

Impact of Cytokine Gene Polymorphism on the HIV-1 Disease Progression and Response to Therapy

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Abstract

Inter-individual variations in HIV infection outcome indicate a role of host genetic variations in the HIV disease progression and response to therapy. Cytokines are early key players in HIV infection, which influence the infection outcome by regulating viral replication, persistence and eradication of its reservoirs as well as host immune response. Genetic variations in cytokine genes can alter protein expression resulting in differential infection outcome. In this review we have summarized the available literature on cytokine and receptor variations in HIV infection outcome and response to therapy. A better understanding of cytokine genetic variation in HIV disease progression and response to therapy will help clinicians in better management of HIV infected individuals.

Keywords: Cytokines; Single nucleotide polymorphism; HIV disease progression; Response to therapy

Introduction

Antiretroviral therapy (ART) has lessened the morbidity and mortality among human immunodeficiency virus (HIV) infected individuals, but failed to eradicate the virus completely from the host due to various factors, the most important being the existence of hidden virus reservoirs in the host. So, it continues to be a major global public health problem, with more than 25 million deaths over the past three decades and approximately 34 million people living with HIV infection (<http://www.who.int/mediacentre/factsheets/fs360/en/index.html>). These statistics have resulted in a continuing intensive research in this arena. The major goal is to elucidate virus and host interactions, identify genes involved in HIV resistance, and restore functionally active lymphocytes in order to facilitate remission [1].

There is considerable heterogeneity among individuals with respect to susceptibility to infection, the rate of depletion of CD4+ T-lymphocytes, which is a hallmark of disease progression and development of acquired immunodeficiency syndrome (AIDS) in the infected host. In typical disease progressors average time for the development of AIDS is 6 to less than 8 years, however, a small subset of HIV-1 infected individuals remain both clinically and immunologically healthy for 10 years or more after sero-conversion termed as long term non progressors (LTNPs) [2]. Conversely, another significant fraction of patients (10-15%) are rapid progressors who have a fast CD4+T-cell decline and occurrence of AIDS-related events within the first few years after infection. There are also individuals, who have had repetitive sexual exposure to HIV-1 in extremely high risk situations, but remain uninfected with HIV-1, known as exposed seronegatives (ESNs) [3]. Besides many other factors playing role in this phenomenon, the host genetic makeup seems to be the most important one. From the past more than three decades, intensive research among these unique HIV cohorts has resulted in the identification of several host genetic variants, especially chemokine co-receptors and their natural ligands, immune response genes (IRG), major histocompatibility complex (MHC), and cytokines genes [4]. Among these hosts genetic variations, a deletion of 32 base-pairs (bp) in the *CCR5* gene remains the most well accepted finding, known to confer resistance to HIV-1 infection in homozygous individuals and by virtue of which it has successfully entered into the recent gene therapy clinical trials among HIV infected individuals [5].

Cytokines play a central role in regulating the innate and adaptive immune response, hence also have an impact on the pathogenesis of

infectious diseases including the HIV infection [6]. Biosynthesis of cytokine levels are well regulated, but inter-individual genetic variations can influence the transcriptional regulation, especially single nucleotide polymorphisms (SNPs) in the promoter and in the exonic region may affect the expression levels of cytokines. This can lead to an altered HIV infection outcome mainly by affecting the establishment, persistence and eradication of HIV (Figure 1). Previously, several studies have reviewed systematically host genetic variations within MHC, chemokines and their natural ligand genes [7-11], but there is a dearth of such reviews on the cytokine and their receptor gene variations in HIV disease progression and response to therapy. Several inconsistencies regarding the association of cytokine gene polymorphism in HIV infection do exist, but here we have exclusively reviewed the role of variations in the cytokine and receptor genes. Besides, in recent years, new cytokines have been shown to influence the HIV pathogenesis, these cytokine genes are also polymorphic and the role of genetic variations in these new players would help in the better understanding of the differential HIV disease progression and/or response to therapy.

