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Review article

IP-10 is highly involved in HIV infection

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ABSTRACT

Interferon-γ (IFN-γ)-induced protein 10 (IP-10 or CXCL-10) is a chemokine involved in trafficking immune cells to inflammatory sites. Numerous studies have reported abnormally high plasma IP-10 levels in the context of human immunodeficiency virus (HIV) infection, and IP-10 is considered an important pro-inflammatory factor in the HIV disease process. The data regarding the roles of IP-10 in HIV infection required collation; this review summarizes the biological characteristics of IP-10, the positive association between plasma IP-10 levels and HIV disease progression, the effect of IP-10 on human immune cells, and potential related mechanisms. This review provides important insights into the role of IP-10 in HIV monitoring and treatment.

1. Introduction

With over one million related deaths annually worldwide, human immunodeficiency virus (HIV) infection is a serious public health problem [1]. Once HIV invades the human body, it induces an intense "cytokine storm" [2]. Of the cytokines involved, interferon-γ (IFN-γ)-induced protein 10 (IP-10) is among the better understood [3]. IP-10, also referred to as chemokine (C-X-C motif) ligand (CXCL)10 [4], is a 10 kDa secreted polypeptide belonging to the CXC chemokine family [5]. Its mRNA was first isolated by Luster et al. in 1985 from monocytes stimulated with IFN-γ [6]. The IP-10 gene maps to chromosome 4q21 [7] and its encoded protein, IP-10, typically forms chemokine dimers, each composed of several loops, one turn of a 3–10 helices at the N-terminus, and three antiparallel beta strands packed against an alpha-helix at the C-terminus [8]. The protein sequence has considerable homology with a cluster of proteins exhibiting chemotactic and mitogenic activities, which are correlated with inflammation and cell proliferation [9].

IP-10 secretion is predominantly driven by IFN-γ [10] and other endogenous cytokines, including interleukin (IL)-2, IL-17, IL-23, IL-27 IFN-α, IFN-β, and tumor necrosis factor (TNF)-α [11–13]. Exogenous lipopolysaccharide (LPS) stimulation can also play a secondary role in inducing IP-10 secretion [14]. IP-10 is widely produced by various cell types on stimulation, including monocytes, T lymphocytes, natural killer (NK) cells, endothelial cells, and stromal cells, among others, where monocytes are responsible for the greatest proportion of IP-10 expression [15].

IP-10 must combine with its receptor, chemokine (C-X-C motif) receptor 3 (CXCR3), to perform its function when it secreted into an immunological milieu. CXCR3 is a classical seven-transmembrane G protein-coupled receptor, and is also the receptor for two other chemokines: a monokine induced by gamma interferon chemokine (CXCL9) and an IFN-inducible T-cell alpha chemoattractant (CXCL11) [16,17]. CXCR3 has three isoforms: CXCR3-A, CXCR3-B, and CXCR-alt. CXCR3-A is the dominant isoform, followed by CXCR3-B, while CXCR-alt is only expressed at very low levels and is often co-expressed with CXCR3-A [18]. CXCR3 can be expressed on Th1 lymphocytes, NK cells, and NKT cells, among other cell types, and lymphocytes can be recruited by IP-10 through this receptor [19–22].

In the context of HIV infection, IP-10 plasma levels are elevated in most HIV-infected individuals [23] and IP-10 was the only cytokine, among 26 tested, that was consistently associated with HIV disease progression (based on $CD4^+$ counts) during the acute HIV infection period [24]. Together, these facts indicate that the IP-10 chemokine is vital to the HIV disease process and highlight that collation of information regarding its functions would be of benefit.

In this review we primarily focus on recent research relating to IP-10 and HIV infection, and evidence demonstrating that IP-10 plasma levels are up-regulated rapidly after HIV infection and are considerably higher in individuals co-infected with HIV and other disease-causing

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agents. IP-10 plasma levels are tightly associated with HIV disease progression and can be reduced, but not to normal levels, by administration of anti-retroviral therapy (ART). IP-10 levels are also increased in the semen, genital tract, cerebrospinal fluid, and lymph nodes from individuals infected with HIV. High levels of IP-10 suppress the functions of T cells and NK cells and promote HIV latency and replication. IP-10 production is induced by the process of HIV infection and regulated through a series of signaling pathways. Moreover, IP-10 is a promising indicator and therapeutic target in HIV infection and may provide novel approaches for monitoring HIV infection and defending against the disease.

