among those, at least three HLA-B alleles viz. HLA-B*27, B*57 and B*35 have consistently been shown to exert a dominant effect on HIV-1 viral escape and disease outcome in various human populations[11]. For example, HLA-B27 that shows a strong association with ankylosing spondylitis and other spondyloarthropathies, has been illustrated to be protective against HIV infection (Fig. 2). Similarly, HLA-B*57 which is responsible for abacavir associated hypersensitivity (B*57:01), also confers protection and is associated with delayed disease progression alongwith gradual decline in viraemia.

The role of HLA-B*35 has been extensively studied in several populations and it may either be protective or predisposing depending upon the sequence variations of its peptide binding motifs[13]. Moreover, it has been shown that the HLA associated outcome also depends on the viral epitopes being targeted[14]. For example, gag NY10 epitope at position 253-262, has been shown to be targeted by CTLs more efficiently in clade C than in clade B infected individuals carrying HLA-B*35:01. The difference in immunogenicity of these clade specific epitopes has been attributed to a single residue substitution of Asp 260 Glu. The latter leads to steric hindrance and affects relative binding affinity between HLA-B*35:01 and the peptide resulting in loss of CTL response[14].

Vaccine genomic approaches have screened host genetic determinants of T cell responses in the MRKAd5 HIV-1 gag/pol/nef Step trial and found that the polymorphism in MHC (particularly HLA-B) showed the strongest association among all the genetic factors evaluated with response to the HIV-1 gag protein[15].

Role of HLA-C

The functional importance of HLA-C in HIV infection has recently been revisited[16]. Earlier studies failed to establish a consistent association of HLA-C alleles with HIV-1 infection, largely due to variation in linkage disequilibrium of HLA-C with HLA-B in different populations. For example, HLA-B*08:01 is linked strongly with HLA-C*07:01 in the Caucasian population but with C*07:02 in the Indian population[17].

Unlike HLA-A and HLA-B molecules, expression of HLA-C is not inhibited by viral Nef[18] and is, therefore, particularly important in priming of CTLs in

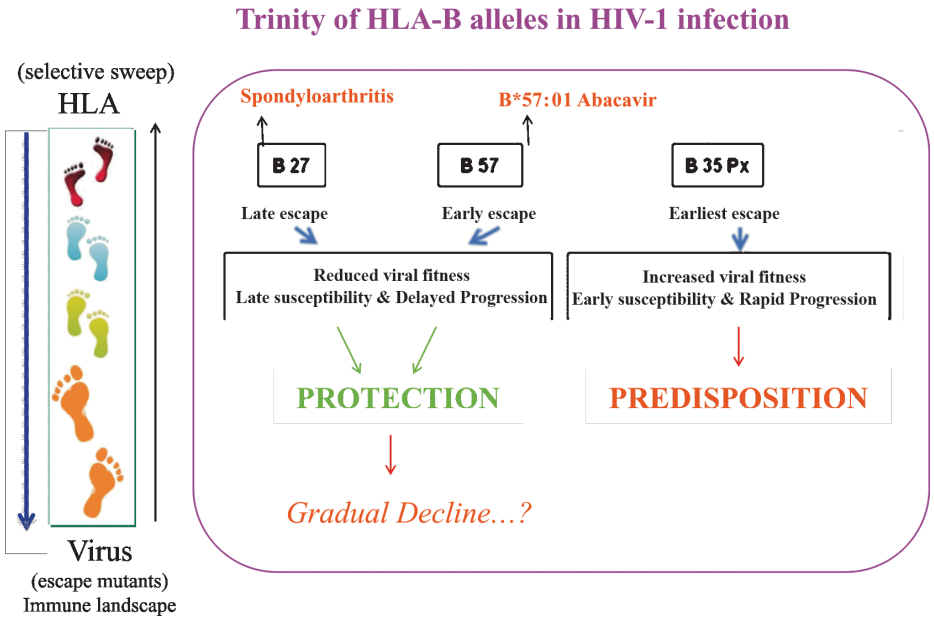


Fig. 2. Association of three HLA-B alleles *viz*. HLA-B27, B57 and B35 with susceptibility to HIV-1/AIDS. The alleles B27 and B57 are protective while B35Px alleles are disease predisposing. It is possible that the protective nature of B27 and B57 may decline in time since the virus is continually trying to evolve escape mutants and change its immune landscape depending upon the HLA signatures of the host. The HLA system which is the human MHC, contains polymorphic class I (HLA-A, B, C), class II (HLA-DR, DQ and DP) and a set of central genes that include complement, tumour necrosis factor (TNF), MHC class 1 polypeptide-related sequence A (MICA) and other genes (For details of the MHC gene products in man please see Ref. 12).

HIV-1 infection. HLA-C is also important because it has a longer half-life than other class I counterparts. It functions as a ligand for the inhibitory killer cell immunoglobulin like receptor (KIRs) and its continued expression protects antigen presenting cells (APCs) from natural killer (NK) cell lysis. High expression of HLA-C promotes effective CTL recognition and maturation.

The level of expression of HLA-C is regulated by multiple polymorphisms in HLA-C sequence. It has been demonstrated that an insertion of a single nucleotide G at 263SNP (ins263 or rs67384697-G) in the 3'UTR region of HLA-C results in creation of a binding site for miRNA (miR-148a) that leads to a rapid degradation of HLA-C. Loss of expression of HLA-C along with HLA-A and B therefore may result in a decrease in CTL recognition and lysis of HIV uninfected cells[19-21].

Another important SNP is at -35 kb (rs9264942) with C/T alleles. The -35kb C allele is a high expressor allele as compared to T. The HLA-C alleles C*08:01/02/04, *12:02/03, *01:02, *02:02, *06:02, *05:01 and *14:02 carry the C allele at this SNP and are high expressor alleles conferring lower odds ratio (OR). On the contrary, other HLA-C alleles that include *03:03/04, *04:01, *07:01/02, *15:02/05/06, *16:01/02/04 and *17:01 are low expressor C alleles that contribute relatively higher OR towards the development of full blown AIDS [20,22]. It may be mentioned that the -35kb C allele is in strong linkage disequilibrium with the 3'UTR deletion while -35 kb T allele shows linkage with the insertion of G in the latter in several populations. The -35T/ins haplotype creates miRNA binding site and downregulation of HLA-C expression. On the other hand, HLA-C alleles, particularly those carrying aromatic amino acids (Phe or Tyr) at position 67 buried deep in α1 helix (also in a few HLA-B alleles) can associate with gp120 of the virus as evident through L31 mab binding [23]. Recently, it has been shown that specific HLA-C alleles like C*03/04/07/12 are able to bind the virus efficiently leading to enhanced HIV-1 infectivity[22].