Cytokines in HIV Pathogenesis

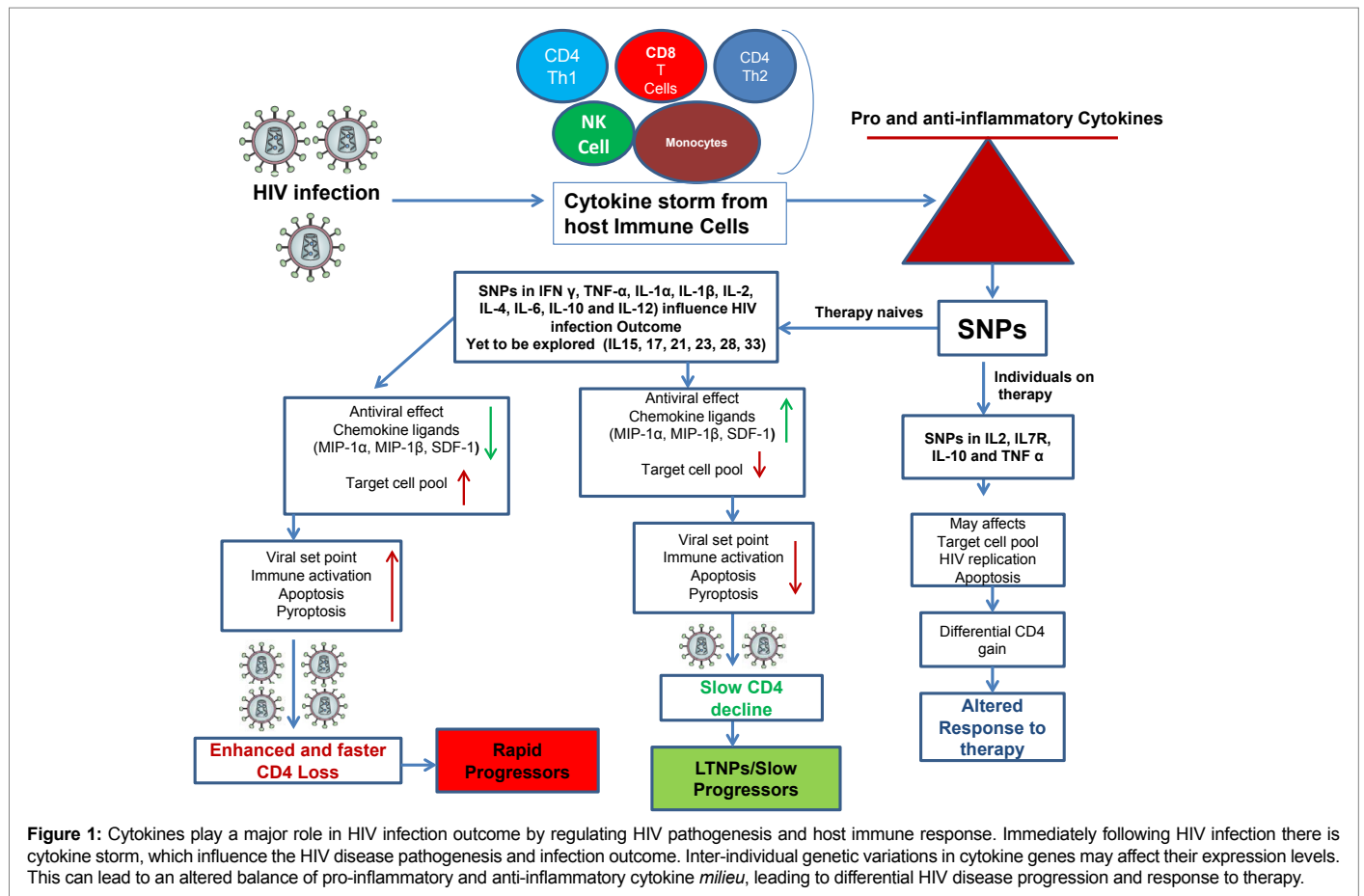
Cytokines are involved early in the pathogenesis of HIV infection and during HIV disease progression; their levels are altered depending on the stage of the disease. Several hypotheses have been proposed to explain the decline of CD4+ T cell count, but nowadays systemic chronic immune activation is considered as the major driving force, which leads to the development of AIDS [12]. A critical balance of pro-inflammatory and anti-inflammatory cytokine plays a major role in systemic immune activation and hence HIV disease progression. So, they have a potential to be used as therapeutic option in HIV infection, in fact some cytokines like IL-2, IL-7 are now being evaluated in clinical

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trials [13] and anti TNF- α therapy is proposed for HIV therapy as well [14]. Monitoring their levels during HIV disease progression could be crucial for the management of disease. Previous research has provided a compelling link between variations in the cytokine genes that have very subtle, but significant consequences on protein expression and hence altered CD4 count loss, thereby affecting HIV disease progression as well as response to therapy. The major cytokine genetic variations that can affect the HIV disease progression and response to therapy were retrieved for systematic review as discussed in detail below.

