Review Article

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Genetic correlates influencing immunopathogenesis of HIV infection

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Variability to HIV infection, its progression as well as responsiveness to antiretroviral therapy (ART) is observed among individuals including viraemia controllers or exposed uninfected, rapid versus slow progressors and ART responders compared to non responders. This differential responsiveness/ vulnerability to HIV-1 is governed by multiple host genetic factors that include HLA, cytokines, chemokines, their receptors and others. This review highlights the influence of these genetic factors on HIV/AIDS outcome; however, in India, the information in this area is very limited and most of these genetic studies have been conducted in Caucasian and South African populations. Considering, the population specific differences in the frequencies of protective or susceptibility favouring alleles and their influence on the disease outcome, it is of utmost importance to strengthen ongoing efforts towards defining largely unknown genetic propensity in Indian population, particularly by recruitment of large cohorts of well categorized exposed uninfected individuals, rapid, long term non progressors and elite viraemic controllers. Multi-parametric analysis of these potentially interactive immunogenetic variables in these cohorts may help to define potential targets for diagnostics and therapy in a population specific manner.

Key words Chemokines - cytokines - clades - exposed uninfected individuals - genetic correlates - genetic variants - HIV - HIV/AIDS - HLA - immunopathogenesis - rapid & slow progressors - viraemia controllers

HIV virology, diversity and clades

The HIV virion has a diameter of about 100 nm, enveloped by host cell derived lipid bilayer acquired during budding from host cell. Briefly, its genome consists of two identical copies of single stranded RNA molecules, is about 9 kilo bases in length, contains 9 open reading frames and is characterized by the presence of structural genes *gag, pol* and *env* and a complex combination of other regulatory/accessory genes. The *gag* gene encodes the structural proteins of the core (p24, p7 and p6) and matrix (p17) and the *env* gene encodes the viral envelope glycoproteins gp120 and gp41, which recognize and bind to host cell surface receptors. The *pol* gene encodes for enzymes involved in viral replication including the reverse transcriptase that converts viral RNA into DNA, the integrase that facilitates incorporation of the viral DNA into host chromosomal DNA (the provirus) and the protease that cleaves large Gag and Pol protein precursors into their components. The accessory or regulatory genes of HIV (*tat, rev, vif, vpr, nef* etc.) modulate virus replication[1].

Virologically, HIV is an extraordinarily variable virus that lacks proofreading mechanisms accompanied by high error rate (0.2-2 mutations per genome per cycle)[2], high replication rate, an apparent high tolerance and selection for change.

Further, the HIV superinfections allow a volatile mechanism for genetic diversification and can permit novel recombinants between distant forms[3]. HIV has diversified into multiple genetic subtypes or clades and is broadly divided into three distinctive groups: group M (for Main), mainly responsible for the global epidemic, group O (for Outlier) and group N (for Not M, Not O). Group O appears to be restricted to west-central Africa[4] and group N - a strain discovered in 1998 in Cameroon - is rare[5]. These groups have genetic sequence differences of >40% in some coding regions. In 2009, another strain was discovered in a Cameroonian woman, which is closely related to gorilla SIV and was designated as HIV-1 group P (Plantier)[6]. However, globally >90 per cent of HIV-1 infections belong to HIV-1 group M and nine genetic subtypes (A,B,C,D,F,G,H,J,K) circulate in the epidemic and two recombinant forms (CRF01_AE and CRF02_AG) are also of major importance. Many other recombinant forms circulate at lower levels in limited geographical range.

Considering the emerging epidemiological numbers at global levels, it is important to mention that as a virus, HIV evolved significantly and smartly to counter act the well known hallmarks of our immune system, *e.g.* it targets the memory $CD4^+$ cells, does not allow immune specificity to work and can generate enormous diversity (defeating hallmarks). Incidentally, not a single convincing vaccination approach has as yet become available to combat HIV/AIDS and that this has compounded the problem even further. Some of the major scientific challenges/hurdles in developing an HIV vaccine include *(i)* inadequate understanding of the immunological correlates of protection against HIV/AIDS, *(ii)* high degree of mutations and variability of HIV, *(iii)* lack of suitable animal models for study, and *(iv)* genetic diversity of HLA molecules, both at the population level as well as in individuals.

These facts and estimates about HIV/AIDS justify the need for an in depth understanding of the disease pathogenesis. It is conceivable that the biological diversity of the virus evolved over a period of time provides human host with definite yet unexplored defensive mechanisms to deal with the infection in a more robust manner. This review highlights the influence of various immune response genes associated with challenges posed by HIV on the host.

Differential vulnerability to HIV/AIDS

HIV infection leads to a progressive decline in peripheral CD4 T cell numbers, T cell dysfunction, thymic dysfunction and defects in both number and functions of antigen presenting cells such as dendritic cells and monocytes. Although, a number of variations are seen in different patients, without therapeutic intervention, majority (70-80%) of HIV infected individuals develop AIDS after 8 to 10 years of clinical latency and the disease commonly proceeds in 3 stages: *(i)* acute primary infection, *(ii)* asymptomatic chronic phase, and *(iii)* symptomatic phase and progression to AIDS. On the contrary, about 10 per cent individuals, known as rapid progressors, develop AIDS within 3 years or less[7]. In contrast, some patients (about 5%), are long term non progressors (LTNPs) and remain asymptomatic for more than 10 years, even in the absence of treatment, maintain low viraemia and normal CD4 counts[8]. Further, the presence of some highly exposed persistently seronegative (HEPS) groups suggest the importance of natural and acquired immunity to HIV, which in turn defines the clinical outcome. Moreover, reports suggest inter-individual variability towards antiretroviral drug responsiveness among AIDS patients, in terms of drug pharmacokinetics and pharmacogenomics[9-11]. Therefore, it is of utmost importance to define and understand which factors contribute to this variability in terms of virological, clinical and immunological control of the virus, development of disease among HIV +ve individuals and how these are going to ultimately influence the HIV epidemic in a region-specific manner. The inter-individual variability of HIV susceptibility and progression towards AIDS is shown in Fig. 1.

Highly exposed persistently seronegative individuals

A large number of cohorts of HIV exposed persistently seronegative (HEPS) individuals have been identified globally. The UCLA Multicenter AIDS Cohort Study (MACS)[12] suggested protection for a group of homosexual men. Similarly, in Kenyan female sex workers heterogeneity towards HIV susceptibility was observed[13]. Further, immunologic studies reported HIV specific T cell immune responses in HIV exposed spouses of discordant couples[14]. This cohort is useful for studying the genetic, immunologic and environmental factors that confer natural protection and viral resistance even after repeated exposures. Generally these HEPS fall into three categories: *(i)* Discordant couples, *(ii)* Individuals

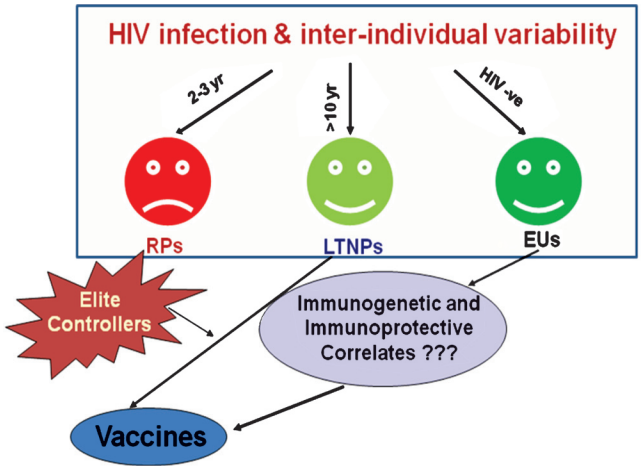

Fig. 1. Inter-individual variability to HIV infection and disease progression. Exposed uninfected (EU) individuals show resistance to HIV acquisition even after multiple exposures and high risk behaviour. Long-term non-progressors (LTNP) maintain stable CD4 levels and low virus load (VL) for ten or more years, Rapid progressors (RPs) who cannot control viraemia and develop AIDS within three years of infection, and Elite controllers (EC), who represent just 1% of HIV-infected persons, control HIV replication to <50 copies/ml.

with high risk sexual behaviour including commercial sex workers (CSWs) and men who have sex with men MSM), and *(iii)* individuals exposed nonsexually that include injection drug users, haemophiliacs, infants born to HIV-infected mothers and other exposed to contaminated blood products.