In recent years, the relative importance of HLA-C in HIV-1/AIDS has been further demonstrated through a set of independent GWAS[24]. These studies have shown that the SNP (rs 9264942) that lies in close proximity to HLA-C regulates its expression and controls viraemia efficiently[24]. Fig. 3 provides an overview of the human

MHC along with the location of important single nucleotide polymorphisms (SNPs) associated with HIV/AIDS as defined through GWAS studies.

It has been suggested that specific HLA alleles that provide antiviral protection when present together in an individual could cooperate and confer even greater protective effects by targeting a greater breadth of viral proteome that results in lower viraemia and higher CD4 T counts[25].

Studies on MHC in viraemia controllers

Collaborative efforts of the International HIV controllers studies[5,26] have presented evidence to suggest that the observed variable immune responses against the virus are a consequence of the binding ability of crucial HLA amino acid residues directly involved in peptide presentation. Studies conducted in Caucasian populations have revealed the importance of amino acid substitutions in the HLA-B peptide binding groove, particularly residues at positions 67, 70 that line the 'pocket B' and position 97 in 'pocket C' of the peptide binding groove. Such substitutions have been shown to be associated with an overriding effect on virus loads among progressors and controllers.

The selective advantage contributed by the protective HLA alleles ultimately depends upon their overall population frequencies. For example, the most frequent HLA alleles may act as 'common restriction elements' for the virus. It is conceivable that circulating viral strains gradually tend to break the protective barrier conferred by common HLA alleles by undergoing specific escape mutations. However, since the virus does not encounter rare HLA alleles often, it may lose its fitness against the latter more easily. Hence, the rare HLA alleles may turn out to be more advantageous as compared to those that are more common HLA in a population[8]. This points towards the need of escape and fitness guided vaccination approaches.

The International HIV Controllers Study Group has also performed genome wide association analyses among 974 controllers and 2648 progressors among European populations[26]. The results of the study indicated that the only SNPs that reached statistically significant levels of association in the two cohorts were those in the extended MHC and the CCR5-CCR2 locus. Together, these two loci contributed 23 per cent of the observed variance of host control.

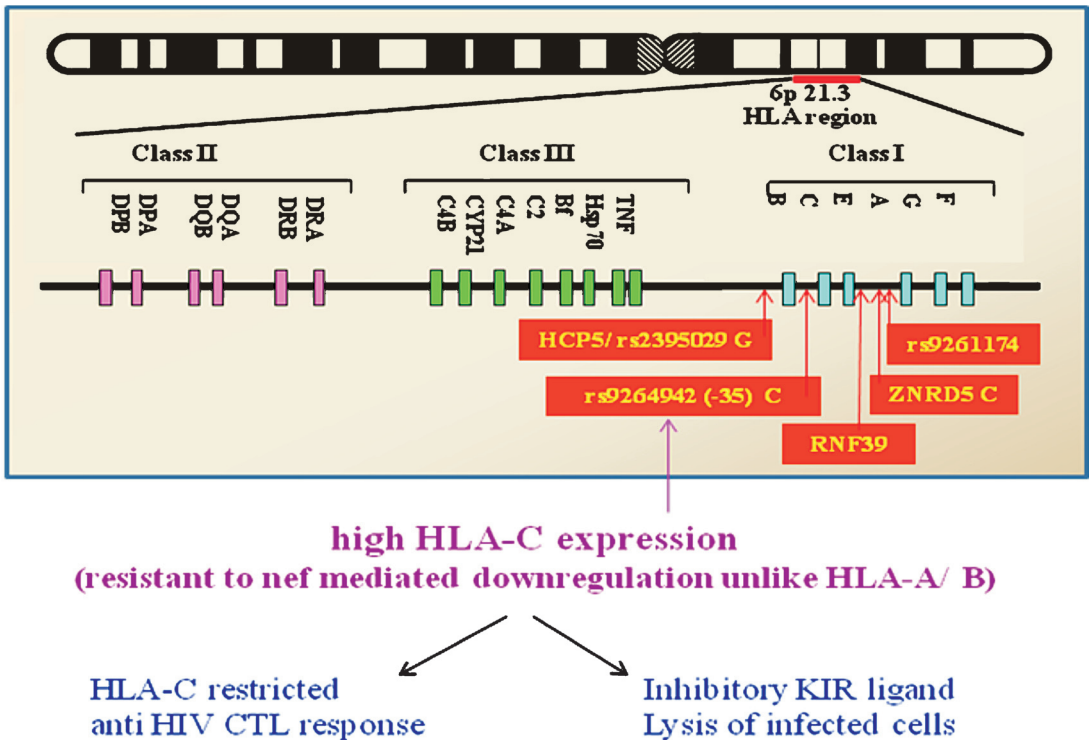


Fig. 3. Gene map of the human MHC on chromosome 6p21.3 showing various single nucleotide polymorphisms (SNPs) identified in the HLA class I region that are associated with HIV-1/AIDS through genome wide association studies (GWAS) studies. Multiple gene loci are implicated in HIV-1 susceptibility and viraemia control.

Another important role of MHC in HIV-1/AIDS is in the context of drug induced hypersensitivity reactions[27]. Pharmacogenomic studies have shown that atleast two drugs commonly used as a part of the HAART therapy are associated with drug induced hypersensitivity (DIH). These include the use of abacavir that induces DIH in patients carrying the HLA-B*57:01 allele[28]. The US Food and Drug Administration (FDA) has made HLA testing mandatory before its use and those carrying this allele are prohibited from using it. Similarly, nevirapine induced drug reactions have been shown to have a strong association with HLA-DRB1*01:01 (and B*35:05, Cw*04)[29]. While these are well established genetic associations that must be prescreened before administering these antiretroviral drugs to HIV infected patients, there could be others in untested populations.

