

Review

Chemokines and Chemokine Receptors in susceptibility to HIV-1 infection and progression to AIDS

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Abstract. A multitude of host genetic factors plays a crucial role in susceptibility to HIV-1 infection and progression to AIDS, which is highly variable among individuals and populations. This review focuses on the chemokine-receptor and chemokine genes, which were extensively studied because of their role as HIV co-receptor or co-receptor competitor and influences the susceptibility to HIV-1 infection and progression to AIDS in HIV-1 infected individuals.

Keywords: HIV-1 infection, Polymorphism, Chemokine receptor, Chemokines

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS) in humans. HIV-1 has continued to spread across the globe, despite attempts by the medical and scientific communities to curb the epidemic. After the discovery of HIV as the causative agent of AIDS in 1981, nearly 21 million people have died worldwide and nearly 33.4 million people are living with HIV-1 infection globally. In 2008 alone, 2.7 million people were newly infected with HIV and 2.0 million people have died [1]. In India, adult HIV prevalence is approximately 0.30%, which corresponds to an estimated 2.5 million people living with HIV in the country [2].

AIDS is a complex and long-term chronic disease, triggered by initial infection with HIV-1, which gradually leads to depletion of the CD4-T-lymphocyte cell population, a prelude to immune system collapse. The course of HIV-1 infection varies widely even among in-

dividuals with similar risk exposure levels [3–5]. There is considerable heterogeneity among individuals in infection susceptibility, in the time required to deplete the CD4 T-lymphocytes population and to develop AIDS-defining diseases [6–8]. However, a small fraction of HIV-1 infected individuals remain both clinically and immunologically healthy for 10 years or more after seroconversion [9–11]. Conversely, the disease of another significant fraction is characterized by an extremely rapid progression to AIDS within 1 year. There are also individuals not infected with HIV-1 who have had repetitive sexual exposure to HIV-1 in extremely high-risk situations, known as exposed uninfected (EUs) [3, 12–15]. Understanding the mechanism that account for slower disease progression and the protection against HIV-1 infection is important for the development of more potent therapeutic regimens and a vaccine.

Although a myriad of social and economic factors strongly influence the HIV-1 pandemic, a possible role of host genetics probably account for a portion of the observed epidemiological heterogeneity in infection susceptibility and in progression rate. Significant studies in the past have demonstrated that genetic polymorphisms in human genes can influence the risk for HIV-1 infection and disease progression [16–19].

Extensive meta-analyses of several large AIDS cohorts have revealed numerous genes which are im-

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plicated in the outcome of HIV-1 infection, leading to the characteristic variability of disease progression seen following HIV-1 infection. The genes that have been identified were called as AIDS restriction genes (ARGs) and are involved in several stages of HIV-1 replication, including viral entry, immune regulation following infection and adaptive immunity to HIV-1 [17].

This review summarizes the chemokines and chemokine receptor variants that modulate the susceptibility and progression to AIDS in HIV infected individuals.

1.1. Chemokines

Chemokines are a group of small (~8–14 kDa), mostly basic, structurally related molecules that regulate cell trafficking of various types of leukocytes through interactions with a subset of seven-transmembrane, G protein-coupled receptors, whereby several different chemokines can signal through the same receptor. They play a critical role in many pathophysiological processes such as allergic responses, infectious and autoimmune diseases, angiogenesis, inflammation, tumor growth and hematopoietic development [20]. About 40 different chemokines have now been identified in humans. They mainly act on neutrophils, monocytes, lymphocytes, and eosinophils and play a pivotal role in host defense mechanisms [21]. They are secreted by a variety of cell types that includes T cells, macrophages, natural killer (NK) cells, B cells and mast cells, and serve to regulate chemotaxis and adhesion. Once secreted, chemokines attach to other cells via chemokine receptors present on the target cell surface. Eighteen chemokine receptors have been identified, each of which can accept one or more than one chemokine [22]. They are subdivided into four families based on the relative arrangement of cysteine (C) residues, namely CC (α chemokines), CXC (β chemokines), C (lymphotactin) and CX3C (fractalkine) [21]. The chemokines CCL3 (macrophage inflammatory protein-1 (MIP-1 α)) and CCL5 (regulated upon activation, normally T-cell expressed and secreted (RANTES)) are natural ligands of CCR5 co-receptor that block entry of non-syncytium inducing (NSI) virions and SDF-1 (stromal derived factor-1) is a ligand for CXCR4 that is used by syncytium inducing (SI) viruses. Discoveries over the past few years have identified a close relationship between chemokines and HIV infection, apart from their well established role in blocking viral entry by binding to their receptors, chemokines have additional role in HIV pathogenesis [20].