Viraemic controllers, rapid and slow progressors

The inter-individual variability of HIV disease progression is supported naturally by the presence of different clinical progression groups in humans and non human primates. Table I demonstrates the general patterns and relationship between viral loads, CD4+ T cell counts and disease progression, however, these patterns and the underlying determinants are only partially understood.

Non human primates: Macaques and Chimpanzees

Non human primates serve as important models to study AIDS and correlates of protection because natural infection of these hosts by the simian immunodeficiency virus (SIV) is characterized by the general lack of progression to AIDS and reduced vertical transmission. Although, recently a few cases of simian AIDS have

Table I. Five clinical progression groups as mentioned and defined in literature[15-19]

Long term non progressors

(A) Elite controllers

1. Asymptomatic, over 10 year after seroconversion
2. Undetectable plasma viral RNA levels for the respective assay (*e.g.*,<75 copies/ml by bDNA or, <50 by ultrasensitive PCR) even without ART
3. Rare non consecutive episodes of viraemia up to 1000 copies/ml
4. Minimum of 3 longitudinal viral load determinations, in the absence of ART, spanning at least a 12-month period

(B) Viraemic controllers

1. Same as in A 1
2. Plasma HIV RNA levels equal or below 2000 copies/ml without ART
3. Rare non consecutive episodes of viraemia above 2000 copies/ml
4. Same as in A 4

(C) Viraemic non controllers

1. Same as in A 1
2. More than 50% of the samples indicating plasma HIV RNA levels above 2.000 copies/ml without ART

Chronic progressors

1. Symptomatic, or initiation of ART within 10 years after seroconversion
2. Minimum of 3 longitudinal viral load determinations, in the absence of ART, indicating a viral set point above 2000 copies/ml

Rapid progressors

1. Two or more CD4 T cell counts below 350 µl within 3 years after seroconversion, with no value ≥350 afterwards in the absence of ART
2. And/or, ART initiated within 3 years after seroconversion, and at least one preceding CD4<350/µl
3. And/or, AIDS or AIDS-related death within 3 years after seroconversion and at least one preceding CD4<350 µl

ART, antiretroviral therapy

been reported in naturally or experimentally infected African green monkeys (AGMs), sooty mengabeys and mandrills, such instances are rare[20].

These natural, nonprogressive SIV infections represent an evolutionary adaptation that allows harmless co-existence between primate lentiviruses and their hosts' immune system. This evolutionary advantage does not result in reduced viral replication but rather it involves phenotypic changes to $CD4^+$ T cells, controlled and limited immune activation and preserved mucosal immunity. It is interesting to note that the HIV-1 epitopes mapped in chimpanzees have been shown to be remarkably similar to those identified in human LTNP cohorts, suggesting that in both species, cytotoxic T lymphocytes (CTLs) could have an important role in protection. Further, considering the genetic and evolutionary relatedness to humans (98% between chimpanzees and humans), vaccine research on these animal models could be greatly beneficial in designing novel therapeutic strategies.

Immune correlates of protection

Studies of immune depletion and passive immunization in animal models strongly suggest that both cell mediated and neutralizing antibodies mediated immune responses provide effective protection from HIV infection and from disease progression. Polyfunctional (IL-2 plus IFNγ) $CD4^+$ and $CD8^+$ T cell responses were found to be superior in viraemic control and maintaining homeostasis of the immune system[21]. Adaptive immune responses comprising neutralizing antibodies and virus specific $CD4^+$ and $CD8^+$ T cells, are the major correlates of protection in functional terms.

Further understanding of these correlates is required to define the differential vulnerability towards HIV-1/AIDS, contributed by the complex interactions between a number of host genetic, immunological and virological factors. The host genetic factors play a major role in defining this heterogeneity of disease progression and susceptibility.

HIV/AIDS restriction vs permissivity: polygenic effect

The heterogeneity in HIV infection after exposure and also in the clinical course of the disease can be studied using cohorts of transmission and disease progression phenotypes, including exposed uninfected individuals, fast and slow progressors. Identifying host genetic factors and alleles, the major cause of this heterogeneity (protection vs risk), and their influences in these HIV infection/transmission and progression phenotypes, are the main objectives of host genetic research in this field. An understanding of the host genetic factors and their interaction with immune and virological factors could yield important information on the immunopathogenesis of HIV infection. In last few years, there is an upgradation of technologies and as a result, the host genetics of HIV/AIDS using candidate gene based approaches is now moving simultaneously towards greater depth of whole genome analysis using advanced gene discovery approaches and integration through systems biology.

Large cohort and candidate gene based studies (done primarily in the Caucasian population) have highlighted the importance of host determinants comprising a number of immune response genes[22] that contribute towards differential vulnerability of individuals to HIV/AIDS outcome. This includes genes that regulate HIV cell entry (like chemokine co-receptors and their ligands), those that influence acquired and innate immunity (major histocompatibility complex, killer cell immunoglobulin-like receptor, and cytokines), as well as others including tripartite interaction motif 5 a (TRIM5α) and apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G (APOBEC3G). The latter have recently been identified and are known to influence HIV-1/AIDS outcome. These host factors and their variants presumably alter the transmission from an infected host primarily by regulating the replication of virus and the concentration of the particles circulating in the blood and mucosal secretions of the potential donor. There is a compelling evidence suggesting influence of genetic variations on HIV viral load set point, rate of CD4 T cells decline, susceptibility to specific AIDS defining illnesses and response to antiviral therapy[23,24].

O'Brien *et al*[22] have performed a meta-analysis of five different cohort studies from Multicenter Hemophilia Cohort Studies (MHCS), AIDS Linked to Intra-Venous Experience (ALIVE), Hemophilia Growth and Developmental Study (HGDS), Multicenter AIDS Cohort Study (MACS), San Francisco City Clinic Men's Study (SFCC). They suggested that evaluation of the 'Genetic Propensity Index' (GPI) of an individual based on the distribution of 'AIDS restriction genes' that limit AIDS (chemokine ligands and receptors or others like the cytokines or HLA or Killer immunoglobulin like receptors (KIRs) could be a useful way of identifying 'at risk' individuals. Hence based on the genetic profile

of three sets of immune associated genes, the genetic propensity indices of individuals vary significantly depending on the presence or absence of protection conferring genes. Thus, if a population possesses more of the protective alleles, it would be expected to have greater number of AIDS free individuals. Therefore, GPI can help predict survival kinetics, improve diagnostics and treatment of AIDS at individual and/or population specific manner.