2. Plasma levels of IP-10 are up-regulated after HIV infection and positively correlated with HIV disease progression

2.1. Plasma levels of IP-10 are elevated after HIV infection

Numerous studies have demonstrated that plasma IP-10 levels are much higher in individuals with HIV compared with those who are HIV-negative [15,25–27]. Plasma IP-10 levels begin to increase on approximately day 6 after the first positive viral load assessment, which is a more rapid response than that observed for 23 other cytokines [23], and decrease relatively promptly (more quickly than CXCL-9, but more gradually than C-C motif ligand 2) [28]. Viremic individuals have abnormally high plasma IP-10 levels compared with both elite and non-elite infection controllers, none of whom were undergoing therapy at the time of testing [29]. Similarly, treatment-naïve viremic controllers and slow progressors had higher levels of IP-10 than elite controllers [30]. Valverde-Villegas et al. reported that there was no significant difference in IP-10 plasma levels between slow and rapid progressors [25]; however, others found that plasma IP-10 levels were strongly correlated with rapid disease progression [31,32]. Some other factors are also clearly correlated with HIV-infection status, including TNF-α, sCD14, sCD163, IL6, and IL10, among others; however, IP-10 is the only factor that differs significantly in elite controllers from both HIV-negative individuals and viremic individuals [29].

2.2. High levels of IP-10 promote HIV disease progression

During HIV infection, plasma IP-10 levels are strongly associated with $CD4^+$ T cell counts and viral loads [15,24–27,29,33–35]. Pre-infection systemic IP-10 levels are closely associated with post-infection $CD4^+$ T cell loss [32]. Post-infection IP-10 levels are also inversely related to $CD4^+$ T cell counts, regardless of those pre- or post-therapy [26,30], particularly in naïve ($CD4^+$ $CD45RA^+$ $62L^+$) and memory ($CD4^+$ $CD45RO^+$) Th cells [36]. IP-10 levels are also correlated with the time to reduction of $CD4^+$ T cell count to 200 cells/μL during Fiebig stages III–V [24]. The majority of studies of the relationship between IP-10 plasma levels and peripheral blood viral loads have reported that IP-10 is positively correlated with viral loads [26,27,37,38]; however, Noel et al. reported that there was no significant relationship between IP-10 and viral loads in elite controllers [29], which may be attributable to the stable viral loads in these individuals. In addition to $CD4^+$ T cell counts and viral loads, $CD8^+$ T cell counts and HIV DNA levels are also meaningful parameters for monitoring disease progression [39]. IP-10 levels correlate positively with both $CD8^+$ T cell counts [36] and HIV DNA levels [32].

2.3. Plasma IP-10 levels remain higher in patients with HIV after ART therapy than those of healthy individuals

During ART, the production of IP-10 is down-regulated in the majority of patients with HIV relative to levels in therapy-naïve individuals; however, they remain higher than those in HIV-uninfected individuals [36,40–43]. Moreover, elevated IP-10 levels are more likely to persist in older individuals [44]. Plasma IP-10 levels are more effectively reduced in patients who undergo treatment for a median of 25 months compared with those who only receive treatment for a median of 12 months [25]. Chronic high plasma IP-10 levels during ART are correlated with treatment failure, as determined by analysis of immunological responders and non-responders [45]. Responders exhibit a steep drop in IP-10 levels after ART treatment, while non-responders may even have elevated IP-10 [45]. However, once these non-responders received successful ART therapy, plasma IP-10 levels show a reduction, indicating that IP-10 is useful for distinguishing between good and poor responders [46]. During ART, plasma IP-10 levels in slow progressors largely depend on when therapy is initiated; initiation in individuals with CD4 counts $< 350/mm^3$ results in higher IP-10 levels than in those who start with CD4 $> 350/mm^3$ [25]. Not only HIV-infected adults, but also HIV-infected children have elevated plasma IP-10 levels, which can also be suppressed by ART therapy [47].