1.2. Chemokine receptor

The entry of HIV-1 into its target cells is mediated by the viral envelope glycoproteins such as gp120, which binds the cellular receptor CD4, the primary virus receptor. However, HIV-1 also needs co-receptor for entry into the target cells. Different chemokine receptors have been implicated in HIV pathogenesis, CCR5 and CXCR4 are the major co-receptors that are used by non-syncytium inducing (R5) and syncytium inducing (X4) virions, respectively. CCR5 is the major co-receptor for entry of macrophage-tropic HIV-1 isolates, which has been reported by several groups independently [23–25]. Majority of primary HIV-1 isolates are predominantly CCR5 tropic and gradually tend to become CXCR4 tropic during late infection. The CCR5 gene is located in the 3p21.3 region of the human genome, together with other inflammatory chemokine receptor genes and is expressed on the surface of monocytes, dendritic cells and activated T cells. Genetic studies have reported various mutations in the promoter and coding region of genes encoding HIV co-receptors and their chemokine ligands, which were associated with resistance to HIV-1 infection and with rapid and slow rate of progression to AIDS [26–28].

2. C-C chemokine receptor-5 (CCR5)

2.1. CCR5 delta 32

CCR5 delta 32 is a polymorphism in the gene encoding the CCR5 chemokine receptor in which a 32-base pair region has been deleted which results in truncation of protein synthesis. Individuals who have two copies of this mutation (i.e. CCR5- Δ 32 homozygous or CCR5- Δ 32/ Δ 32) have non-functional receptors. This non-functionality renders CCR5- Δ 32/ Δ 32 individuals immune to R5 strains and they are protected from HIV-1 infection [19,29,30]. Individuals who possess one copy of CCR5- Δ 32 and one copy of CCR5-wildtype (CCR5- Δ 32 heterozygous or CCR5- Δ 32/wt) may have altered chemokine receptor activity which results in delayed progression to AIDS [31–33], and CCR5- Δ 32 heterozygous genotype is neither essential nor sufficient for protection against disease progression [34]. However, recent studies has shown that the CCR5- Δ 32 protein in CCR5 deficient individuals may act as a negative modulator of HIV-1 entry by scavenging molecules involved in HIV-1 entry [35,36]. The role of the CCR5- Δ 32 mutation on susceptibility and

resistance to HIV-1 infection has been reported previously by several groups. The frequency of CCR5 delta 32 is found to be 9.6% in the Spanish [37] and upto 15% in Caucasians [19]. A study in North Indian population shows the protective allele occurred at a low frequency (0.95%) with not a single individual homozygous for the variant (Rathore et al., 2009), and only 1.3% is present in South Indians [38] and other Asian population too [39]. In contrast, the CCR5 delta 32 allele is virtually absent among native African ethnic group [30]. The marginal presence of the CCR5 delta 32 allele seen in Asian population could plausibly be due to gene flow from Caucasians population.

2.2. CCR5 promoter

Single nucleotide polymorphisms (SNPs) in the CCR5 promoter region affect the levels of CCR5 expression and rates of HIV-1 disease progression [26, 40]. Several studies have been carried out to evaluate the association of CCR5 -59029 A/G polymorphism with course of HIV-1 infection. It has been demonstrated that HIV-1 infected person with CCR5-59029 GG polymorphism had slower progression to AIDS [27, 40–42]. In contrast, in Australian population, CCR5 59029 AA homozygotes were found underrepresented in the non-progressors group as compared with other HIV-1 positive groups, suggesting that individuals lacking the homozygous AA genotype would progress to AIDS more slowly [40]. However, a recent study has failed to find any such disease retarding effect of G nucleotide [43] in North Indians, as has been previously reported in London cohort [44], North Indians [45] and White Europeans [46].

There are several studies reporting no association of CCR5-59029 AG polymorphism with susceptibility to HIV-1 infection [27,45,47,48]. However, a recent study in North Indians HES individual, CCR5-59029 AG genotype was found to be significantly enriched as has also been reported in Caucasian Exposed Seronegative (ES) individuals [13]. These observations suggest that CCR5-59029 AG may partially be responsible for providing resistance against acquisition of HIV-1 infection.