Genes that code entry gatekeepers

Molecular events involved in the process of viral entry into host cells are highly intricate. Briefly, HIV-1 engages its envelope proteins (gp120, gp41) sequentially and exploits host cell surface co-receptors CCR5 or CXCR4 along with CD4 to gain entry into the cell. Cell surface density of vacant chemokine co-receptors CCR5/ CXCR4 may act as gatekeepers to the virus. On the contrary, their saturation with the corresponding ligands (MIP1a/b, Regulated upon activation normal T cell expressed and secreted (RANTES) for CCR5 and SDF-1 for CXCR4, respectively) could obstruct viral entry and retard its subsequent transmission[1-4,8,10].

(i) Chemokine co-receptors

CCR5: Genetic variability in the CCR5 co-receptor has been of considerable interest and it is so far the only genetic locus illustrated with translational value against HIV-1. A natural knockout deletion of 32 nucleotide bases (Δ32) renders this receptor non functional and blocks the virus from gaining entry. However, this naturally protective polymorphism is not so frequent and its prevalence shows a declining trend on transition from the North Europe (10 to 16%), southeast towards Mediterranean region (~10 to 4%) and gradually disappears among African and East Asian populations[30]. Incidentally, the protective CCR5Δ32 allele is almost absent in the Indian population[31].

The CCR5 promoter region embraces multiple SNPs that regulate its cell surface expression and hence influence viral entry. Several studies have shown that the CCR5 haplogroup HHE favours HIV-1 infection and development of AIDS in multiple populations including Caucasians, Thais and the North Indians[32]. Similarly, the haplogroup HHD is associated with fast progression among the African populations. Because of the population specific variations, the genetic influence on virus transmission and disease progression also vary in a race specific manner.

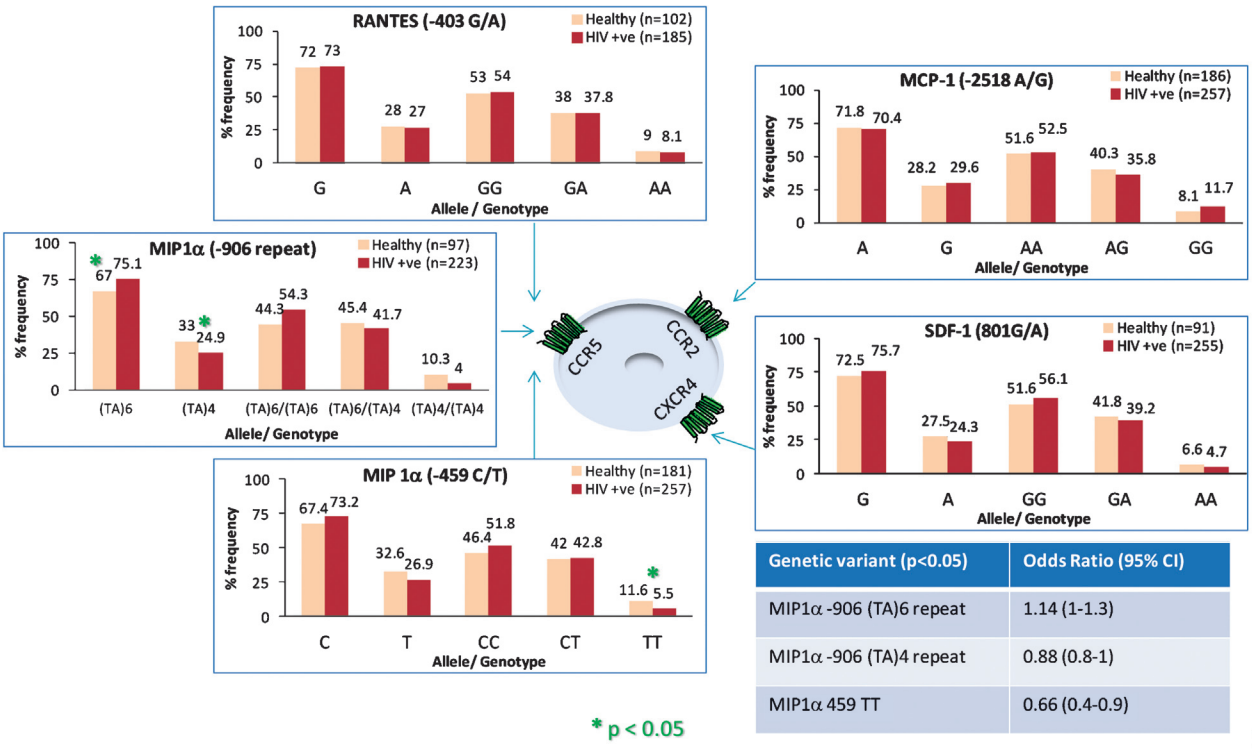
CCR2: The *CCR2* gene is located in the vicinity of *CCR5* on chromosome 3 and both the loci show strong linkage disequilibrium. A particular SNP (G190A or V64I) has been reported to be associated with slower progression to AIDS. The protective A allele at this SNP is found at a frequency of ~12 per cent in north Indians[33] and 3-17 per cent in south Indians[34]. These studies and those by others have suggested that although CCR2 is an important genetic marker, the influence of CCR2 V64I polymorphism on susceptibility to HIV may not be direct. It is now clear that it might affect the pace of progression in part or entirely through its linkage with other variants, particularly in the CCR5 promoter[32].

(ii) Chemokine ligands

MCP1: The monocyte chemoattractant protein-1 (MCP-1/CCL2) is a potent chemokine that mediates macrophage activation and recruitment. It is a ligand for CCR2 and has been reported to be associated with encephalitis and dementia among HIV infected individuals. The MCP-1 -2518 G allele in the promoter region has been reported to be associated with higher MCP-1 expression and with reduced risk of HIV-1 acquisition[35]. On the other hand, the same genotype was found associated with faster disease progression and development of AIDS associated dementia in HIV infected European, African and Hispanic Americans[36], thus highlighting the race specificity of the associations.

It has been shown that the 'G' allele occurs with a frequency of 23-25 per cent among Caucasians (25.8% in Germans, 25% in Italians, 23.9% in Hungarians and 23.8% in Czechs)[37]. On the other hand, it occurs with a considerably higher frequency of 50-65 per cent among Asian populations (65% in Koreans, 63.8% in Japanese and 51% in Chinese population)[38].