2.4. IP-10 is particularly elevated in individuals with HIV and co-infections

Once HIV invades the human body, it severely exhausts the capacity of the immune system to defend against disease [48]. IP-10 is reported to be produced at even higher levels in individuals who are co-infected with HIV and hepatitis C virus (HCV), tuberculosis (TB) or cryptosporidiosis when compared with HIV mono-infected individuals [49,50].

In HIV/HCV co-infected individuals, plasma IP-10 levels are positively associated with the extent of liver fibrosis and plasma levels of liver enzymes [49,51,52]. Additionally, IP-10 facilitates HCV replication [53]. Of note, pretreatment plasma IP-10 levels are significant lower in HCV treatment responders than non-responders, therefore IP-10 might be a biomarker for HCV treatment outcomes in HIV/HCV co-infected individuals [54].

In HIV/TB co-infected individuals, plasma IP-10 levels are more likely to be elevated in TB-untreated bacteriologically confirmed cases than in clinically diagnosed cases and decrease steeply 7 days after starting anti-TB treatment, indicating that the kinetics of IP-10 alteration can be a predictor of TB diagnosis, particularly during the first week of anti-TB treatment [55]. Plasma IP-10 levels are also positively associated with the rate of TB recurrence [56].

IP-10 is secreted at much higher levels by the intestinal epithelial cells of individuals co-infected with HIV and cryptosporidiosis compared with those infected with HIV alone, and IP-10 levels correlate with parasite burden and IL-1α concentration. Following effective antiretroviral and antiparasitic therapy, intestinal IP-10 levels decrease to normal levels, suggesting that IP-10 may attract inflammatory cells to the intestine, further promoting immunopathogenesis [50].

2.5. IP-10 levels are increased in other body fluids and tissues of HIV-infected individuals

In addition to high plasma IP-10 levels, IP-10 is also abnormally elevated in semen after HIV infection [57,58]; however, semen IP-10 levels are not correlated with either $CD4^+$ T cell counts or viral loads (in either peripheral blood or semen) [58]. IP-10 levels are much higher in the genital tract of HIV-infected females and associated with genital viral load, although one study reported that no significant differences in genital IP-10 levels were observed between participants with detectable, and those with undetectable, genital tract viral load [59–61]. IP-10 is also overproduced in the cerebrospinal fluid of HIV-infected individuals [62] and is correlated with HIV RNA and white blood cell counts in the cerebrospinal fluid [41]. During cases of mother-to-children transmission, IP-10 levels appear to be increased in-utero in the placenta of mothers with HIV; each log (10) elevation was correlated with a three-fold increase in the risk of mother-to-children transmission [63]. In an SIV-exposed macaque model, IP-10 levels were increased in both the mucosa and peripheral lymph nodes, and high virus dose drove more rapid kinetic changes in this chemokine [64,65]. As the largest lymphoid tissue and the most important HIV/SIV replication site, the

intestines produce abundant IP-10, and the small intestine produces more IP-10 than the colon and rectum. The primary source of IP-10 in the intestine is macrophages, as well as some lymphocytes [32].

3. High levels of IP-10 suppress immune cell function

Since the expression levels of IP-10 increase abnormally during HIV infection, researchers have explored the impact of this chemokine on immune cells. To date, publications describing the impact of IP-10 in HIV infection have mainly focused on T and NK cells.

3.1. The effect of IP-10 on T cell functions

T cells are the primary targets of HIV, hence researchers investigating the impact of high IP-10 levels initially focused on this cell type. Ramirez et al. found that high levels of recombinant human IP-10 can suppress T cell responses to the gag protein (an HIV specific antigen) and decreases the production of IFN-γ by T cells [40]. IP-10 down-regulates IFN-γ production through activating transducer and activator of transcription-1 (STAT-1) signaling and suppressing the p38 pathway, while weakening calcium responses in an IP-10 dose-dependent manner. Additionally, treatment with high levels of IP-10 impairs the proliferative capacity of these T cells [40].