Methodology

We conducted a comprehensive literature search for the research articles reporting the role of cytokine gene polymorphism on the HIV-1 disease progression and response to therapy using the most common electronic databases (PubMed and MedLine) (Table 1). The search for research articles was limited to English. We widened our search by using the different key words for polymorphism (SNPs or genetic variation), therapy (ART or HAART) and retrieved 154 articles published on

Cytokine Gene	Genetic variation position	Impact on HIV disease progression and response to therapy	References
<i>IFN-γ</i>	+874T/A -179G/T	A allele associated with fast disease progression T allele associated with fast disease progression	[10,21] [23]
<i>TNF-α</i>	-238G/A -308G/A	GA genotype associated with slow disease progression Inconclusive reports for HIV disease progression	[36] [37,39,40]
<i>IL-1α</i>	-889C/T, +4845G/T	T allele controls HIV replication in patients undergoing therapy	[45]
<i>IL-1β</i>	+3954C/T	T allele risk factor for HIV infection	[56]
<i>IL-2</i>	-330G/T +160T/G	No association with disease progression	[64]
<i>IL-4</i> <i>IL-4Rα</i>	-589C/T 150V	Inconclusive reports for T allele with disease progression 150 a risk factor for HIV infection	[70-76] [77]
<i>IL-6</i>	-174G/C	Inconclusive reports for disease progression	[64,82]
<i>IL-7R</i>	+2087T/C +3101A/G	Inconclusive reports for response to therapy G allele associated with faster CD4 T cell recovery	[86,87,88] [87]
<i>IL-10</i>	-1082A/G -592C/A	G allele associated with slow disease progression Inconclusive reports with disease progression	[33] [82,98-100]
<i>IL-12</i>	-1188A/C	No association with HIV disease progression	[21,64]

Table 1: Cytokine gene polymorphisms which affect the HIV disease progression and response to therapy.

the cytokine gene polymorphism and HIV disease progression, 17 on the response to therapy. We also screened references of selected publications to identify additional articles on the research topic and a total of 80 publications were selected based upon the inclusion criteria as follows: (a) Case-control design; (b) Sufficient statistical data analysis provided like p value, odds ratio and confidence intervals. Studies were excluded if no control population was included.

Interferon (IFN)- γ

IFN- γ is a cytokine secreted mainly by T helper type 1(Th1) cells and natural killer (NK) cells; it is one of the major antiviral cytokines. IFN- γ coordinates the trafficking of specific immune cells to sites of inflammation through up-regulation of adhesion molecules and natural chemokine ligands of CCR5 that are regulated on activation, normal T cells expressed and secreted (RANTES), macrophage inflammatory protein-1 alpha (MIP-1 α), and macrophage inflammatory protein-1 beta (MIP-1 β) [15]. It promotes a general antiviral state by inducing the conversion of the constitutive proteasome to immune-proteasome [16], up-regulating expression of the TAP transporter proteins [17] and increasing expression and stability of MHC class I molecules [18]. Previously, depending upon the cell type and stage of HIV disease, both suppressive and inductive effects of IFN- γ in virus replication have been reported [19]. Alterations in IFN- γ levels have been noted in several infections including HIV, and not surprisingly intensive searches to identify association of *IFN- γ* gene variants with these conditions have been carried out [20]. Like most of the cytokines, *IFN- γ* gene coding region has been found to be invariant; however, some polymorphisms such as +874T/A in the first intron and -179G/T in the promoter region have been identified and shown to be associated with pathological features of HIV infection in therapy naïve individuals. Some studies have reported associations of the *IFN- γ* +874T/A polymorphism in HIV-1 infected individuals. It has been suggested that individuals homozygous for AA genotype at +874 positions in *IFN- γ* gene have a significantly higher risk of infection and progression to AIDS [10,21]. We have also observed associations of low IFN- γ producing genotype (AA) with faster HIV disease progression and high frequency of TT genotype (high IFN- γ) in ESNs cohort (Personal unpublished data). Another important observation regarding *IFN- γ* (+874T/A) polymorphism is significant difference in the allele frequency among healthy individual worldwide, studies indicate a lower frequency of T allele (+874T/A) among Asians (including Indian) as compared to Caucasian population [22]. The second polymorphism of *IFN- γ* in promoter region (-179G/T) has been investigated in African American HIV-1 seroconverters, the TT genotype at this locus was shown to be associated with accelerated progression to CD4 <200 cells/ μ L, a finding which suggested that this polymorphism in *IFN- γ* is a risk factor for AIDS progression [23]. However, this SNP is most probably absent in Indian population as reported by us and no other published report is available as yet.