Fellay *et al*[25] have proposed that an additive genetic score could predict HIV-1 disease progression. The progression outcome (initiation of combined antiretroviral treatment with CD4+ T cells < 500/μl) during the first 5 years after estimated date of seroconversion were determined in categories defined by HIV-1 viral load and by a simple additive genetic score in individuals of Caucasian ancestry (n=1071). In this study, the individuals were stratified with minimum score of 0 for those who were homozygous for the major allele at rs2395029 (a proxy for HLA-B*5701), rs9264942 (HLA-C -35 variant), rs9261174 (ZNRD1), and CCR5-D32. The study suggested that the calculated genetic score refines the prediction of progression, beyond the information provided by viral load only, throughout the range of set point values.

The results of various candidate gene studies and the meta-analysis of several large AIDS cohorts have revealed multiple genetic variants, *i.e* AIDS restriction genes that affect HIV entry, intracellular replication as well as innate and adaptive host responses (Table II).

These AIDS restriction genes (ARGs) including chemokine receptors, their ligands, MHC molecules, cytokines, their receptors, factors that are directly involved in HIV-1 cell entry, immune recognition and antigen presentation, are discussed further.

Influence of HLA on HIV/AIDS

The human leukocyte antigen (HLA) system is encoded by the most polymorphic region of the human genome, the major histocompatibility complex (MHC). The collection of the genes arrayed within this region spans 4×10^6 nucleotides on the short arm of chromosomes 6 at position 6p21.3. These genes are arranged in three distinct regions, each comprising of a cluster of immune response genes (Fig. 2A).

The inherent features of the MHC include *(i)* extreme polymorphism of this region across various ethnic groups (most polymorphic genomic region), suggesting its evolutionary significance and selection pressure at this region. A total of ~6400 HLA alleles have been named and numbers of allelic variants are expanding with the time[44,45]; *(ii)* high degree of linkage among various loci; and *(iii)* ability to present antigenic peptides promiscuously to generate immune responses. These features make this system of particular interest in biology and medicine, protect humans from ever evolving pathogens that enter the body, develop cell mediated and humoral immune responses, and also determine whether a transplanted tissue will be accepted as self or rejected as foreign.

Presentation of antigenic peptides to $CD8^+$ and $CD4^+$ T cells is restricted by MHC class I and class II molecules, respectively, which are expressed on the surfaces of antigen-presenting cells (Fig. 2B). Most of the amino acid substitutions are concentrated in the peptide binding groove of HLA molecules and thus define the nature of epitope peptides to be presented to CD8+ and CD4+ T cells. The virus-specific CD8+ T cells play key role in controlling viral replication by targeting HIV-1 peptides presented through class I molecules on infected cells and by establishing a dynamic equilibrium between the evolving virus and the HLA-restricted adaptive host immune response[46].

The genetic diversity in the HLA system influences different aspects of HIV-1/AIDS like viral transmission, control of dynamics of viral equilibration and progression, development of opportunistic infections and even response to therapy including the observed hypersensitivity to ART drugs[23,24,26,38]. Further, the HLA class I restricted immune responses exert direct effect by imprinting mutations in HIV-1, which in turn defines viral diversity, its replicative and evolutionary fitness. Hence, identification of the conserved immunodominant HIV epitopes that can be presented by HLA alleles most commonly found in a population would have implications for designing MHC based vaccines. Incidentally, HLA diversity imposes a potential limitation on the development of candidate vaccine designs, and there are uncertainties on population or clade specific vaccine approaches over global vaccine approach. During the last few years genome wide studies have highlighted the role of human lymphocyte antigen system[47] amongst the securely identified host factors associated with HIV/AIDS outcome. Some of the well established HLA associations with the HIV infection and progression are summarized below:

HLA class I alleles: Two alleles *HLA-B**27 and *B**57 have consistently been found to be associated with

Table II. Summary of studies focused on human genetic variants involved in modulating HIV pathogenesis. These have been grouped into genes influencing HIV entry, post HIV entry and those associated with acquired and protective immunity

Chromosome (genetic loci)	Gene product	Gene variant	Association	Refs
HIV entry				
Viral co-receptors				
3p21	CCR2	64I	Delayed progression	27
3p21	CCR5	Δ32	Protection/resistance, delayed progression	28
3p21	CCR5	C20S	Protection in the presence of Δ32	29
3p21	CCR5	C101X	Protection in the presence of Δ32	29
3p21	CCR5	G106R, C178R, C269F	HIV resistance /Delay AIDS	29
3p21	CCR5	59029AA	Faster progression	29
3p21	CCR5	P1 [Promoter haplotypes]	Faster progression	29
3p21	CCR5	HHC Promoter haplogroup	Faster progression in Japanese	30
3p21	CCR5	HHE Promoter haplogroup	Faster progression in Caucasians	31
3p21	CX3CR1	I249/M280	Faster progression	29
19p13	DC-SIGN	Promoter variant	Parenteral infection	32
Co-receptor ligands				
17q11	MCP1/MCP3/Eotaxin	H7 haplotype	Decrease susceptibility to infection	32
17q12	MIP-1 α (CCL3L1)	Gene copy number	Susceptibility to infection	33
17q12	MIP-1β (CCL4L1)	L2	Susceptibility to infection	34
17q12	RANTES (CCL5)	-403A , -28G (promoter)	Delayed progression	35
17q12	RANTES (CCL5)	In 1.1C (intronic)	Faster progression	36
10q11	SDF-1(CXCL12)	3'A	Delayed progression?	37
Post HIV entry				
11p15	TRIM 5α	Haplotype 9	Increase transmission	32
11p15	TRIM 5α	136Q,43Y	Protection/resistance	32
22q13	APOBEC3G	186R, C40693T	Faster progression, Increase transmission	32
11p15	TSG101	-183C	Rapid CD4 T cell decline	32
Acquired/innate immunity				
6p21	HLA	B*27	Delayed progression	38
6p21		B*18	Faster progression	38
6p21		B*57	Delayed progression	38
6p21		B*35Px	Faster progression	38
19q13; 6p21	KIR3DS1	3DS1 + HLA-Bw4-80Ile	Delayed progression	39
19q13; 6p21		3DL1 + HLA-B*57	Delayed progression	40
Cytokine genes				
12q14	Th1([γ-IFN)	+874T allele	Delayed progression	41
1q31	Th2 (IL10)	IL10-5′-592A	Faster progression	42
5q31	Th2 (IL4)	-590T	Faster progression	43