Studies carried out by our group (unpublished data) on chemokine ligands among north Indians are summarized in Fig. 4. The 'G' allele of *MCP-1* occurs at a frequency of 28 per cent among north Indians. The allelic and genotypic frequencies of -2518MCP-1 A/G were found to be comparable between HIV +ve subjects and healthy controls. These findings are consistent with a previous study from south India, in which the



Genetic variant (p<0.05)	Odds Ratio (95% CI)
MIP1α -906 (TA)6 repeat	1.14 (1-1.3)
MIP1α -906 (TA)4 repeat	0.88 (0.8-1)
MIP1α 459 TT	0.66 (0.4-0.9)

Fig. 4. A comparison of frequencies of genetic polymorphisms in CCR5 chemokine ligands (RANTES, MIP1a), CCR2 ligand (MCP1) and CXCR4 ligand (SDF-1) among the healthy north Indian population and HIV-1 infected individuals. The three significant findings in MIP1α associations and their odds ratios respectively are shown inside an insert on right lower side panel of the figure (*Source*: unpublished data). **P*<0.05; Healthy vs HIV-1 seropositive individuals.

frequency of 'G' allele was reported to be 34 per cent, and showed no association with HIV susceptibility and development of tuberculosis[39]. Further, a cumulative analysis of *MCP-1* and its ligand CCR2 genetic variants together did not reveal association of this receptor-ligand genetic axis with susceptibility towards HIV infection in north Indians.

SDF1 (CXCL12): The stromal cell–derived factor 1 is the only chemokine ligand known for the HIV-1 co-receptor CXCR4. Transition from G to A at position +801 in the 3′ untranslated region of the *CXCL12*β gene transcript has been associated with delayed progression to AIDS[40] and with HIV-1 resistance in seronegative high-risk individuals[41]. This might be due to the overproduction of SDF1 in certain tissue compartments thereby deregulating the CCR5-CXCR4 switch. In contrast, other studies have reported an association of A allele to poor survival of AIDS patients[42] or no effect on HIV disease progression[43].

In our studies, the SDF-1 allelic and genotypic frequencies were found to be similar in HIV +ve subjects as compared to healthy controls, and among concordant versus discordant couples, suggesting that the variant might not have any role in HIV susceptibility/ resistance or transmission (unpublished data). The observed SDF1-3'A frequency (27.5%) and its lack of association with HIV susceptibility, viral acquisition and transmission in our results are in conformity with a previous report from north India[44]. The SDF1-3'A frequency ranges from 17-35 per cent in south Indians, Thais and 17-22 per cent among many other populations worldwide[45]. We observed a relatively lower frequency of 'A' allele in rapid progressors (8.8%) as compared to the total HIV +ve cohort (24.3%) or LTNPs (25%) or EUs (25.9%). These results indicate that this allele might confer resistance to disease progression. Our results are in conformity with the earlier reports suggesting an association of this allele with delayed onset of AIDS[40,45].

CCL5/RANTES: This chemokine is a ligand for CCR5 and therefore may inhibit viral entry by competitive binding and CCR5 down-modulation. The promoter genotype -403GA-28CC has been shown to be associated not only with HIV-1 susceptibility but also

delayed onset of AIDS in European Americans (EA)[46]. Similarly, RANTES haplotypes comprising -403A and -28G were found to be associated with lower susceptibility to infection in a Chinese cohort[47,48] and slower disease progression in the Japanese and Thai cohorts[49]. In our studies, the allelic and genotypic frequencies of RANTES -403 G and A alleles were found to be comparable between HIV +ve subjects and healthy controls and among concordant and discordant couples, suggesting that these variants might not confer HIV susceptibility/resistance or influence transmission among north Indians (unpublished data). These results are in conformity with a previous report from north India[44]. The 'A' allele was, however, found to be relatively lower in the LTNP cohort (16.7%) as compared to the rapid progressors (RPs) (26.5%), EUs (29.6%), total HIV +ve subjects (27%) and healthy controls (28%). These trends suggest a lack of protection conferred by the 'A' allele towards disease progression. This is in accordance with reports in African Americans which also suggest no effect of these variants on HIV-1 infection and AIDS progression[50].

MIP-1- α: The macrophage inflammatory protein-1-alpha is produced by stimulated T lymphocytes, macrophages, neutrophils and monocytes. This chemokine contributes to acute cellular immune responses via recruitment and activation of macrophages and T cells inducing the production of inflammatory cytokines. A biallelic dinucleotide (TA) repeat exists within the promoter region at -906 of the *MIP-1A* gene[51]. In the North Indian population, we observed a statistically significant increase in the frequency of $(TA)_6$ in HIV infected patients (75.1%) as compared to the healthy controls (67%). Conversely, the frequency of the other variant of this repeat motif, namely $(TA)_4$ occurred with a significantly lower frequency in HIV +ve subjects in our study (unpublished data). Similarly, a relatively lower frequency of $(TA)_4$ was observed in the LTNP cohort (8.3%) as compared to RPs (26.5%), EUs (24.1%), total HIV +ve (24.9%) and healthy subjects (33%). These results suggest a direct role of the *MIP1α* variants in HIV susceptibility/ resistance. Alternatively, the observations might reflect on linkage disequilibrium of this polymorphism with another as yet unknown genetic marker. Incidentally, our observations made in the north Indian population are in conformity with those reported among the Japanese[52].

We also evaluated the role of genetic polymorphism of *MIP-1α* +459C/T in HIV infection. The homozygous TT genotype was found with a significantly lower frequency in HIV +ve subjects (5.45%) as compared to healthy controls (11.6%), suggesting its possible role in protection or linkage with some other genetic marker. The +459 T frequency was also found to be lower in the LTNP cohort (8.3%) as compared to RPs (32.2%), EUs (29.6%), total HIV +ve (26.85%) and healthy subjects (32.6%) (unpublished data). These results are in accordance with a recent study conducted in African Americans in which a haplotype TT (comprising MIP-1α +459 C/T linked with MIP-1α +113 C/T) was found to be associated with a significantly lower risk of HIV-1 acquisition as compared to the ancestral haplotype CC (unpublished data). Further, the allelic and genotypic frequencies observed here are similar with those reported in European, African and Hispanic Americans.

