REVIEW

Microbial translocation, residual viremia and immune senescence in the pathogenesis of HIV-1 infection

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Abstract

The pathophysiological mechanisms that underlie the progression of human immunodeficiency virus-1 (HIV-1) disease to full-blown AIDS are not well understood. Findings suggest that, during HIV-1 infection, plasma lipopolysaccharide (LPS) levels, which are used as an indicator of microbial translocation (MT), are elevated throughout the acute and chronic phases of HIV-1 disease. The translocation of bacterial products through the damaged gastrointestinal barrier into the systemic circulation has been described as a driver of immune activation. In contrast, comorbidities that are associated with HIV-1 infection have been attributed to chronic inflammation and immune system dysfunction secondary to MT or low-level HIV-1 replication in plasma and cell reservoirs. Moreover, accelerated aging is significantly associated with chronic inflammation, immune activation, and immune senescence. In this review, we aimed to investigate the role of inflammation as a pivotal marker in the pathogenesis of HIV-1 disease. We will discuss the key features of chronic inflammation and immune activation that are observed during the natural course of the disease and those features that are detected in cART-modified infection. The review will focus on the following aspects of HIV-1 infection: (1) MT; (2) the role of residual viremia; and (3) "immune senescence" or "inflammaging." Many questions remain unanswered about the potential mechanisms that are involved in HIV-1 pathogenesis. Further studies are needed to better investigate the mechanisms that underlie immune activation and their correlation with HIV-1 disease progression.

Key words: Human immunodeficiency virus-1; Combined antiretroviral therapy; Immune activation; Microbial translocation; Residual viremia; Immune senescence

Core tip: The aim of this review was to summarize the most relevant mechanisms in human immunodeficiency virus-1 pathogenesis by focusing on the role of microbial translocation, residual viremia, and immune senescence or "inflammaging" in disease progression to full-blown AIDS. Moreover, the impact of antiretroviral therapy on these mechanisms was investigated.

INTRODUCTION

Combined antiretroviral therapy (cART) has led to a

lower morbidity and mortality in human immunodeficiency virus type 1 (HIV-1)-infected patients by significantly improving clinical and laboratory parameters. However, the long-term use of cART is associated with adverse side effects that are generally not directly related to HIV-1 infection. These effects include cardiovascular diseases, kidney impairment, osteoporosis, and hepatotoxicities[1]. Moreover, the prolonged survival of patients and the persistence of virus particles in tissue may directly or indirectly contribute to the development of cancers, neurocognitive impairment and a more rapid progression of hepatitis C infection. Chronic inflammation, chronic immune activation, and immune senescence are the pathological hallmarks of HIV-1 infection that lead to these conditions in HIV-1-infected subjects, mainly in subjects with persistently decreased CD4$^+$ T cell counts. Cardiovascular events in HIV-1-infected patients may occur because of the following reasons: (1) these subjects have a higher cardiovascular risk than the general population; (2) the HIV-1 virus can increase the risk of atherosclerosis in patients; and (3) several antiretroviral regimens may influence the atherosclerotic profile of patients due to significant lipidic changes. Therefore, many ischemic cardiovascular events may occur during long-term HIV-1 infection and accelerated atherosclerotic processes may be related either to the infection or to the chronic use of cART[2]. Experimental studies have demonstrated the direct effect of several viral components on the endothelium[3], including the increased expression of adhesion molecules, such as intercellular adhesion molecule and E-selectin; a pro-thrombotic state with increased levels of von Willebrand factor, plasminogen activator inhibitor-1, and tissue plasminogen activator; leukocyte recruitment into the sub-endothelium; and atherosclerotic plaque growth[4,5].

Different factors may contribute to the establishment of immune activation during HIV-1 infection. HIV-1-specific mechanisms and non-specific generalized responses to infection may promote the chronic and aberrant activation of the immune system. An early loss of gut mucosal integrity, the pro-inflammatory cytokine milieu, co-infections, and the subsequent marked destruction of the lymph node architecture are the main factors that contribute to the ongoing activation of the innate and adaptive immune systems. The severe depletion of memory CD4$^+$ T cells, especially cells that express the CCR5 receptor, occurs in the gut mucosa during primary HIV-1 infection and simian immunodeficiency virus (SIV) infection[6].

A massive loss of mucosal T helper 17 (Th17) CD4$^+$ T cells in the SIV-infected rhesus macaque, an animal model of AIDS, has been linked to impaired immune responses in the gut mucosa to an enteric pathogen, which leads to the lack of local control of the pathogen and consequently its translocation[7]. Therefore, both the loss of immune mucosal function and the breakdown of the intestinal barrier may allow the translocation of microbial products into the systemic circulation. Findings suggest that plasma lipopolysaccharide (LPS) levels, which are used as a marker of microbial translocation (MT), are elevated during chronic HIV-1 infection[8]. Regarding cytokine imbalance patterns, higher levels of inflammation markers and coagulation factors, such as high-sensitivity C-reactive protein (h-PCR), D-dimer, and interleukin-6 (IL-6), have been observed in HIV-1-infected patients[9].

Overall, these changes in cytokine and coagulation profiles are associated with an increased risk of cardiovascular diseases, opportunistic conditions, and other mortality causes in subjects with CD4$^+$ T cell counts that are persistently below 500 cells/μL[10,11].

Considering the strong evidence that persistent immune activation is a key cause of HIV-1 disease progression, understanding the mechanisms that drive immune activation during chronic infection is important for developing new strategies that target this process.