Source: Adapted and modified from Ref. 26

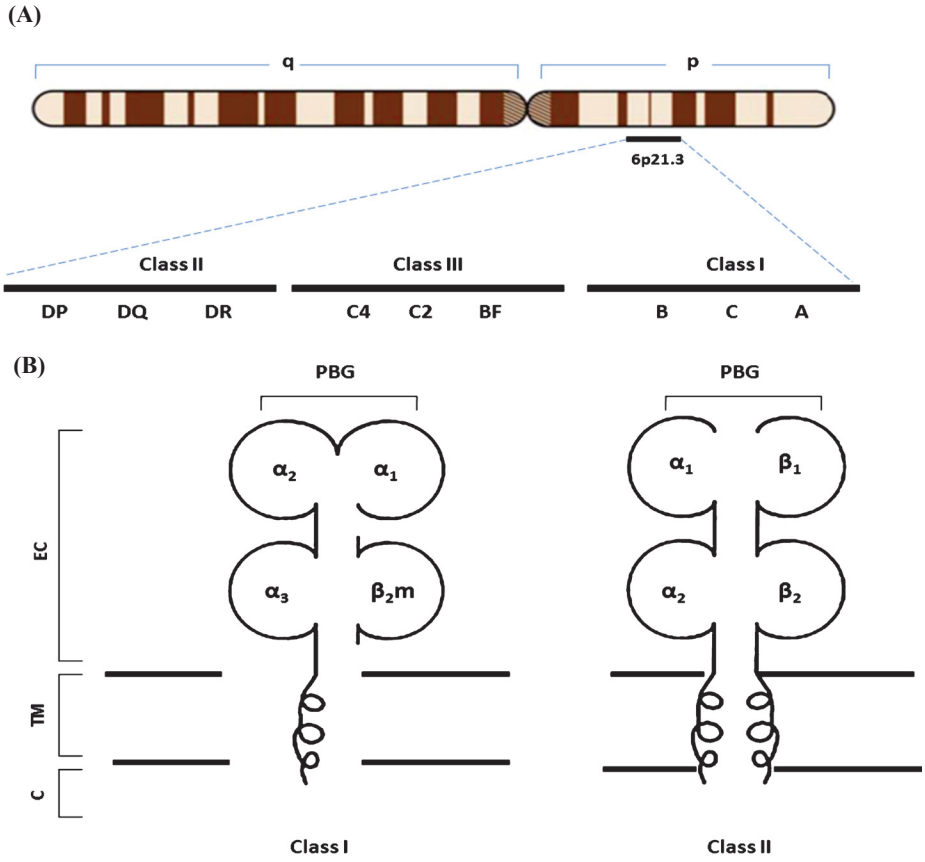

Fig. 2. (A) Chromosomal location and gene map showing multiple genes within the MHC region on the short arm of chromosome 6 (6p21.3) of man. **(B)** Schematic view of HLA class II and class I molecular structures showing the peptide binding groove/clefts formed between α1 and β1 domains in class II and α1 and α2 domains in class I molecules, respectively. The membrane proximal domains (α2, β2 of class II and β2 microglobulin and α3 of class I) are conserved and non polymorphic.

a favourable prognosis, irrespective of differences in ethnicity, virus clade, and risk group[48]. Several molecular subtypes of B*27 (~96) are known that differ from the more common B*2705 'prototype' by one or a few amino acid residues. The presence of Glu^{--} at position 45 (negative charge) in the B pocket of HLA-B*27 alleles allows strong selection of peptides with a positively charged Arg^{++} at position 2 which in turn could be responsible for slow disease progression[49]. The other known protective alleles *i.e.* B57 restrict CTL responses, specifically targeting multiple HIV-1 peptides against *gag* and reverse transcriptase motifs. This broad peptide recognition specificity of B57 could account for compromised viral fitness leading to its AIDS protective nature.

In contrast, other allelic groups (B22 serogroups, HLA-B*35 and B*53) have been shown to be associated with unfavourable prognosis or higher viral RNA levels in HIV patients. Currently, the HLA-B*35 can be split into 210 subtypes and these set of alleles can be grouped into B*35Px or B*35Py depending on their ability to bind peptides. The HLA-B*35Py molecules preferentially bind peptides carrying a tyrosine residue (Y) at position 9 of the peptide while B*35Px molecules have no such preferential binding. Previous reports suggest that HIV infected individuals carrying B*35Px alleles (*e.g.* B*3502/03/04) progress to AIDS faster as compared to those carrying HLA-B*35Py set of alleles (B*3501/08), who progress rather slowly[50]. The differential peptide preference and relative efficiency of B*35Px and B*35Py in presenting specific HIV-1 epitopes to CTLs, presumably, could lead to either ineffective or a protective immune response. Fig. 3 summarizes the brief overview of the proposed mechanisms of these alleles as described by Gao *et al*[51].

Considering their importance and based on the published allele frequency data[52], the distribution pattern of these protective and risk conferring alleles in various populations in comparison to the data on north

Fig. 3. 'Trinity' of HLA-B alleles (B*27, B*57 and B*35), that exert their effect at distinct intervals of viral pathogenesis.

Indians from our study[24] is shown in Fig. 4. As can be observed, the overall pattern of distribution of trinity of these alleles is similar in various populations with B*35 being the predominant allele.

Heterozygosity and homozygosity: Carrington and co-workers first showed that heterozygosity at class I loci (A, B, C) was associated with delayed AIDS progression among HIV-1 infected patients, on the other hand, homozygotes progressed rather rapidly to AIDS and death[53]. This could be as a result of diversity in presentation of antigenic peptides to effector T cells by the presence of larger allelic diversity. Therefore, it takes longer for escape mutants to arise in heterozygous compared with homozygous individuals. On the other hand, homozygisity of HLA-Bw4 bearing B alleles, was found associated with a significant advantage against HIV viraemia[54]. This can be as a result of regulation of natural killer cell activity because Bw4 acts as a ligand for KIRs on these cells.

HLA class I supertypes: HLA alleles can be grouped together as HLA supertypes on the basis of their overlapping peptide binding properties, where different members of a supertype bind similar peptides, yet exhibiting distinct repertoires[55]. Some HLA supertypes have previously been shown to be associated with HIV transmission and with circulating HIV concentration[23,24,26,38]. For example, Kenyan women carrying *HLA-A2/A6802* supertype were found protected from HIV-1 subtype A infection and reduced MTC transmission[56]. Similarly, in the MACS cohort, the same *HLA-A2/A6802* supertype observed more frequently among HEPS individuals than among those with HIV-1 subtype B seroconversion[57].

In the B locus, alleles in the HLA-B7 supertype (includes B7, B35, B51, B53, B55, B56, B67 and B78), which are relatively common in most populations[55], were found to be associated with high viraemia, poor CTL responses and fast progression to AIDS in Caucasoid and African-Americans infected predominantly with HIV-1 subtype B[53,58-60]. Some of the HLA-B7 supertype alleles (namely, B*3502, *3503, *3504 and

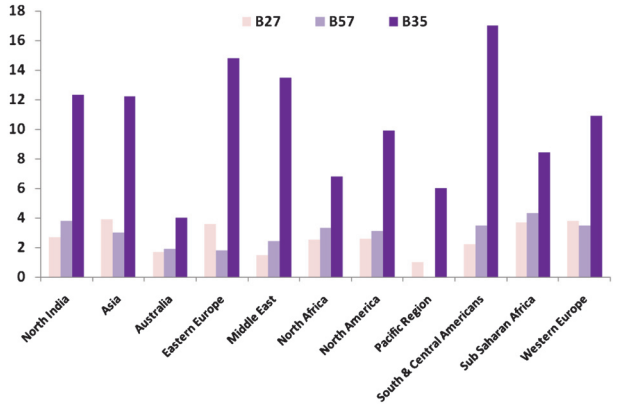

Fig. 4. Distribution of 'trinity' of HLA-B alleles (B*27, B*57 and B*35). Data on north Indians from our study[24], while those in other ethnic groups from[52].

*5301), that associate with faster progression to AIDS, preferentially engage with antigenic supermotifs with certain residues (Leu, Val, Met) at their C' terminal. On the other hand, other alleles of the HLA-B7 supertype (B*3501 and *3508) (not associated with faster disease progression) prefer to engage supermotifs with just a tyrosine at the C terminal[51].

HLA class II alleles: Diversity at HLA class II loci could influence antigen presentation and viraemic control by influencing the virus specific $CD4^+$ T cell responses and induction of HIV specific CTLs. However, only limited information is available on the role of class II alleles/haplotypes with HIV-1 disease[61-63]. Previously a correlation was observed between homozygosity at HLA-DRB1 and reduced risk of developing pulmonary TB among HIV infected subjects[64]. In a perinatal study, higher frequency of HLA-DRB1*03 in infected infants and DRB1*15 allele in uninfected infants born from HIV positive mothers has also been reported[65]. Further, HLA-DR2 was reported as a susceptibility marker in south Indian HIV patients[66].