Comparative genomics

Zoonotic infection studies of SIV among non human primate models particularly chimpanzees, Sooty mangabeys and African green monkeys have provided important information on the co-evolution of SIV and potential host genes that led to development of resistance to progression to AIDS. It is known that the chimpanzees can be infected with HIV-1/ SIVcpz virus but do not progress to AIDS like disease. It is believed that they experienced a selective sweep resulting in marked reduction in their MHC class I allelic and haplotypic repertoire in the past caused by an HIV-1/SIV like retrovirus pandemic[6]. Similarly, there is evidence for unique patterns of natural selection among non MHC genes in chimpanzees that include relative conservation in CCR5 promoter, CXCR4 and CX3CR1 genes, high CNVs in CCL3L1 and long term persistence of advantageous alleles, *e.g.*, in T cell transmembrane immunoglobulin and mucin 1 (TIM1). A strong positive selection has been suggested among genes for post entry restriction factors like APOBEC family, TRIM5a and others[1,2]. Our studies have shown that the CCL3L1 copy numbers in north Indians (2.34)[53] are relatively lower than those observed in the Japanese[6] and other populations[53]. Incidentally, these copies occur with a far greater number in the chimpanzees (>10) and could, therefore, be considered as one of their immuneprotective mechanisms against the virus.

Lessons learnt from primate studies could help identify analogous genes that can interfere with cross species transmissions and allow nonpathogenic outcomes. Another advantage of such studies could be in the context of Paleovirology where the genome

data gathered could be utilized to reconstruct extinct viruses and ancestral states of present day virus and then extrapolate how ancestral viruses were evaded by the host specific restriction factor(s).

Post-entry restriction factors

Infection by HIV-1 depends on a number of host cell factors, some of which can act as viral restriction elements with species specific variations. The TRIM and APOBEC3 families are explicit examples of such factors and a clear understanding of their interactions with HIV-1 could have important implications for designing effective therapeutics. In this context, several attempts are being made to develop additional antiretroviral drugs and other mechanisms of enhancing their anti HIV-1 restriction activity against the virus.

TRIMs (Tripartite - motif containing super family) represents antiviral restriction factors that act as stringent post-entry replication blocks in a species specific manner. For example, member TRIM5a from rhesus monkeys can restrict HIV-1 production after viral entry. The human TRIM5a, however, can restrict HIV-1 only weakly but can restrict N topic murine leukemia virus (MLV) more potently. Sequence variants in this molecule have been extensively studied with respect to their anti HIV activity. Functional polymorphisms in exon 2, particularly 43Tyr carrying haplotypes have been linked with reduced susceptibility to HIV-1 in French, Japanese and Indian populations[54], although its antiviral activity is relatively lower and may be attributed in part to differences in the viral clades. A further study on variants in the linker region of TRIM5a has revealed that a SNP rs11038628 (249D) is associated with HIV-1 susceptibility and attenuated activity in the Indian population[55].

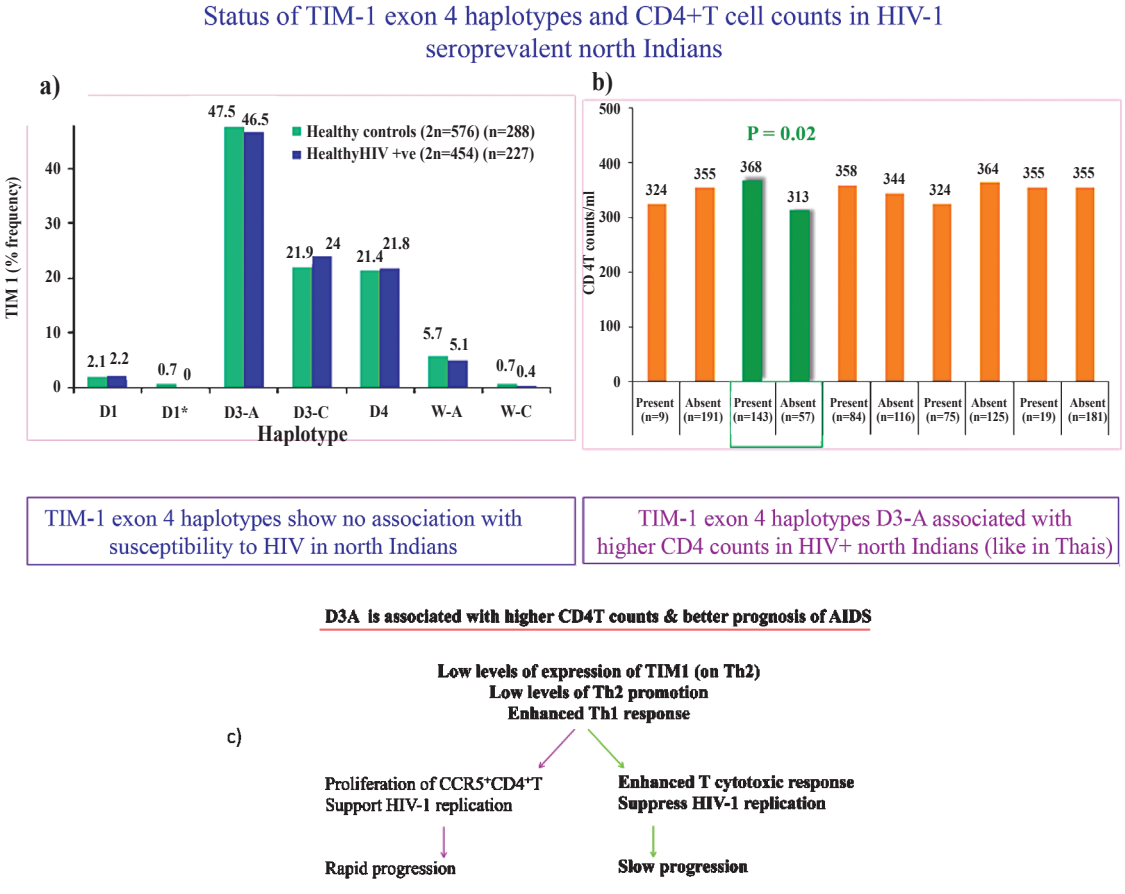


Fig. 5. A correlation of prevalence of TIM1 haplotypes and CD4 T cell counts in the north Indian population. The panel (a) shows % frequencies of TIM1 haplotypes among healthy and HIV-1 seropositive individuals. Panel (b) shows higher CD4T counts among individuals carrying D3A haplotypes among patients. Panel (c) shows two possible outcomes of lower levels of TIM1 expression among individuals carrying D3A, one favouring HIV-1 replication and the other favouring slower progression.