As a chemokine, the most important function of IP-10 is activation of lymphocytes and induction of the influx of these cells to inflamed regions [66]. In HIV-infected individuals, plasma IP-10 levels are positively associated with the proportion of human leukocyte antigen (HLA)-DR$^+$ CD38$^+$ activated CD4$^+$ and CD8$^+$ T cells [29], regardless of whether the patient is undergoing ART [36]. IP-10 can also facilitate the polarization of naïve CD4$^+$ T cells towards effector Th17 cells [67], promoting the progression of inflammation. Among a total of approximately 50 different chemokines, neutralization of IP-10 can sufficiently suppress inflammation without being compensated for by other chemokines [68]. During a period of active HIV infection, the T cell zones of lymph nodes produce large amounts of IP-10, which attracts numerous susceptible T cells to the lymph nodes. These T cells are stranded in infected lymphoid organs, and this retention can facilitate virus spread among susceptible cells, potentially aiding in HIV disease progression [69]. Nevertheless, the response of CXCR3$^+$ T cells to IP-10 is impaired after prolonged immune activation, resulting in impediment of CXCR3$^+$ T cell immigration into infected sites from the peripheral blood. Some have considered this impairment may be attributable to inefficient actin polymerization and cofilin hyperactivation [70], while others hypothesize that it might be explained by internalization of CXCR3 by T cells in response to high levels of IP-10 in the milieu [32].

3.2. The impact of IP-10 on NK cells

Aside from the effects of IP-10 on T cells in HIV infection, IP-10 also influences NK cells. Previous studies from our laboratory demonstrated that treatment with high concentrations of IP-10 suppressed CXCR3$^+$ NK cell function; however, no obvious impact was observed on CXCR3$^-$ NK cells. IFN-γ secretion and 107a expression by CXCR3$^+$ NK cells were significantly down-regulated, while the capacity of NK cells to lyse K562 cells was suppressed by exposure to high levels of IP-10 [71]. Hence, our laboratory findings suggest that IP-10 can effectively impair NK cell function in HIV-infected individuals.

4. IP-10 facilitates HIV infection and replication

4.1. IP-10 increases susceptibly to HIV infection

HIV can be transmitted through blood, semen, mucosa, and placenta, and when HIV- serodiscordant couples both have high IP-10 levels, the probability of transmission is much higher than for couples with lower IP-10 levels [72]. In a prospective cohort study of HIV-negative individuals, researchers traced changes in IP-10 levels in both genital mucosa and blood over an extended period, and divided subjects into two groups based on their outcome: (1) those who were HIV-infected and (2) those who remained HIV-negative. They found that high IP-10 levels in the mucosa correlated with HIV acquisition, and that this correlation was stronger than that with plasma levels [73]. A recent study reported that, after HIV exposure, IP-10 expression levels were increased in human cervical and colonic mucosa tissue epithelia, which may facilitate the transmission process through increasing IP-10 recruitment of HIV target cells to the mucosa surface [74]. Another study revealed that HIV-exposed seronegative sex workers have significantly lower IP-10 levels in their mucosa, which may lead to reduced trafficking across the genital mucosa and protect them from HIV infection, supporting the results described above [75]. These findings indicate that individuals with high IP-10 levels are hyper-sensitive to HIV infection. Semen is enriched for IP-10, with concentrations approximately 70 times those in plasma [57], particularly in HIV-infected individuals, who have even higher IP-10 levels in semen [58]. Viral receiver target cells can be strongly attracted to mucosal surfaces by high levels of seminal IP-10, leading to their infection with HIV.

4.2. IP-10 facilitates HIV latency, viral replication and cell proliferation

Upon IP-10 treatment and in vitro HIV infection, resting CD4$^+$ T cells have a higher level of viral integration and a similar level of reverse transcription activity, compared with untreated resting CD4$^+$ T cells, which indicates that IP-10 may promote latent HIV infection. The mechanism involved in this process was explored using CCL19, a chemokine resembling IP-10, and the results proved that CCL19 can dephosphorylate cofilin and change the state of filamentous actin, resulting in effective promotion of HIV nuclear localization and integration [76]. Therefore, we hypothesize that IP-10 may also facilitate HIV latency in a similar manner. Brian et al. reported that treatment of HIV-infected macrophages and lymphocytes with high doses of IP-10 led to dose-dependent increases in HIV replication in these cells. Although IP-10 cannot activate HIV gene expression, it can cause accumulation of HIV DNA in macrophages and lymphocytes prior to viral transcription [38]. The mechanism by which IP-10 promotes HIV replication requires further elucidation; it is possible that this is achieved through promotion of cell proliferation. Indeed, IP-10 does function to promote cell proliferation through binding to its receptor, CXCR3-A (a CXCR3 subtype), which cooperates with Gαi to activate PI3K/AKT or mitogen-activated protein kinase (MAPK; ERK and JNK) signaling pathways (among others), thereby promoting cell proliferation. Another CXCR3 subtype, CXCR3-B, can induce apoptosis by cooperating with Gαs to activate adenyl cyclase and generate cAMP [77–79]. In individuals with HIV, the proportion of CXCR3-A relative to CXCR3-B is much higher than that in healthy controls [71], implying that IP-10 may promote the proliferation of HIV-infected cells, facilitating disease progression. However, this abnormal CXCR3-A ratio can be corrected by ART [71], suggesting that a therapeutic strategy of blocking IP-10 receptors, specifically focusing on CXCR3-A, could potentially achieve superior outcomes.