Haplotypic associations: Two extended haplotypes, namely HLA-A1-Cw7-B8-DR3-DQ2 (ancestral haplotype AH8.1) and HLA-A11-Cw4-B35-DR1-DQ1 have been implicated in faster progression to AIDS among the Caucasian HIV +ve subjects[60,67]. However, the mechanisms underlying for the observed loss of CD4+ T cells are yet unexplored. The association of AH8.1 with susceptibility to several autoimmune diseases, including type 1 diabetes, dermatitis herpetiformis, systemic lupus erythematosus, common variable immunodeficiency and IgA deficiency are well

reported among Caucasians[68]. The hyper-activation and/or autoimmunity conferred by this haplotype might be involved in the progressive immunodeficiency in AIDS. Incidentally, the AH8.1 haplotype is rather rare in the Indian population and has been compensated by another related haplotype HLA-A26-Cw7-B8-DR3-DQ2 designated as AH 8.2[69], which is strongly associated with susceptibility to autoimmune diseases like celiac disease[70] and type 1 diabetes[71] in north Indians, however, its impact in HIV infection remains obscure. An over-representation of haplotype HLA-A*1101- B*3520-Cw*1507 has been reported among Indian patients with AIDS[72].

HLA and drug hypersensitivity: MHC ancestral haplotype HLA-B*5701-DRB1*07 (AH57.1) has strong association with abacavir hypersensitivity syndrome (AHS) with 2 to 8 per cent of HIV infected Caucasian patients develop hypersensitivity within 10 to 40 days after initiation of chemotherapy[9]. Further, HLA-B*5701 has been found to be highly predictive of clinically diagnosed AHS in several study cohorts[10]. Accordingly, mandatory screening of B*5701 before abacavir therapy has been recommended in the US and Europe[73]. A recent report suggests that the drug induces specific HLA-B*5701 restricted CD8+ T cell responses[74]. The residues 116 and 114 in the 'pocket F' of the peptide binding cleft of a B*5701 molecule are of particular importance and contribute towards drug specific binding. In addition, associations of HLA-DRB1*0101 and Cw8 with sensitivity to nevirapine, have been observed[11].

Rare HLA alleles: Recent epitope based studies have shown that HLA alleles encountered by HIV in hosts with common HLA alleles generally require limited virus diversification to attain escape status and evade resulting in higher viral loads. On the other hand, in individuals with rare HLA class I alleles, there is possibly an unexpected encounter of the virus with HLA, leading to greater adaptive evolution albeit with low fitness/reversion[75], thus resulting in decreased viral loads by offering 'selective advantage' to the host against the pre-adapted virus. A recent report from the Japanese population has suggested the evolutionary impact of host HLA phenotype on virus fitness. According to the study, the highly prevalent HLA-B*51 (~20%) was protective initially, but over a span of 25 yr, the virus evolved and had adapted a mutation I135X linked to B*51 to a point of fixation. Accordingly, the protective effect of this allele is beginning to wane gradually[76].

Chemokine system: HIV entry gateways and blockers

The chemokines and their receptors comprise an expanding group of immunoregulatory molecules involved in regulating leukocyte trafficking during development, homeostasis, inflammation and infection. These are 8-10 kDa proteins sharing 20-95% homology in amino acid sequences[77] and are classified on the basis of the arrangement of four conserved cysteine residues into four families: *(i)* the α chemokine family where the first two cysteines are separated by an amino acid (cysteine-X amino acid-cysteine, or CXC), *(ii)* the β-chemokine family where these two cysteines are adjacent (cysteine-cysteine, or CC), *(iii)* Lymphotactin, a "C" chemokine, is homologous to CC members but lacks the first and third canonical cysteines, and *(iv)* Fractalkine, represents a class in which the chemokine moiety sits atop a membrane anchored mucin like stalk and contains a unique CX3C motif. The chemokine receptors belong to the seven transmembrane G protein coupled receptor group. Although the families lack sequence homology, they share a common transmembrane core (TMI-VII) with three intracellular (i1-i3) and extracellular (e1-e3) loops. Two conserved cysteines in e1 and e2 are disulphide bonded. The TM I-VII traverses the membrane with grouping of ectodomains to generate chemokine binding sites. Interactions with the respective ligands change the core conformation of the receptors which in turn expose G protein binding site for downstream signaling.

In the middle of 1996, a novel mechanism of HIV and host factors' interaction was revealed upon the identification of chemokine receptors as requisite strain specific co-receptors for viral fusion and subsequent entry into host cells[78]. Another study identified the CC chemokines macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES as the primary mediators of soluble $CD8^+$ T cell derived HIV inhibitory activity[79]. Since then, various chemokine receptors and their ligands have been implicated in HIV pathogenesis and viral entry process. However, influence of chemokines on HIV outcome, their production and activity must be considered in the context of cytokine regulatory network, as well as the *strain* of HIV.

Among various chemokine receptors, CCR5 and CXCR4 are the major co-receptors used by HIV. Based on co-receptor usage, viral variants can be grouped as CCR5 (R5) or CXCR4 (R4) or both (R5X4) (Fig. 5). The former are the nonsyncitium inducing while the latter are predominantly syncitium inducing virions.

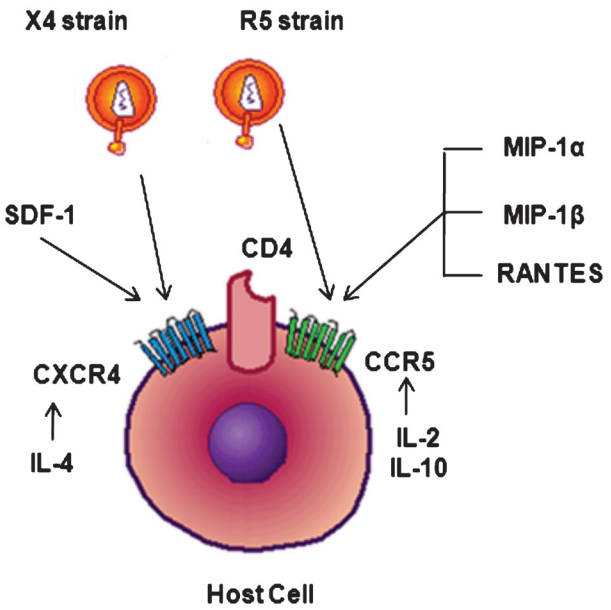

Fig. 5. Chemokines and their receptors network guiding the HIV entry. CCR5 and CXCR4 co-receptor utilization by the HIV R5 and X4 virions in the macrophages and T cells respectively. MIP-1, macrophage inflammatory protein-1; RANTES, regulated upon activation normal T cell expressed and secreted; SDF-1, stromal derived factor-1; CCR5, receptor 5 for β family (cysteine-cysteine, or CC) of chemokines; CXCR4, receptor for α family (cysteine-X-cysteine, or CXC) of chemokines.

The major determinants of HIV tropism were identified within the third variable (V3) domain of gp120, however, the largest co-receptor binding surface is provided by the bridging sheet and adjacent structures. The N terminal domains of CCR5 or CXCR4 are modified post-translationally with sulphate moieties on tyrosine residues, which could possibly allow electrostatic interaction with positively charged amino acid residues in the bridging sheet and the V3 base. However, the signaling function of the co-receptors is not required for HIV entry[80].

Several genetic variants of genes encoding HIV co-receptors and their respective chemokine ligands (*e.g.* for CCR5: RANTES, macrophage inflammatory protein α, β and MCP-2, for CXCR4: SDF-1) have been described, and some of these variants have been reported to be associated with resistance to HIV infection and/or disease progression.