Tumor necrosis factor-alpha (TNF- α)

TNF- α is a pro-inflammatory cytokine, produced by a variety of cells, especially activated macrophages [24] TNF- α is important for a number of T cell dependent immune processes, including polarization to a Th1 type response, induction of apoptosis, and regulation of proliferation [25,26]. The *TNF- α* gene is mapped on the chromosome 6 in the class III region of the major histocompatibility complex [27]. TNF- α is known to trigger activation of transcription factor nuclear factor (NF)- κ B, which can bind to the HIV long terminal repeats (LTR) and promote viral transcription [28,29]. *TNF- α* gene is highly polymorphic, several SNPs in the promoter (-238G/A, -308G/A, -857C/

T, -863C/A and -1031T/C) region have been described [30], resulting in the altered expression levels [31]. Among these SNPs, variations at -238 and -308 position, which result in G to A substitution are most widely studied and associated with HIV and many other viral infections [32-34]. The presence of -308 SNP has been related to an increase in *TNF- α* gene transcription [35]. The presence of -308A allele has been associated with HIV disease progression. In Caucasian population, GA genotype at -238 position in *TNF- α* gene, has been observed to be associated with very slow disease progression in LTNP in [36]. More recently, we reported the association of high *TNF- α* producing haplotype (CAG) with faster HIV disease progression, due to high rate of cell death in carriers of this haplotype [37]. Previously, in Spaniard cohort, individual polymorphisms at -238G/A, -308G/A and -863C/A loci were not found to be associated with vulnerability to HIV infection, however the haplotype analysis revealed that haplotype GAC was more frequently represented in the exposed uninfected, suggesting that certain haplotypes within *TNF- α* gene may positively modulate the risk of HIV infection [38]. A recent study from Indian population showed association of GA genotype (-308) with perinatal transmission [39]. However, still many controversies exist regarding the protein expression level of *TNF- α* and polymorphisms at -238 and -308 positions. Some studies suggest A allele at these positions to be a low producer of *TNF- α* and these SNPs being in LD with HLA-B*5701, the carriers have an HLA mediated 'protective' effect during HIV-1 infection [40]. Further extended haplotype and expression analysis is needed to establish the role of genetic variations in the *TNF- α* gene.

Interleukin-1 α (IL-1 α)

IL-1 α is a pro-inflammatory cytokine, mainly released by macrophages neutrophils, epithelial cells, and endothelial cells [41]. It is regarded as the primary mediator for systemic inflammatory response. *IL-1 α* gene is mapped within the *IL-1* gene cluster on chromosome 2q13-21. Two SNPs in the *IL-1 α* gene at position -889 C/T in the promoter region and +4845G/T have been shown to influence the expression levels, with T allele being a high producer [42-44]. In the context of HIV infection, studies have shown that T allele at -889 or +4845 position in *IL-1 α* gene may predict the control of HIV replication in individuals undergoing therapy [45]. Besides, a tandem-repeat polymorphism of the *IL-1RA* gene (antagonist of *IL-1 α*) is also associated with control of HIV-1 viremia in naïve as well as antiretroviral treated patients [46].

Interleukin-1 β (IL-1 β)

IL-1 β is also a pro-inflammatory cytokine, mapped on chromosome 2 and is part of a gene cluster comprising *IL-1 α* , *IL-1 β* , and *IL-1RN* [47,48]. IL-1 β is mainly produced by activated macrophages as a 31-kd pro-protein, it is converted into its active form by proteolytic cleavage of caspase 1 [49,50]. Several polymorphisms have been identified in the *IL-1 β* gene, among these 2 in the promoter (-511C/T and -31T/C) and 1 in exon 5 (+3954C/T) are extensively studied. The T allele of the exon 5 polymorphism has previously been reported to be associated with an increased protein secretion phenotype [51]. In the context of HIV infection, the balance between IL-1 α/β and IL-1Ra has been reported to modulate HIV-1 expression in monocytes [52,53]. While IL-1 α/β has been shown to enhance HIV-1 replication, the IL-1Ra, agonist of these, can reduce HIV-1 replication levels in monocytes [54,55]. The role of IL-1 β polymorphism at +3954C/T position has earlier been reported in HIV infected therapy naïve individuals [56]. Recent studies have suggested pyroptosis to be a major mechanism of bystander CD4 T cell depletion, which is an inflammatory cascade primarily initiated through the innate immune sensing of HIV-1 DNA and IL-1 β is known to play a key role in initiation of this phenomenon [57].