5. Possible mechanisms of IP-10 up-regulation

As its name suggests, IP-10 is primarily induced by IFN-γ, and during HIV infection this may be achieved by the synergistic effects of STATs, NFκB, MAPK and PI3K signaling pathways, among others [80,81]. In general, IFN-γ needs to synergize with other cytokines (such as TNF-α) to strongly induce IP-10 secretion [82]. HIV stimulated IFN-γ and TNF-α induce IP-10 production in astrocytes, at both the RNA and protein levels. This induction is regulated by the activation of STAT-1 and NFκB [82,83]. Synergy of IFN-γ with platelet-derived growth factor (PDGF) is also reported to augment IP-10 production in a transcriptional or posttranscriptional manner, although PDGF itself cannot

induce IP-10 production [81]. IP-10 production can also be induced by IFN-α in human rhinovirus infection, activated by the JAK/STAT pathway [84].

Besides cytokines, other regulatory factors also have important roles in IP-10 induction. When monocytes and dendritic cells are treated with intact HIV, IP-10 production is significantly elevated. Moreover, use of a TLR7/9 antagonist can inhibit IP-10 production, indicating that TLR7/9 is involved in the induction of IP-10 secretion and that this indirect induction may involve IFN-α [33]. A study from our laboratory showed that IP-10 can be suppressed by microRNA-21 in HIV-infected monocytes in a post-transcriptional manner; however, this fine regulation is less pronounced in macrophages, possibly because its effects are suppressed by elevated levels of IFN-stimulated gene 15 (ISG-15). ISG-15 can effectively promote IP-10 expression in macrophages, which diminishes the effects of microRNA-21 [15]. In an experiment using SIV-infected primates, simultaneous high levels of IP-10 and ISG-15 were observed, and it was suggested that their expression levels were promoted via the STAT-1 signaling pathway, but inhibited by suppressor of cytokine signaling 1 (SOCS1) and SOSC3 [65].

HIV itself can contribute to IP-10 induction. This process depends on viral entry and viral replication, particularly via the activity of transactivator of transcription (Tat). Tat is an HIV accessory protein, which facilitates viral invasion and transactivation, and it may induce IP-10 expression through the activation of AKT, P38 and JNK signaling pathways and their downstream transcription factors (NFκB and STAT-1), in cooperation with IFN-γ and TNF-α [82,85]. In contrast, the gp120 protein cannot induce IP-10 production [53,69]. Nevertheless, it has been postulated that gp120 can directly induce IP-10 expression in a novel IFN- and STAT-1-independent manner in the HIV-infected central nervous system [86]. Michele et al. argued that induction of IP-10 expression requires gp120-mediated viral binding, whereas gp120 binding alone is insufficient, since IP-10 expression also depends on internalized productive viral infection to stimulate downstream events [74,87] (Fig. 1).

In addition to HIV-related studies, numerous signaling pathways have been reported to influence IP-10 expression in other contexts. For example, in myeloproliferative neoplasms, mutation of Janus-Kinase 2 induces the expression of IP-10 through activation of downstream NFκB signaling [88]. In addition, Fc-98 (a benzenediamine derivate) can reduce IP-10 production through repression of unmethylated CpG motif-induced activation of MAPK and STAT-1 signaling [89]. CpG motifs are used to mimic bacterial DNA and can be recognized by TLR9, which may contribute to HIV recognition (see above). Moreover, a type of dietary isothiocyanate, sulforaphane (SFN), also inhibits IP-10 expression through decreasing the levels of interferon regulatory factor-1 and down-regulating phosphorylation of STAT-1 and protein kinase B [90]. Together, these signaling pathways may provide clues to the mechanisms underlying abnormal IP-10 elevation in HIV infection.