2.3. MIP-1 α P (Macrophage Inhibitory Protein-1 α P; CCL3L1)

CCL3L1 is the most potent CCR5 agonist and the strongest inhibitor of infection by R5 HIV-1 strains [49]. The CCL3L1 gene is located on chromo-

some 17q11.2, encodes a 93-amino acid preprotein MIP-1 α . It contains 3 exons and spans about 1.9 kb [50]. Recently, copy number variations in CCL3L1 have been reported to be linked to the susceptibility to HIV-1 infection, which varies among individuals. [16]. Individuals with ≤ 2 copies of CCL3L1 gene from the median for their population group had a significantly higher risk for acquiring HIV-1, whereas those with > 2 copies above mean had significantly less risk. Moreover, a gene dose lower than the cohort median was associated with increased risk of progressing more rapidly to AIDS and death. Similar findings by Nakajima et al. [51] also reported that average copy number of CCL3L1 in the HIV-1 infected subjects with hemophilia was significantly lower than in control. Furthermore, the subjects possessing 2 or less copies of CCL3L1 had significantly higher risk of acquiring HIV-1 [51]. In contrast to the previous studies, a recent study by Rathore et al. in North Indians found no significant influence of CCL3L1 copy number lower or higher than the median copy number on HIV-1 susceptibility and disease progression [43], as has also been reported previously [52]. Moreover, Nakajima et al. also reported that CCL3L1 copy number variations had no significant effect on the disease progression among the LTNP (Long Term Non-Progressors) subjects, when compared between non-progressors and patients under treatment [51]. Analysis of HIV-infected European individuals also failed to detect any statistically significant association between the distribution of CCL3L1 gene copy number and rate of progression to AIDS [53]. Thus, in the absence of finding any association, it can be speculated that expression of CCL3L1 mRNA may be independent of CCL3L1 gene copy number and may be regulated/influenced by other factors [54].

2.4. RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted; CCL5)

RANTES encoded by CCL5 gene is a CC chemokine, located on chromosome 17q11.2-q12, that chemoattracts leukocyte. It plays a critical role in T-lymphocytes activation and proliferation. It is produced principally by CD8+ T-lymphocytes, platelets and epithelial cells [55,56]. It is one of the natural ligands for the chemokine receptor CCR5 and potently suppresses in vitro replication of the R5 strains of HIV-1 [56,57]. RANTES acts by blocking binding of the HIV envelope gp120 to CCR5 and by reducing surface levels of CCR5 [58].

Several SNPs in the RANTES gene have been reported to influence the natural course of HIV-1 infection by up- or down-regulating RANTES gene activity. The most frequent of those polymorphic sites comprise RANTES -403 G/A and RANTES -28 C/G in the promoter region and RANTES In1.1 T/C in the first intron region [59,60]. Both promoter polymorphism increase RANTES transcription and may delay HIV-1 disease progression [60,61]. Conversely, the RANTES In1.1 C allele seems to decrease RANTES transcriptional activity and is probably associated with an increased risk for HIV-1 infection and progression to AIDS [59]. Previous studies on North Indians [62,63], Whites [12] and white Spaniards [64], it has been shown that RANTES -403 A/G and -28 C/G gene polymorphism does not influence the susceptibility against HIV-1 infection. In contrast RANTES -403 A allele increases the susceptibility to HIV-1 infection in White Americans [59,65] and Han Chinese [60] while -403 G allele is a risk factor for HIV-1 transmission among Chinese subjects [66]. In case of RANTES In 1.1 T/C, a study has reported that In 1.1 T allele and genotype is associated with increased susceptibility to HIV-1 infection, which is in contrast with previous studies in African-Americans that RANTES In 1.1 C allele results in reduced RANTES transcription and is associated with increased susceptibility to HIV-1 infection, while in Ugandan individuals RANTES In1.1 C allele was associated with protection from death [67].

2.5. C-C chemokine receptor-2 (CCR2)

CCR2 is a chemokine receptor which could also function as a co-receptor for HIV-1 in some circumstances. The CCR2 gene is located on chromosome 3, which lies within 10kbp from CCR5, and is in strong linkage disequilibrium with the CCR5 gene. A G to A transition results in the substitution of valine to isoleucine at amino acid position 64 (V64I) in the first transmembrane region of the CCR2 gene has been reported [28]. This transition has been associated with delayed disease progression to AIDS, about 2–4 years delay in homozygous mutant allele compared to the wild type [28,68]. CCR2-64I is quite common with frequencies of about 10% in Caucasians, 15% in African Americans, 17% in Hispanics and 25% in Asians, 11.76% in North Indians and 17% in South Indians [28,38,69,70]. A study from Thailand has reported that homozygosity for CCR2-64I is associated with reduced risk of acquiring infection among HIV-1 discordant couples [71]. However, the mechanism through which CCR2-V64I confers a protective effect remains largely unknown.