Interleukin-2 (IL-2)

The IL-2 gene is mapped on chromosome 4. Mainly produced by CD4 and CD8 T cells, IL-2 plays crucial role in regulating both immune activation and homeostasis [58,59]. IL-2 mainly regulates CD4+ T cell production and their survival. In HIV-infected individuals, deficiency of IL-2 production is one of the first immunological defects reported [60]. IL-2 production is related to CD4+ T cell counts and clinical status of the infected individuals, hence, it plays a critical role in HIV disease progression [61]. Besides, it is known to inhibit apoptosis induced by cross-linking of gp120 and CD4 receptor on CD4+ T cells [62]. IL-2 has been used in clinical trials for the treatment of HIV infection. However, it was found to be ineffective in preventing progression to an AIDS in two large clinical trials [63]. Genetic variations in *IL-2* gene at positions (-330G/T and +160T/G) in North Americans have been studied in therapy naïve individuals with no significant association with HIV infection outcome [64].

Interleukin-4 (IL-4)

IL-4 is a pleiotropic cytokine produced primarily by activated CD4+ T lymphocytes, mast cells, and basophils [65,66]. It regulates the humoral immunity by the differentiation of precursor T helper cells into the Th2 subset [67]. IL-4 plays a crucial role in shaping the nature of immune response, including the induction and expression of DC-SIGN *in-vitro* differentiated dendritic cells [68]. In context to HIV-1 infection, IL-4 is reported to differentially regulate two major HIV-1 co-receptors, CXCR4 for syncytium inducing (SI) variants and CCR5 for non-syncytium inducing (NSI) viruses. IL-4 down-regulates CCR5 expression and thus inhibits replication of HIV-1 NSI isolates in human T cells and macrophages. On the other hand, IL-4 up-regulates the expression of CXCR4 leading to induction of SI variants, mainly observed in advanced stage of HIV disease progression [69]. In addition, the combination of these effects of IL-4 on HIV-1 replication may be involved in the phenotypic switch from NSI to SI as well as disease progression in HIV-1 infection. Thus, IL-4 plays an important role in viral evolution and HIV disease progression. In *IL-4* gene two SNPs at -589C/T and -33 positions and one in IL-4 receptor (*IL-4R α* I50V) have been associated with differential outcome in therapy naïve individuals. Two previous studies based on two independent cohorts (Japanese and French) showed a protective effect of *IL-4* -589T, by reducing viral load in early infection and subsequently delayed HIV disease progression [70,71]. In contrary to this, one study of homosexual men showed a delayed acquisition of X4 virus in carriers of T allele and no association with HIV disease progression [72]. Subsequent studies showed either no association of the *IL-4*-589T SNP with HIV disease progression [73,74], or protective effect of this polymorphism was observed [64,75,76]. One study from the Indian population showed no association between the *IL-4*-589T allele and HIV-1 susceptibility/progression, however *IL-4R α* I50V was found to be a risk factor for HIV-1 infection [77]. It is possible that different results of IL-4 promoter polymorphism and HIV-1 susceptibility/progression might be due to multi gene interactions and linkage disequilibrium of *IL-4* SNPs leading to *cis* and *trans* effect, that might affect disease progression in HIV-1-infected individuals and has variable effects depending upon race/ethnicity.

Interleukin-6 (IL-6)

IL-6, a multifunctional cytokine that has been implicated in a variety of cellular functions including cell proliferation and differentiation, hematopoiesis and induction of acute phase reaction, inhibits apoptosis, and leads to an increase in vascular endothelial growth factor [78]. It is localized on chromosome 7p21-24 with an upstream

promoter containing 303 bp [79,80]. *IL-6* gene is polymorphic within its promoter region (G to C transversion at position -174) is associated with reduced IL-6 production [81]. For IL-6, strong association was observed between *IL6* -174G/C and susceptibility to AIDS related malignancies like Kaposi sarcoma in HIV-infected men. Among other two studies, one showed a lower frequency of low producing genotype CC in HIV infected therapy naïve cohort [64], while another showed the combination of low IL-6 producing genotype (CC) and high IL-10 producing genotype (CC at 592C/A) to be non-significantly associated with rapid disease progression [82]. Although, IL-6 is an important cytokine, but there is a lack of information on IL-6 polymorphism in HIV infected individuals, further studies on unique HIV cohorts are needed to establish its role in HIV disease progression.