6. Future strategies to target IP-10 in HIV infection

IP-10 has potential for use as an indicator to effectively monitor HIV disease progression and/or as a therapeutic target to alleviate the harm caused by HIV infection, and some preliminary trials have paved the way for subsequent clinical applications.

6.1. Use of IP-10 as an indicator of HIV infection

Based on the strong association of IP-10 with HIV infection, and as measurement of IP-10 levels in plasma samples is convenient and low-cost, IP-10 could be used as a predictive factor to monitor various HIV-related situations. Some researchers advocate the use of IP-10 to indicate acute HIV infection in resource-limited, low-income countries [91]. Pastor et al. have proven that, for detection of acute HIV infection in low-income countries, measurement of plasma IP-10 level has 95.5% sensitivity and 76.0% specificity when the cut-off value is set at IP-10 ≥ 161.6 pg/mL [91]. IP-10 is also an independent predictor of rapid HIV progression during the early stage of infection, with predictive power superior to viremia and $CD4^+$ T cell count [31,32]. Resource-limited low-income countries not only need to detect acute HIV infection, but must also monitor the effects of ART in individuals with chronic HIV infections. Pastor et al. also found that measurement of IP-10 plasma levels had 91.9% sensitivity and 59.9% specificity for identifying ART responders with undetectable viral loads (< 38.0 pg/mL), when the cut-off value was set at IP-10 ≥ 44.2 pg/mL [92]. IP-10 is also an excellent indicator in HIV/TB co-infected individuals. IFN-γ is the biomarker traditionally used to detect TB; however, its accuracy is severely impaired in individuals with HIV-induced immune depression, and IP-10 is among the most promising alternative markers, as it has a higher sensitivity for active TB than IFN-γ; however, regrettably, it has lower specificity [93]. IP-10 performs slightly better or comparably relative to QuantiFERON-TB Gold In-tube (QFT-IT). Moreover, IP-10 is less dependent on $CD4^+$ T cell counts and mitogen responses than QFT-IT [94] and can also predict the risk of acquiring active TB in HIV mono-infected individuals with similar accuracy to QFT-IT [95].

6.2. IP-10 as a therapeutic target in HIV infection

As a therapeutic target, IP-10 has been blocked or neutralized to alleviate the progression of transplant rejection and autoimmune diseases [96,97], and some phase II clinical trials have even been conducted [98]. Nevertheless, targeting of IP-10 for treatment of HIV infection has not progressed. Blocking IP-10 using a neutralizing antibody leads to increased IFN-γ secretion, T cell proliferation, and $CD8^+$ T cell degranulation of perforin/granzyme B in peripheral blood mononuclear cells isolated from HIV-infected individuals [40]. The function of NK cells from HIV-infected individuals can also be restored by blocking IP-10 [71]. Moreover, blocking IP-10 can also suppress HIV replication in monocyte-derived macrophages and lymphocytes [38]. Some studies have attempted to use CXCR3 neutralizing antibody or CXCR3 antagonists to abrogate IP-10 function, with similar results to those achieved using IP-10 antibody [69,71,99]. Therefore, IP-10 represents an interesting target for evaluation with the aim of achieving immune reconstruction following HIV infection.

7. Conclusion

Numerous studies have demonstrated that plasma IP-10 levels are abnormally increased after HIV infection and tightly associated with HIV disease progression. Moreover, plasma IP-10 levels in individuals with HIV infection remain higher than those of healthy controls, even after ART. IP-10 levels are also elevated in other tissue and body fluids during HIV infection. High IP-10 levels may increase susceptibility to HIV infection in HIV high-risk populations, and can also increase HIV replication and impair immune cell function in HIV-infected individuals. The possible mechanism underlying increases in may involve a combination of HIV particles or HIV proteins and TLR7/9, which can be regulated by microRNA-21 during HIV infection (Fig. 1). Additionally, the strong association of IP-10 with HIV plasma viral load highlights its potential for use as an indicator of HIV infection and/or a therapeutic target for HIV treatment.

Declaration of interest

None.