Chemokine receptors: CCR2 and CCR5 variants

(i) The CCR2-64I variant - A valine to isoleucine substitution at position 64 within the first transmembrane region of CCR2 has been associated with 2-4 years delay in disease progression to AIDS compared to individuals carrying the wild type allele in homozygous state[27,81]. Among the HIV-1 discordant couples in Thailand, CCR2 64I homozygosity was found associated with a reduced risk of viral transmission[82]. The population frequency of this 64I allele is 8-10 per cent among Caucasians, 15-17 per cent among subjects of African origin[27,81] and 20.6 per cent in the Chinese populations[83]. The close proximity of CCR2 gene to CCR5 on chromosome 3p21.3[84] suggests that the observed impact of this mutation could possibly be as a result of linkage with highly polymorphic CCR5 promoter region.

We observed no significant difference in the allelic distribution of CCR2-64I between healthy (11.7%) and HIV+ subjects (11.1%) in north Indians[85]. According to our results, 64I mutation may be an important determinant of HIV infection and/ or disease progression but does not appear to be associated with acquisition of HIV infection in subjects of north Indian origin. Our findings are consistent with another study on exposed but uninfected partners of HIV-1 infected individuals from north India which showed no correlation of CCR2 polymorphism with susceptibility against HIV[86].

(ii) CCR5 Δ32 mutation - CCR5 acts as a major co-receptor for entry of R5 isolates and is generally expressed on the surface of monocytes/macrophages, dendritic cells, microglial cells and activated T cells. *CCR5* gene is highly polymorphic and variants have been found to be associated with resistance to HIV-1 infection and rate of disease progression[27]. In this naturally occurring knockout deletion the presence of a premature stop codon results in truncation of the protein synthesized, which is not expressed on the cell surface, thus effectively restrict HIV-1 cell entry in homozygous people and delayed AIDS progression in heterozygotes[27,28]. In Northern Europe, CCR5-Δ32 occurs at a frequency of 10-16 per cent and its frequency decreases in a Southeast cline toward the Mediterranean and the mutation gradually disappears toward the African and Asian populations[87]. In our studies[88], we could not identify any homozygous CCR5-Δ32 individual among 193 healthy controls and 257 HIV infected individuals, however, four in the former group and 10 HIV +ve subjects were found to have this deletion in heterozygous state. Low occurrence of this mutant (Δ32) allele was in accordance with the previous published reports in the healthy Indian population[89-91], which suggest that this protective mutation is overall rare in this population.

(iii) CCR5 promoter region variants - The promoter region of *CCR5* gene is highly polymorphic and based on distribution of SNPs has been organized into seven different haplotypes, namely, HHA, HHB, HHC, HHD, HHE, HHF (F*1, F*2), and HHG (G*1, G*2)[84]. These *CCR5* promoter haplotypes are associated with susceptibility to HIV infection and disease outcome[29]. It is suggested that individuals who are homozygous for allele *CCR5**59029G may progress to AIDS more slowly compared to those who are homozygous for the *CCR5**59029A allele[92]. The *CCR5**59356 T allele occurs more frequently in African Americans as compared to Hispanic or Caucasian persons, and its homozygosity or presence of HHD haplotype has been correlated with increased rate of perinatal transmission[93]. Further, HHE homozygosity was associated with both HIV infection and rapid progression in Caucasians[31]. In addition, it has been reported to be associated with HIV-1 infection, accelerated CD4 decline, and disease progression in Thai IDUs and HEPS individuals[94,95]. Similarly, HHC is correlated with faster disease progression among African Americans[84]. On the contrary, in the Thai population, this haplotype is reported with slower disease progression[94]. The HHG*2 and HHF*2 haplotypes have also been found associated with slower HIV disease progression among Caucasian and African-American individuals, respectively, probably because of the protective effects of d32 and CCR2 64I respectively[84].

Our studies[88] of five SNPs in the CCR5 promoter region (positions 59029, 59353, 59356, 59402, and 59653) indicated significantly higher frequencies of allele *CCR5* 59402A in the HIV-positive individuals than healthy individuals (66.4 vs 57.1%) and in CDC stage C patients (76%) versus stages A and B patients together (60%). Similar findings were observed at genotypic level suggesting that the *CCR5**59402A allele might favour the likelihood of acquisition of HIV-1 infection and development of AIDS in HIV+ve Indian patients.

Higher frequency of homozygous *CCR5* promoter haplotype ACCAC (~HHE) was observed in the stage C HIV-positive patients (48.6%) compared with those in stages A and B put together (38.5%)[88]. These results suggest possible role of HHE in the development of AIDS related symptoms in Indian population. In accordance to our results, haplogroup HHE has been associated with enhanced acquisition and rate of progression to AIDS in Caucasians[96] and Thais[94,95].

Chemokines: MCP-1, SDF-1, RANTES and MIP-1α variants

The beta-chemokines macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5) are the natural ligands of CCR5 and SDF-1 is for CXCR4 co-receptor. Two additional variants named CCL3L1 and CCL4L1, encoded by genes arising from the duplication of CCL3 and CCL4, respectively, have also been reported[97]. Chemokines induce internalization of their receptors, thus abrogating its ability to promote HIV-1 infection and further modulate the disease progression.

(i) MCP-1 -2518 A/G transition - Monocyte chemoattractant protein-1 (MCP-1/CCL2), regulates migration and infiltration of monocytes, macrophages, basophils, mast cells, T cells, natural killer cells and dendritic cells to sites of injury. CCL2 along with its receptor CCR2 have been demonstrated to be induced and involved in a variety of diseases[98]. MCP-1 mediated macrophage recruitment and activation could potentially influence HIV infection and pathogenesis by directly infecting macrophages at infection site, then may serve as "Trojan horses" for dissemination of the virus to lymph nodes and other organs. This macrophage dependent viral amplification at local sites of infection seems to be a pre- requisite for efficient dissemination of the virus during very early stages. In addition, several reports link MCP-1 expression, HIV-1 replication and inhibition of HIV-1 infection *in vitro*[99].

MCP-1 A/G transition in the promoter region modulates the levels of MCP-1 expression. The G allele results in increased MCP-1 production at transcriptional and protein level compared to A allele[100] and homozygosity for the MCP-1 –2578G allele has been shown to be associated with a 50 per cent reduction in the risk of HIV-1 acquisition. Interestingly, in HIV-1 infected individuals, the same genotype was associated with faster disease progression and a 4.5-fold increased risk of developing HIV associated dementia in large cohort studies comprising European, African and Hispanic Americans[101]. In Caucasians the allelic frequency of 'G' is 23 to 25 per cent (25.8% in Germans, 25% in Italians, 23.9% in Hungarians and 23.8% in Czechs)[102]. On the other hand, most Asian populations report relatively higher frequency for the 'G' allele, *i.e.* 50-65 per cent (65% in Koreans, 63.8% in Japanese and 51% in Chinese population)[103]. One study from south India reported that the frequency of G allele was 34 per cent[104]. The study did not reveal

any association of this variant with HIV susceptibility and development of tuberculosis in HIV +ve cohort.