Interleukin-7 (IL-7) and Interleukin-7 receptor (IL-7R)

IL-7 is a hematopoietic growth factor secreted mainly by stromal cells in the bone marrow and thymus. IL-7 is a 25-kD glycoprotein, essential for T-cell development, survival, and proliferation [83]. It exerts its biological effects through the IL-7R complex, IL-7 receptor α chain (CD127), which binds IL-7, and thymic stromal lymphopoietin and the IL-2 receptor γ chain (CD132). It has been found to be a cofactor for V(D)J rearrangement of T-cell receptor beta during early T-cell development [84]. More recently IL-7 has entered the clinical arena and has been shown that it is capable of inducing increase in the numbers of CD4+ and CD8+ T cells, although it can lead to increase in latent HIV replication also [85]. Receptor of IL-7 gene, mainly the α chain is polymorphic with the existence of four non-synonymous SNPs in the exons; rs1494558 (+510C/T in exon 2), rs1494555 (+1237A/G in exon 4), rs6897932 (+2087T/C in exon 6) and rs3194051 (+3101A/G in exon 8), all of these give rise to amino acid substitutions that impact the expression of IL7RA and/or clinical outcome of HIV infection. In fact it is the major cytokine receptor which influences the response to therapy in patients undergoing therapy. Previously, an association between IL-7R rs6897932 polymorphism and faster CD4 count recovery in individuals undergoing therapy has been reported in Caucasians, however in contrast, in African population same polymorphism (rs6897932) is shown to be associated with slow recovery while another polymorphism, rs3194051 was associated with faster CD4 T-cell recovery [86,87]. In Danish cohort undergoing therapy, polymorphisms in the IL-7R (rs6897932; T-allele) was found to be a significant predictor of faster immune recovery after initiation of therapy [88], while in Zimbabwe cohort same polymorphism (rs6897932) T-allele homozygosity was found to be associated with a lower rate of decline in the CD4 cell count in untreated HIV infected individuals [89]. Thus, polymorphisms in or adjacent to the *IL-7R* gene may result in an altered expression of IL-7R on T cells and/or a dysfunctional interaction between IL-7 and IL-7R that may affect the CD4 cell count and progression to AIDS and death [90]. However, further extended analysis of *IL-7R* gene along with functional analysis may be helpful to clear these inconsistencies. Also, there is a lack of *IL-7R* gene polymorphism studies from Asian population; this could have implication in clinical management of HIV infected individuals undergoing therapy.

Interleukin-10 (IL-10)

IL-10 is a pleiotropic cytokine produced mainly by monocytes, macrophages, Th-2 cells and B-lymphocytes. It can both stimulate as well as suppress the immune response [91]. IL-10 has been shown to inhibit various immune reactions, such as antigen presentation, cytokine production, macrophage activation, and antigen specific T cell proliferation [92]. It can also suppress IFN- γ , TNF- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), and lymphotoxin