2.6. CXC chemokine receptor-4 (CXCR4)

The highly conserved CXCR4 gene is an obvious target as CXCR4 serves as a co-receptor by X4 strains of HIV-1 to gain entry into the cells. CXCR4 gene is located on chromosome 2. CXCR4 using viruses are often identified in individuals with more advanced disease and are associated with more rapid disease progression. Screening of the entire transcription unit resulted in the detection of two rare polymorphisms but no association with progression to AIDS was found [72]. Mutations in the CXCR4 gene are generally rare and have not been implicated in HIV-1/AIDS pathogenesis [73].

2.7. SDF-1 (stromal cell derived factor-1)

SDF-1 also known as CXC chemokine ligand 12 (CXCL12), is the only known natural ligand for the HIV-1 coreceptor CXCR4 which inhibits infection of T cell line-tropic (T-tropic) or syncytium-inducing viruses normally found during late-stage HIV disease [74, 75] by downregulating the surface expression of the HIV-1 coreceptor, CXCR4 [76,77]. The SDF-1 gene is located on chromosome 10. A G/A transition at position 801 in the 3' untranslated region (UTR) of SDF1 have been reported. HIV-1 infected individuals homozygous for SDF-3'A have been reported to have slower progression to AIDS compared to individuals with SDF-3'G [78,79]. This mutation is common among all geographical regions of the world. Mutation may upregulate the synthesis of SDF-1, thus competitively inhibiting X4 HIV from binding. SDF-3'A is found at a frequency of 21% in Caucasians, 16% in Hispanics, 5.7% in African Americans, 25.7% in Asians [78] and 2.4% in North Indians [63,80] and 11.7% in South Indians [38].

2.8. CXC chemokine receptor-6 (CXCR6)

CXCR6 is a G-coupled seven-transmembrane receptor, has gained interest as another portal for HIV-1 entry because it is a principal coreceptor for SIV [81–84]. CXCR6 is a secondary co-receptor for HIV that can mediate fusion of HIV-1 to CD4+ cells with HIV-1 envelope from M-tropic and dualtropic strains, and CXCR6 enhances HIV-1 infectivity, suggesting a potential role in progression of HIV-1 [83]. A polymorphism G/A at position 1469 results in a non-conservative change in codon 3 (CXCR6-E3K) of the N terminus of the co-receptor. Individuals homozygous or heterozygous for the CXCR6-3E allele were more likely to die a PCP

mediated AIDS related death than were individuals homozygous for CXCR6-3K [85] and in a recent study CXCR6 was reported to be associated with long term non-progressors [86].

2.9. CX3C chemokine receptor-1 (CX3CR1)

CX3CR1 is a leukocyte chemotactic and adhesion receptor for the human chemokine fractalkine. It is a minor co-receptor for HIV-1 infection and expressed on brain. Two non-synonymous polymorphisms in CX3CR1 gene have been reported, resulting in a valine to isoleucine change at position 249 (V249I) and threonine to methionine change at position 280 (T280M) [87]. The influence of CX3CR1 polymorphism on HIV-1 susceptibility and disease progression is controversial. Individuals homozygous for M280 progressed to AIDS more rapidly than other genotypes [87,88]. However, further studies did not confirm this observation [63,89,90]. Another study reported that I249 is associated with long term non-progressors [91] whereas children with the wild type haplotype V249-T280 experienced less disease progression and central nervous system impairment, suggesting that the role of CX3CR1 in the alteration of disease progression might be the recruitment of immunomodulatory cells responsible for the control of HIV-1 [92].

3. Conclusion

AIDS is a multifactorial disease and is regulated by a range of different factors; therefore it is necessary to understand an individual's genetic profile in regulating the outcome of the disease. A lot of studies have been done to explore the role of genetic variants in chemokine receptors and chemokines associated with the susceptibility and progression to AIDS. The implication of these findings further needs to be explored in well defined cohorts with larger sample size and correlated with the levels of viremia and CD4 counts in Indian and other populations. The study of host genes involved in differential susceptibility and disease course is crucial for understanding of the immunopathogenesis of HIV-1 infections and for the development of immunotherapeutic and prophylactic strategies.

Acknowledgement

The Senior Research Fellowship provided by Indian Council of Medical Research, New Delhi to Mr. Animesh Chatterjee is greatly acknowledged.

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