(ii) CXCL12 (SDF1-3'A variant) - CXC chemokine ligand 12 (CXCL12), or stromal cell–derived factor 1 (SDF1), is the only known natural ligand for the HIV-1 co-receptor CXCR4. Two isoforms, CXCL12α and β are expressed as a result of alternative splicing of a single gene. A SNP designated *SDF1*-3′UTR-801G>A (rs1801157), was identified at position +801 relative to the start codon in the 3′ untranslated region (3′UTR) of the *CXCL12*β gene transcript[37]. The transition was found associated with delayed onset of AIDS[37], other studies in contrast suggested association to decreased[105] survival after AIDS diagnosis; or no effect on disease progression[106]. The SNP in the heterozygous state was found associated with increased vertical transmission from mother to child in an African study[107]. Another study revealed association with resistance to HIV-1 infection in seronegative high-risk individuals[108]. Studies investigating plasma CXCL12 protein levels in HIV-1–seropositive patients, exposed high-risk HIV-1–seronegative individuals, and healthy HIV-1–seronegative controls with consideration of *SDF1*-3′A genotypes have also reported inconsistent associations.

The frequency of SDF1-3'A ranges from 17-35 per cent in South Indians, Thais[108,109] and many other populations worldwide (17-22%)[110]. A report from Indian population suggested lack of association of this variant with HIV susceptibility, however, in the same study GG genotype was found associated with susceptibility to pulmonary TB in HIV patients[104].

Mutations in the *CXCR4* gene are generally rare and have not been implicated in HIV-1/AIDS pathogenesis. The delay in onset of AIDS observed in SDF1-3'A homozygotes might result from overproduction of SDF1 in certain tissue compartments, regulating the CCR5-CXCR4 switching. The controversial role of *CXCL12 (SDF1*-3′A SNP) and *CXCR4* mutations in HIV-1/AIDS pathogenesis need to be defined in ethnically distinct populations.

(iii) CCL5/RANTES - Regulated upon activation normal T cell expressed and secreted (RANTES) inhibits CCR5-mediated viral entry by competitive binding and down-modulating CCR5[79]. In EU individuals and HIV slow progressors, elevated levels of circulating RANTES chemokines have been observed previously[111]. Two SNP sites have been identified in the promoter region of RANTES, namely, -28C/G (rs1800825) and -403G/A (rs2107538)[112]. In one study -28G variant, but not -403A, was reported to upregulate RANTES transcription[112] whereas in another -403A was reported to upregulate RANTES transcription without consideration of -28C/G[113].

Reports suggested association of RANTES -403A and -28G haplotypes with slower disease progression in Japanese and Thai cohorts[112,114] and lower susceptibility to infection in a Chinese cohort[115]. The genotype -403GA-28CC was found to be risk conferring to HIV-1 infection but resisted AIDS progression compared to genotype -403GG-28CC in European Americans (EA)[35]. On the other hand, in African Americans, no effect on HIV-1 susceptibility and AIDS progression by these variants has been observed[116]. Similarly, a report from the Indian population suggests lack of association of these variants with HIV infection[86].

(iv) CCL3L1 copy number variants - Human CC chemokine ligand 3-like 1 gene (CCL3L1) is located on human chromosome 17q11.2 and is highly variable in copy numbers due to a hot spot for segmental duplications. This copy number variation has been found linked to HIV/AIDS susceptibility with a lower copy number is associated with a higher risk of HIV-1 acquisition and rapid progression towards AIDS and death[33]. Although chemokines bind their receptors and influence viral entry, their role as mediators of inflammation influences the overall cell mediated immunity (CMI) following infection. Dolen *et al*[117] have reported that this effect on cell mediated immunity as the major protective mechanism acting through the CCL3L1 and CCR5 axis.

Our study[118] on CCL3L1 copy number polymorphism has revealed that Indian population has a relatively low CCL3L1 copy number as compared to the Japanese counterparts (2.34 vs 5 in controls) (2.13 vs 3.35 in HIV +ve cohrts). The copy number of this protective gene was found higher in chimpanzees (>7) compared to both Indian and Japanese populations which is in concordance with their natural resistance against infection and progression. However, our study did not reveal any association with susceptibility to HIV infection as far as this copy number mutation is concerned.

Genetic risk groups: Chemokines & their receptors

On the basis of various protection and risk conferring genetic variants of chemokines and their receptors Ahuja *et al*[119] have defined various risk groups as 'low'

(CCL3L1 high, CCR5 non detrimental), 'moderate' (CCL3L1 high, CCR5 detrimental) and (CCL3L1 low, CCR5 non detrimental) and 'high risk' genetic groups (CCL3L1 low, CCR5 detrimental). They observed significant influence of these risk groups on *(i)* CD4 depletion before HAART[120], *(ii)* CD4 recovery after HAART, and *(iii)* assessment of AIDS risk[119] (Fig. 6).

Cytokine gene variants in HIV-1/AIDS

Cytokines are low molecular weight proteins that act as soluble mediators and regulators of the immune response. These molecules are secreted by a variety of cells, bind specific membrane bound receptors on target cells and act in a paracrine or autocrine manner. One cytokine can have a range of differential effects on different target cells (pleiotropy). Further, two different cytokines can have the same effect (redundancy). Cytokines are able to regulate production and function of other cytokines in a positive or negative manner.

Since the launch of HapMap project, several polymorphisms have been found in genes encoding cytokines and their receptors, leading to differential production of cytokines and, therefore, are responsible for the observed inter-individual differences in cytokine production. For example, the G to A transition at site -308 in the human TNF-α promoter region results in six to seven fold increase in transcriptional activity[121]. Based on distribution of cytokine gene variants, each person can be considered as a mosaic of high, intermediate and low producing phenotypes. The same has been reported for IL-10 (-1082 A/G, -819 C/T and -592 C/A), TGF-β (codon 10 C/T, codon 25 G/C),

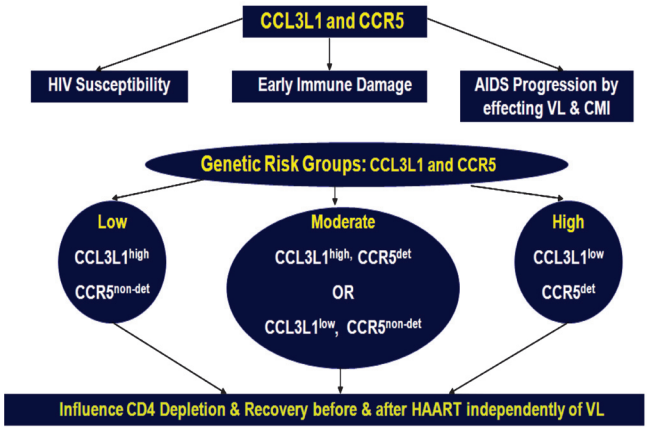

Fig. 6. Genetic risk groups in CCL3L1-CCR5 axis categorized as low, moderate and high risk conferring depending on their influence on HIV/AIDS outcome. VL, viral load; CMI, cell mediated immunity; HAART, highly active antiretroviral therapy.

TNF-α (-308 G/A), TNF-β (+252 A/G), IFN-γ (+874 T/A), IL-6 (-174 G/C) and IL-4Rα (+1902 G/A)[122]. This in turn influences susceptibility and/or resistance to various infectious and autoimmune diseases via variable immunomodulation. In case of HIV, it is now becoming clearer that the rate of transition from one stage to the other during the course of HIV infection is characterized by TH1 to TH2 shift. An optimal balance between type 1/type 2 responses is associated with long-term nonprogressive HIV-1 infection[123]. However, unlike chemokine and their receptors, only limited numbers of studies have been conducted on pro- and anti-inflammatory cytokine gene variants and their possible role in HIV pathogenesis[41,114,124-126].

(i) Pro-inflammatory cytokines - Pro-inflammatory cytokine IL-1α enhances HIV-1 production through NF-*k*B-mediated activation of viral replication[127]. In fact, elevated levels of IL-1 have been earlier reported in AIDS patients[128] and also have been correlated with predicting viraemia in AIDS patients[129].