production [91]. IL-10 has been found to up-regulate the CXCR4 expression and X4 HIV infection of dendritic cells *in-vitro*, although this did not affect the efficiency of viral transmission to autologous CD4+T cells, an event involving DC-SIGN rather than conventional viral receptors [93]. Depending on the concentration of IL-10, both inhibitory and inductive effects on *in-vitro* HIV replication have been observed; indicating its action as a double edged sword. IL-10 levels have been found to be elevated, particularly in the lymph nodes of HIV-infected individuals, whereas progression to AIDS has been correlated with an IL-10 promoter variant associated with a decreased IL-10 expression [94]. It has been suggested that IL-10 acts as a general inhibitor of proliferative and cytokine responses of both Th1 and Th2 cells *in-vitro* as well as *in-vivo*. The levels of IL-10 production are crucial to immune regulation and controlling the balance between the inflammatory and humoral responses. The capacity for IL-10 production in individuals is correlated with the genetic composition of the IL-10 locus. It has been reported that approximately 75% of the variation in IL-10 secretion capacity in humans, derive from genetic factors and these genetic differences contribute to disease susceptibility [95]. Several polymorphic sites within the *IL-10* gene promoter region have been described, including three bi-allelic polymorphisms at position -1082A/G, -819C/T, and -592C/A from the transcription start site [96]. It has been proposed that the -1082A/G polymorphism lies in a putative ETS like transcription factor binding site, while the -819C/T polymorphism may affect an estrogen receptor element. Similarly, -592C/A polymorphism has been shown to be in a region of the negative regulatory function, making them important loci for study in relation to disorders affected by levels [97]. Shin et al. (2000) reported that the individuals carrying the A allele at -592 position in *IL-10* gene were at increased risk for HIV-1 infection, and once infected, they progressed to AIDS more rapidly, especially in the later stages of HIV-1 infection [94]. Subsequent studies however reported inconsistently about the association for the same SNP with HIV disease progression [82,98-100]. At -1082 position of the *IL-10* gene, in Zimbabwean cohort, carriers of G allele (enhanced IL-10 production) were reported to have reduced mortality and attenuated CD4 count decline in therapy naïve individuals [33], indicating an important role of *IL-10* gene polymorphism in HIV disease progression. Interestingly, recently we also observed that a combination of low IL-10 (at -592 position) and low IFN- γ (+874 position) producing genotype 'AA' in these two genes was associated with faster disease progression (unpublished personal data). So, there is a need to study the combinatorial effect of variations in multiple interacting genes to better understand the intricate role of cytokine genetic polymorphisms in HIV disease progression as well as in other infectious diseases.

Interleukin-12 (IL-12)

IL-12 is naturally produced by dendritic cells, macrophages and lymphocytes [101]. It is involved in the differentiation of naïve T cells into Th1 cells and is known as a T cell-stimulating factor, which can stimulate the growth and function of T cells [102]. It stimulates the production of IFN- γ and TNF- α from T cells and NK cells, and reduces IL-4 mediated suppression of IFN- γ . In the context of HIV infection, contradictory reports are available which indicate that both immune over-activation and immune-deficiency are reflected in IL-12 production during HIV infection. Although, IL-12 could be useful to enhance deficient cell-mediated immunity, it also has potential pro-inflammatory and HIV-enhancing effects. Therefore, more studies are needed to unravel the role of dysregulated IL-12 production in HIV pathogenesis. IL-12 is a heterodimer of the polypeptides p35 and p40. *IL-12 B*, the gene encoding IL-12 p40, is polymorphic, and a functional

SNP of the 3'-untranslated region at position -1188 resulting in A to C change. However, in context of HIV no association has been found with HIV disease progression [21, 64].

Limitations of Current Review Article

Although, we have reviewed literature systematically but sample size in selected research articles is not uniform. Hence, selection of studies with larger sample size is needed to better understand the intricate role of cytokines. Besides, lack of functional studies in the majority of research articles is also the major limitation to reach at conclusions.

Current Interests and Future Prospects

In the recent years, role of IL-15, IL-17, IL-21, IL-23, IL-28B and IL-33 cytokines has just started to come into the light. Recently, IL-21 was reported to induce antiviral microRNA-29 in CD4+ T cells through STAT3, which further limits the HIV-1 infection [103]. Functional SNPs exist in the genes encoding these cytokines, however, in case of HIV infection; there is a need to establish the role of genetic association in these cytokines with disease profile. With the recent revolution in genome editing tools like zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and type II clustered regularly interspaced short palindromic repeats (CRISPER/Cas9, has successfully modified autologous CD4 cells by editing *CCR5* gene (introducing $\Delta 32$ mutation) and subsequent infusion of edited CD4+ T cells in patients has shown encouraging results [5,104]. So, continuous efforts should be undertaken in diverse human populations infected with a variety of HIV-1 subtypes in order to understand fully the complexity of host genetic variations, knowledge gained from this could be used to completely eradicate the HIV infection. Recent advancements in genomic and transcriptomic arena have widened the scope of functional aspects of variations on *cis* and *trans* quantitative trait loci. In fact, it has just started to gain better insight and may be helpful in explaining controversies regarding the expression analysis. Advanced data analysis skills like haplotyping, linkage disequilibrium and multifactor dimension reduction analysis of cytokine variations can provide a better insight into the altered balance of pro-inflammatory and anti-inflammatory cytokines. Finally, the functional analysis of the impact of genetic variations would also be important to fully understand both, the inconsistencies as well as differential HIV disease progression arising out of these genetic alterations.

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