Table II. Summary of India-wide genetic studies on HIV-1 infected population

	Genetic variant (a1/a2)	Indian Population	Sample size (Cohort)	Allele/Haplotype/Genotype frequency (%)					Key observation	Ref.
				a_ 1 (%)	a_2 (%)	g_ 1 (%)	g_ 2 (%)	g_ 3 (%)		
1	CCR2 190G/A			**G**	**A**	**GG**	**GA**	**AA**		
		North	500 (HC)	90.9	9.1	81.8	18.2	0		61
			75(HC)	86	14	74.6	22.6	2.6	No association	44
			35 (EU)	82.9	17.1	68.5	28.5	2.8		
			50 (HIV)	85.7	14.3	72	24	2		
			221 (HC)	88.2	11.7	78.2	19.9	1.8	No association	33
			180 (HIV)	88.8	11.1	80	17.7	2.2		
		North East	711 (IVDUs)	74.1	25.9	51	47	2	No association	62
		South	206 (HC)	91.3	8.7	84	14.6	1.4	No association	39
			151 (HIV+TB-)	92.4	7.6	84.8	15.2	0		
			112 (HIV+TB+)	90.1	9.9	81.1	18	0.9		
			525 (HC)	90.9	9.1	82.7	16.4	1		34
2	CCR5 Δ32			wt	Δ32	wt/wt	wt/Δ32	Δ32/Δ32		
		North	500 (HC)	98.5	1.5	97	3	0	Rare	61
			100 (HC)	99	1	98	2	0	Rare	63
			119 (HC)	100	0	100	0	0	Absent	32
			180 (HIV)	100	0	100	0	0		
			779 (HC)	98.8	1.2	97.7	2.3	0	Rare	64
		West	147 (HC)	100	0	100	0	0		
		East	111 (HC)	100	0	100	0	0		
		South	845 (HC)	99.6	0.4	99.2	0.8	0		
		South	525 (HC)	99.4	0.6	98.9	1.1	0	Rare	34
3				CCR5 Promoter Variants & haplotypes					CCR5*59402A associated with susceptibility, OR=1.5 (0.9-2.4). Homozygosity of haplotype ACCAC linked with disease severity	32
	CCR5-59029G/A	North		G	A	GG	GA	AA		
			119 (HC)	61.3	38.7	35.3	52.1	12.6		
			180 (HIV)	56.4	43.6	35.6	41.7	22.8		
	CCR5-59353T/C			T	C	TT	TC	CC		
			119 (HC)	61.3	38.7	35.3	52.1	12.6		
			180 (HIV)	56.4	43.6	35.6	41.7	22.8		
	CCR5-59356C/T			**C**	**T**	**CC**	**CT**	**TT**		
			119 (HC)	97.9	2.1	96.7	2.5	0.8		
			180 (HIV)	98.1	1.9	97.2	1.7	1.1		
	CCR5-59402A/G			**A**	**G**	**AA**	**AG**	**GG**		
			119 (HC)	57.1	42.9	30.2	53.8	16		
			180 (HIV)	66.4	33.6	46.1	40.6	13.3		
	CCR5-59653C/T			C	T	CC	CT	TT		
			119 (HC)	100	0	100	0	0		
			180 (HIV)	98.9	1.1	97.8	2.2	0		

Contd...

	Genetic variant (a1/a2)	Indian Population	Sample size (Cohort)	Allele/Haplotype/Genotype frequency (%)					Key observation	Ref.
				a_ 1 (%)	a_2 (%)	g_ 1 (%)	g_ 2 (%)	g_ 3 (%)		
4	SDF G/A			G	A	GG	GA	AA		
		North	500 (HC)	79.6	20.4	61.6	36	2.4		61
			100 (HC)	60	40					65
			100 (HC)	79.5	20.5	63	33	4	A allele associated with resistance, OR=0.2 (0.1-0.4)	66
			150 (HRSTD)	70.7	29.3	59	23	18		
			100 (HIV)	91.5	8.5	90	3	7		
			75(HC)	85.3	14.7	74.6	21.3	4	No association with susceptibility	44
			35 (EU)	78.6	21.4	65.7	31.4	5.7		
			50 (HIV)	83	17	70	26	4		
		North East	711 (IVDUs)	87.3	12.7	76.9	20.8	2.2	No association	62
		South	206 (HC)	74.9	25.1	55.1	39.5	5.4	GG genotype may be associated with PTB coinfection, OR=1.57 (1-2.47)	39
			151 (HIV+TB-)	76.8	23.2	59.6	34.4	6		
			112 (HIV+TB+)	83	17	67.8	30.4	1.8		
		South	525 (HC)	74.7	25.3	55.4	38.5	6.1		34
5	MCP-12518 A/G			**A**	**G**	**AA**	**AG**	**GG**		
		South	126 (HC)	67.1	32.9	46	42	11.9		67
			206 (HC)	65.8	34.2	45.8	39.9	14.3	No association	39
			151 (HIV+TB-)	62.6	37.4	41.1	43	15.9		
			112 (HIV+TB+)	68.7	31.3	48.2	41.1	10.7		
6	RANTES-28C/G			**C**	**G**	**CC**	**CG**	**GG**		
		North	75(HC)	98.7	1.3	97.3	2.6	0	No association	44
			35 (EU)	98.6	1.4	97.1	2.8	0		
			50 (HIV)	100	0	100	0	0		
7	RANTES-403 G/A			**G**	**A**	**GG**	**GA**	**AA**		
		North	75(HC)	88	12	78.6	18.6	2.6	No association	44
			35 (EU)	81.4	18.6	65.7	31.4	2.8		
			50 (HIV)	84.7	15.3	72	22	4		

Contd...