Author contributions

JL, XY, ZW, and YJ wrote the manuscript. HS revised the manuscript. All authors revised the manuscript and approved it for publication.

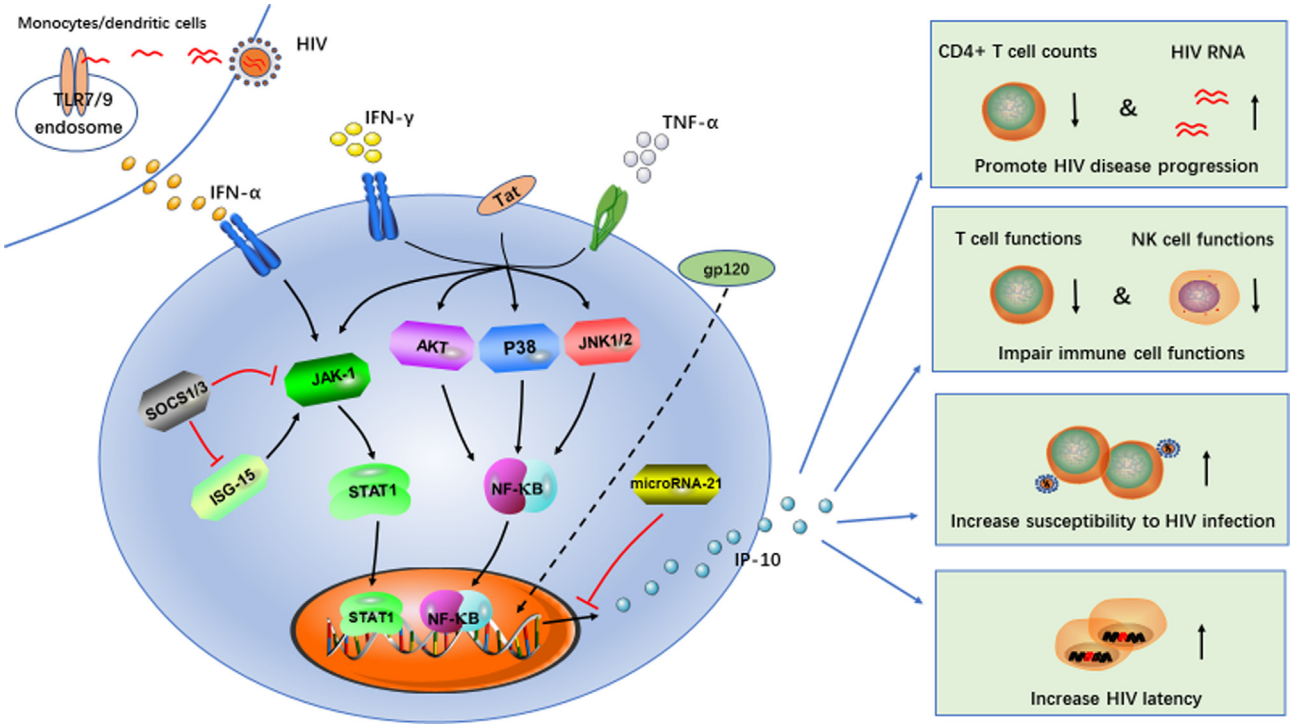

Fig. 1. Schematic of the possible mechanisms involved in IP-10 induction and the effects of elevated IP-10 on the immune system during HIV infection. On HIV infection, monocytes and dendritic cells secrete increased amounts of IFN-α through TLR7/9 dependent mechanisms, and IFN-α further stimulates immune cells to produce IP-10, through the JAK-STAT-1 signaling pathway. IFN-γ, HIV accessory protein Tat and TNF-α cooperate with one another to induce IP-10 through NFκB and STAT-1 signaling. Also, gp120 may induce IP-10 via an unknown pathway. ISG-15 can promote IP-10 production through stimulation of JAK-1; however, SOCS1/3 can suppress ISG-15 and STAT-1 signaling. Additionally, microRNA-21 suppresses IP-10 production in a post-transcriptional manner. Increased IP-10 levels can promote HIV disease progression, manifested as loss of $CD4^+$ T cells, increased viral loads, impaired immune cell function (T cells and NK cells), increase susceptibility to HIV infection, and elevated HIV latency.

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