γ-IFN is another important cytokine that plays a pivotal role in defense against viruses and intracellular pathogens and in the induction of immune mediated inflammatory responses[130]. A 12CA repeat microstatellate allele at the first intron of the IFN-γ gene and the +874T polymorphisms are associated with a higher level of *in-vitro* cytokine production[131]. Further, decreased frequency of IFN-γ high producer genotype (+874TT) has also been reported in the Korean HIV infected population[41].

The gene for tumour necrosis factor- α lies between the HLA class I and class II loci and in view of its biological effects, polymorphism within this gene might contribute to some of the associations seen between HLA and various diseases[132]. Haplotypes containing HLA-DR3 and HLA-DR4 have been reported to be associated with higher levels of TNF[132,133]. Both TNF-α and lymphotoxin (TNF-β) are involved in the activation of transcription factor NF-*k*B and increased levels of TNF-α have been observed in AIDS patients[134].

(ii) Anti-inflammatory cytokines - IL4 is a pleiotropic cytokine with various immune-modulating functions including induction of immunoglobulin E (IgE) production in B cells and downregulation of primary co-receptor CCR5, and upregulation of CXCR4[135]. An increased frequency of IL4-590T (high producer) allele and IL4-590TT genotype in HIV+ cohort suggests that this polymorphism could be a risk factor for susceptibility to HIV infection in the Indian

Table III. Per cent frequency distribution of cytokine alleles/ genotypes associated with high/low expresser phenotypes in major population groups, including the study in north Indians

Cytokine variant	Genotype (expression)	Frequency* in populations (%)			
		North Indians	Asian	White	Black
IL-2 (-330 G/T)	GG (high)	29	14	6	0
	GT	50	48	43	12
	TT (low)	21	38	51	88
TNFα (-308 A/G)	AA (high)	2	3	6	4
	GA	13	21	27	18
	GG (low)	85	76	67	78
IL-6 (-174 C/G)	GG (high)	82	93	40	80
	GC	31	7	44	18
	CC (low)	8	0	16	2

*Refs 24, 138 study on north Indians

population. Also, IL4-590T allele has been reported with susceptibility to TB in south India[136].

Another important anti-inflammatory cytokine is IL10, its gene is highly polymorphic, and is thought to contribute upto 75% of inter-individual variability in IL10 production. Genetic variants documented at IL10 -1082, -819, -592 loci constitute three well conserved haplotypes: GCC (high producer), ACC and ATA (low producer)[137]**.** Several studies have highlighted that elevated levels of IL-10 (Th2) lead to faster progression of HIV diseases[42].

We have reported the population distribution of various pro and anti- inflammatory cytokine gene polymorphisms in the north Indian population[138]. Table III summarizes the distribution pattern of some of the cytokine alleles/genotypes associated with high/low expresser phenotypes as studied in major population groups[139] as compared to our observations made on north Indians.

The analyses reveal interesting results: *(i)* the high secretion IL 2 genotype IL-2 (-330 GG) was found to be predominant in Indians, while the low secretion −genotype TT is found predominantly in the Blacks, *(ii)* The TNFa-308 low secretion genotype (GG) occur more frequently in north Indians, and *(iii)* The high secretor genotype for IL 6 (-174 GG) found under represented in Caucasians.

Advances in gene discovery: genome wide scans

Recently, there has been a shift from candidate-gene studies to genome-wide studies to identify novel host

Table IV. Summary of GWAS results in association with HIV/AIDS

Year	Identified SNP (gene in proximity) & Chromosomal loci	Effect	Study group (Refs)
2007	rs2395029 (HCP5), 6p21.3 rs9264942 (HLA-C), 6p21.3 rs3869068 (ZNRD1), 6p21.3	Lower viral loads Lower viral loads Loss of CD4+ cells	Euro-CHAVI[140]
2008	rs2572886 (LY6), 8q24	Higher viral loads	Swiss HIV cohort[144]
2008	rs2395029 (HCP5), 6p21.3 rs10484554 (HLA-C), 6p21.3 rs6503919 (DDX40), chr17 rs2575735 (YPEL2 Syndecan2),	β=-0.92 β=-0.53 β=-0.21 β=-0.18	ANRS 01 PRIMO[141]
2009	rs4118325 (PRMT6), chr1 rs1522232 (SOX5), chr12 rs10800098 (RXRG), chr1 rs1020064 (TGFBRAP1), chr2	OR=0.24 OR=0.45 OR=3.29 OR=0.34	ANRS 03[142]
2009	rs2395029 (HCP5), 6p21.3 rs10484554 (HLA-C), 6p21.3 rs8321 (ZNRD1), 6p21.3	OR=3.47 NA NA	ANRS 02[143]

ANRS, Agence Nationale de Recherches sur le Sida et les He´ patites Virales (France); CEPH; Centre d'E´ tude de Polymorphism Humain (France); CHAVI, Center for HIV-AIDS Vaccine Immunology (USA); FDR, false discovery rate; NA, not applicable; OR, odds ratio; SC, seroconverter; SNP, single nucleotide polymorphism; VL, virus load.
Source: As modified from Ref. 47

factors required for HIV replication and to understand immunopathogenesis. These advances in identifying disease associated genes via functional and genetic approaches are briefly described as follows:

(i) Genome wide association studies (GWAS) - The approach towards genome wide association studies is valuable in identifying novel SNPs implicated in HIV/AIDS. However, these studies have been limited to European or European-descent individuals. Various specialized cohorts have been studied extensively (Table IV). Fellay *et al*[140] used progression to a CD4 count of <350 or virus set-point as outcomes in their longitudinal study. In another study, SNP association was assessed with plasma HIV-RNA and HIV-DNA levels in peripheral blood mononuclear cells (PBMCs) during the primary infection[141]. Further, some studies are based on comparison of AIDS-free survival between rapid and long-term nonprogressors[142,143]. Despite differences in the study designs, the HLA region emerged as the major factor influencing the HIV/AIDS.

Genome-wide functional scanning-RNA interference (RNAi)

The use of silencing RNA (siRNA) and small hairpin (sh) RNA technologies to knock-down gene transcription are powerful tools to identify HIV disease associated genes and dependency factors. Different studies have knocked-down about 20000 genes one by one and then analyzed transient HIV infection of the cells *in vitro*[145-147]. Yeung *et al*[148] used shRNA to chronically silence each of 54509 mRNAs in Jurket T cell clones. Although in each of these studies >250 genes were identified as HIV dependency factors, three genes (MED6, mediator complex subunit 6 that participates in RNA polymerase II transcription, MED7, a cofactor that involves in Sp1 transcriptional activation, and RELA, a component of NF-kB complex) overlapped in most of the studies.

Concluding remarks and future perspectives

Several immunoregulatory genes that include HLA, cytokines, chemokines and their receptors have been implicated for the discriminative host responsiveness and are considered as "AIDS restriction genes" in various candidate gene based studies. The population specific genetic differences could result in varying influences on virus acquisition, transmission and progression, ultimately modulating the disease outcome. In recent years there has been a shift towards genome wide genetic and functional studies. Most studies defining the influence of host genetic factors in HIV infection have been carried out on Caucasian subjects and those of Mongoloid ethnic background, with almost little or no information on the Indian population which is characterized by infection with the HIV clade C virus. It is essential to have large well categorized cohorts comprising exposed uninfected individuals, rapid, long term nonprogressors and elite viraemic controllers. Analysis of these independent and potentially interactive variables may shed light on the underlying pathophysiology to help define potential targets for population specific diagnostics and therapy.

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