	Genetic variant (a1/a2)	Indian Population	Sample size (Cohort)	Allele/Haplotype/Genotype frequency (%)					Key observation	Ref.
				a_ 1 (%)	a_2 (%)	g_ 1 (%)	g_ 2 (%)	g_ 3 (%)		
8	APOBEC 3B (29.5kb del)			wt	del	wt/wt	wt/del	del/del		
		North	251 (HIV)	84.3	15.7	72.1	24.3	3.6	No association	57
			192 (HC)	82.9	17.1	68.8	28.2	3.0		
9	TAP1 V333I (A/G)			A	G	AA	AG	GG		
		South	183 (HC)	74	26	51.9	44.3	3.8	GG associated with TB co-infection, OR=3.03 (1.04-8.91)	68
			130 (HIV+TB-)	78.3	21.7	60.5	35.6	3.9		
			110 (HIV+TB+)	68.7	31.3	48.2	40.9	10.9		
			105 (HIV-TB+)	73.8	26.2	53.3	41	5.7		
10	TAP1 Asp637Gly (A/G)			**A**	**G**	**AA**	**AG**	**GG**		
		South	102 (HC)	77	23	59.8	34.3	5.9	GA associated with TB co-infection, OR=2.32 (1.31-4.08)	68
			102 (HIV+TB-)	81.4	18.6	65.7	31.4	2.9		
			105 (HIV+TB+)	72.4	27.6	46.6	51.4	2		
			100 (HIV-TB+)	76	24	59	34	7		
11	IL-18-137 G/C			**G**	**C**	**GG**	**GC**	**CC**		
		North	500 (HC)	65.3	34.7	27	65.4	7.6	GG associated with HIV infection, OR=1.47 (1.12-1.92))	69
			500 (HIV)	59.8	40.2	35.2	60.2	4.6		
12	IL-10-1082A/G			A	**G**	**AA**	**AG**	**GG**		
		South	102 (HC)	77	23	55.8	42.2	2	GG, AG & AA associated with TB co-infection (OR=4.63), HIV (OR=2.99) & TB resp. (OR=2.14)	70
			121 (HIV+TB-)	64	36	29.8	68.5	1.7		
			106 (HIV+TB+)	74.1	25.9	56.6	34.9	8.5		
			104 (HIV-TB+)	85.1	14.9	73.1	24	2.9		
13	CCL3L1 Copy number	North	100 (HC)	2.34 (avg. copy number)					No association	53
			101 (HIV	2.13 (avg. copy number)						
14	DC-SIGN exon 4 repeat	North	100 (HC)	100					No association	66
			150 (HRSTD)	All the subjects had 7/7 repeat polymorphism genotypes						
			100 (HIV)							
15	DC-SIGN-R exon 4 repeat	North		Genotypes						
				3/3	4/4	5/5	6/5	6/6	7/5	7/6	7/7	7/4	8/5	8/7	8/8	9/5	9/6	9/7	9/9		
			262 (HC)		0.76	8.39	3.05		29	6.11	41.2	0.76	0	0		0	0.76	9.16	0.76	5/5 genotype was associated with a significantly reduced risk of HIV-1 in exposed seronegative individuals.	71
			168 (HIV)		0	3.57	3.57		23.8	3.57	47.6	1.19	1.19	1.19		2.38	0	11.9	0		
			47 (EUs)		0	12.7	2.12		34	4.25	36.2	2.12	0	2.12		0	0	6.38	0		

Contd...

	Genetic variant (a1/a2)	Indian Population	Sample size (Cohort)	Allele/Haplotype/Genotype frequency (%)					Key observation	Ref.
				a_ 1 (%)	a_2 (%)	g_ 1 (%)	g_ 2 (%)	g_ 3 (%)		
				17	25	54	4		No association	72
			150 (HRSTD)	0.6 0.6 19.3	0.6 25.3	4.6 42.6	3.3 0.6	0.6		
			100 (HIV)	11	34	47	1 6 1			
16	TRIM5α exon 2 variants and haplotypes			Gly110Arg	G176del	His43Tyr	Val112Phe	Arg136Gln	43Tyr allele and linked haplotype associated with resistance, OR=0.52 (0.31-0.89)	53
		North	101 (HIV)	0	0	22.7	19.2	17.7		
			99 (HC)	0	0	13.4	19.8	17.3		
17	TIM-1 exon 4 haplotypes			D1	D3-A	D3-C	D4	W-A	No association with susceptibility. D3-A associated with higher CD4 counts	58
		North	288 (HC)	2.1	47.5	21.9	21.4	5.7		
			227 (HIV)	2.2	46.5	24	21.8	5.1		
18				VDR 3'UTR Haplotype					b-A-T haplotype may be associated with protection against HIV-1	73
		South	144 (HC)			b-A-T=13.3				
			233 (HIV)			b-A-T=6.6				
			105 (HIV+TB+)			b-A-T=6.6				
19				MBL Codon 54 exon 1					Low expressor, B/B genotype is associated with a 4 x higher risk of acquiring HIV-1; OR=4.89 (1.54-15.62)	74
		North	305 (HC)			B/B=1.3				
			180 (HIV)			B/B=6.11				
			50 (EU)			B/B=2				
20	MBL2 codons 52, 54, 57, structural alleles: A, D, B, C, promoter alleles: X and Y			Structural alleles				Promoter alleles	YA/YA diplotype and high MBL levels may predispose to TB co-infection (in HIV+ patients)	75
		South		A	B	C	D	X	Y	
			146 (HC)	77.1	14.7	4.8	3.8	29.8	70.2	
			151 (HIV+TB-)	73.5	17.9	3.1	5.3	22.2	77.8	
			109 (HIV+TB+)	78	14.2	3.2	4.6	22.9	77.1	
			148 (HIV-TB+)	69.9	17.2	4.7	8.8	20.3	79.3	

HC: healthy controls, EU: exposed uninfected individuals, MBL : mannose binding lectin, IVDU : intravenous drug users, PTB : pulmonary tuberculosis, HRSTD : High risk HIV seronegative sexually transmitted disease.

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APOBEC3 (Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like3) is an endogenous restriction factor for HIV-1 and HBV and has seven family members. All APOBEC3 family members have one (3A, 3C, 3H) or two (3B, 3D, 3E, 3F, 3G) cytidine deaminase motifs that possess antiviral activity. The APOBEC3G deaminates dC to dU resulting in lethal G to A hypermutations in the virus; but can be counteracted by the viral vif dependent proteasomal degradation. Variations in *APOBEC3* genes might enhance resistance to vif and influence antiviral activity. A recent study has shown that an African variant of APOBEC3G H186R is associated with high viral load and progression to AIDS[56,57]. Similarly, a deletion of 29.5 kb from the 5th exon to 8th exon of *APOBEC3B* leads to complete loss of APOBEC3B and this has been reported to be associated with increased risk of HIV-1 infection and disease progression[56].

Studies carried out by our group have revealed that this deletion is present in the north Indian population at a relatively higher frequency (~15%) as compared to those observed in European Americans (7.5%) or the African Americans (3.9%)[57]. However, both in our studies as well as those carried out by the Japanese, this deletion polymorphism is not associated with an increased risk to HIV-1 infection.

TIM (T cell transmembrane immunoglobulin and mucin) family of molecules regulate Th1/ Th2 responses and are crucial in regulating both host immune responsiveness as well as viral replication. TIMs have been under strong selective pressure and their genes exhibit high non synonymous: synonymous substitution ratios. The TIM family has been one of the targets of selective sweep caused by SIV in chimpanzees as evident by the loss of polymorphism in this species. The TIM1 receptor is expressed preferentially on Th2 cells and is a co-activator of Th2 immune responses. Its mucin domain has undergone extensive overdominant selection and a particular haplotype D3-A has been associated with relatively higher CD4 T cell counts among HIV-1 infected individuals in several populations including Indians (Fig. 5a and 5b), Japanese and the Thais[58]. As explained in Fig. 5c, this haplotype is associated with low level of expression of TIM1 which indicates lower Th2 promotion; or enhanced Th1 responses in converse. The latter could favour CD4 T cell proliferation and thus support HIV -1 replication on one hand and augment CTL responses on the other albeit depends upon additional viral and host factors.

It has been reported that an upregulation of TIM3 in HIV-1 progressive patients leads to apoptosis of CD8 T cells[59]. However, individuals carrying HLA-B27 or B57 protective alleles show no such upregulation of

Points to remember

1. The observed differential responses in patients with HIV-1 infection strongly suggest a genetic basis of susceptibility to infection and progression to AIDS.
2. Viraemia controllers are able to resist HIV-1 infection due to their specific genetic architecture and presence of unique prototypes.
3. Non human primates have experienced HIV-1/SIV like viral endemic in the past and evolved as a virtue of specific non synonymous substitutions in immune associated genes.
4. Resistance factors among viraemia controllers and primates like chimpanzees hold the key for identifying crucial genetic markers that are protective in humans.
5. Some genetic factors may be protective against HIV, but may predispose to other pathological conditions. The best example is that of HLA-B*57 which confers protection to HIV infection but is associated with drug induced hypersensitivity following abacavir therapy.
6. The resistance empowered by protective factors, *e.g.*, HLA may eventually be evaded by the virus because keeps evolving into escape mutant forms.
7. Multiline consortia studies are needed to delineate such protective markers among HLA and non HLA genes like *TIM1*, *TRIM5a*, *APOBEC3*, chemokines, *etc.* Such studies would be helpful in improving our basic understanding about the mechanisms involved so that these biomarkers could eventually be translated into clinical practice.
8. Stem cell therapy offers a bright possibility of curing HIV-1 infection. However, further studies with stringent follow ups are necessary to reach a consensus.

TIM3 and, therefore, these cells are able to evade Treg cell suppression[59,60].

Genomic portrait of HIV-1 studies in the Indian population

Numerous reports are now available on the Indian population regarding the influence of genetic factors with reference to HIV-1 infection and AIDS. A compendium of these studies is summarized in Table II.

Is a 'cure' from HIV-1 infection possible?

The first documented case of a 'cure' from HIV infection came from the Charité Universitätsmedizin Berlin, Germany, in February 2007[76,77]. The 40 year old Caucasian male had a 10 year history of HIV infection and a more recent diagnosis of acute myeloid leukaemia (AML). He had been taking HAART for the previous four years which included efavirenz 600 mg, emtricitabine 200 mg and tenofavir 300mg. At the time of AML diagnosis, his CD4+ count was 415 cells/μl and HIV-1 RNA was undetectable. He was offered allogeneic haematopoietic stem cell transplantation (HSCT), seven months after diagnosis. The HSCT donor was HLA compatible for A, B, C, DR and DQ alleles and also homozygous for CCR5Δ32 allele. The HAART was interrupted soon following the HSCT. On a follow up of five years, the patient showed no detectable plasma HIV levels. There was a progressive improvement in his circulating and gut mucosal CD4 T cell counts over the ensuing five years. Interestingly, the patient exhibited a high frequency of activated memory CD4+ cells. These were shown in *ex vivo* experiments to be the favoured targets for infection by any CXCR4-tropic HIV-1 strains. This report demonstrates that although the recovered T cell population is resistant to CCR5-mediated HIV cell entry, these are not resistant to CXCR4-mediated cell entry by X4 tropic HIV. While this case study indicates the scope of gene therapy as a possible cure for HIV, it also raises issues of enhancing sensitivity of currently employed viral assays, risks from long lived non haematopoietic cell reservoirs, and restraints of X4 viruses. These are critical issues and hopefully answers to some of these would become available on long term follow ups.

The second report was recently relayed from Harvard Medical School, Boston, USA, about two HIV patients who later developed Hodgkins lymphoma and underwent allogeneic HSCT from HLA matched donors[78]. The main difference in these patients from the Berlin patient was that the donors in Boston were not carrying CCR5 Δ 32 deletion. Although, it is too early to comment, the good news is that the patients appear to be free of the HIV disease so far and are not dependent on HAART therapy.

The third recent report is from the University of Mississipi Medical Center, Jackson, USA, about an infant and a similar report of a group of 14 adult individuals, who were all given an early treatment and were able to resist infection[79-81]. These reports highlight the importance of identifying potential HIV patients at very early in their infection stage so that they could benefit from directed HAART interventions.

Acknowledgment

The financial assistance from the Department of Biotechnology (DBT), Department of Science and Technology (DST) and Indian Council of Medical Research (ICMR) Government of India is gratefully acknowledged. The authors acknowledge all the collaborators from the All India Institute of Medical Sciences (AIIMS) New Delhi, National AIDS Research Institute (NARI) Pune, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, National Institute for Research in Tuberculosis (NIRT), Chennai, Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE) Chennai, Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Kashmir, New York University (NYU) School of Medicine, New York and Tokyo Medical and Dental University, Japan, for providing inputs and efforts. The Fogarty AITRP Fellowship for AIDS international training research program provided to the first author (GK) for training at the New York University is gratefully acknowledged.

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