CHRONIC IMMUNE ACTIVATION

The current simplified model of HIV-1 pathogenesis integrates the following three main events that occur during the natural or cART-modified course of viral infection: (1) the massive depletion of CD4$^+$ T lymphocytes; (2) paradoxical immune activation; and (3) the exhaustion of immune resources.

These events are briefly analyzed in the following paragraphs and are depicted in Figure 1: (1) During primary infection, HIV-1 can infect a large number of CD4$^+$ T cells, particularly the activated memory T cell subset that expresses the CCR5 ligand. This process is associated with high levels of viral replication[12]. The depletion of CD4$^+$ T cells that is observed in the setting of HIV/SIV (the simian equivalent of HIV) infection is due to the involvement of the central memory CD4$^+$ T cell population. Additionally, this event is based on the establishment of reservoirs of latently infected cells[13,14]. Studies in primates that were infected with SIV and in HIV-1-infected humans have revealed that massive CD4$^+$ T cell depletion occurs in mucosal tissue throughout all of the stages of HIV-1 infection[15]. Plasma HIV-1 viremia (the level of HIV-1 RNA in plasma) increases to peak levels until the adaptive immune response, particularly the onset of HIV-1-specific CD8$^+$ T cells, which generally indicates the end of the acute phase of infection. However, the damage to the immune system is significant: HIV-1 has established a latent reservoir and rooted itself in the host, and extensive viral replication has resulted in the massive depletion of CD4$^+$ T cells, especially in mucosal lymphoid tissue (MALT). Therefore, the compromised integrity of MALT may result in MT from the gut into the systemic circulation[16,17]; (2) HIV-1 infection is associated with chronic immune activation, which appears more pronounced in patients with an advanced cellular immunodeficiency[18,19]. This immune activation is charac-
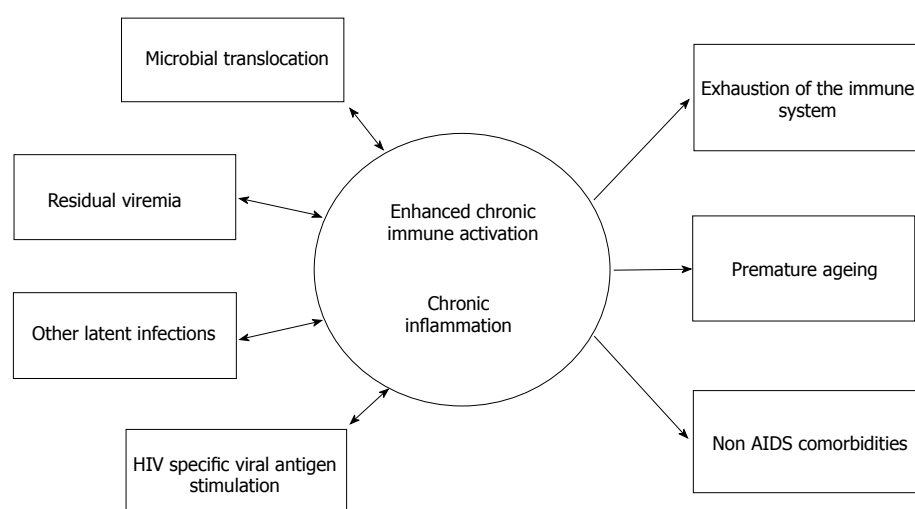
Figure 1 Factors associated with chronic inflammation and immune activation in human immunodeficiency virus-1 disease. HIV: Human immunodeficiency virus-1.

terized by the presence of chronically activated T cells, B cells and monocytes/macrophages; the increased expression of various leukocyte activation markers; the production of pro-inflammatory cytokines; and an increase in cell proliferation[20]. High levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-6 and IL-1β, in both plasma and lymph nodes have been observed in the early stages of HIV-1 infection[21,22]. In addition, the secretion of chemokines, such as MIP-1α, MIP-1β and regulated upon activation, normal T cell expressed and presumably secreted (RANTES), is increased in these patients[23,24]. The persistent inflammation status is most likely due to several factors, including the ongoing production of HIV-1; the presence of co-pathogens, such as cytomegalovirus (CMV) or herpes viruses (HSVs); the translocation of LPS across a damaged gut mucosa; the loss of T regulatory lymphocytes and other immunoregulatory cells; and irreversible fibrosis of the thymus and the lymph node infrastructure. CMV causes life-long antigenic stimulation and the subsequent development of an expanded population of well-differentiated, apoptosis-resistant, senescent T cells with limited proliferative potential[25,26]. During HIV-1 infection, the depletion of CD4+ T cells may result in the suboptimal immune control of these persistent viral infectious agents, which permits the reactivation and replication of CMV and Epstein-Barr virus (EBV) infections. Several authors have hypothesized that co-infections with other viruses may contribute to the "accelerated aging" syndrome that is observed in HIV-1 patient populations[27]. Therefore, this state of generalized chronic immune activation is currently considered the hallmark of pathogenic HIV-1 and SIV infections and has a higher independent predictive value of disease progression than viral replication[28]; and (3) During all of the stages of HIV-1 infection, the presence of strong and persistent immune activation is the primary cause of senescence and apoptosis of the immune system and ulti-

mately leads to the exhaustion of immune resources. Immune activation and inflammation result in fibrosis of lymphatic tissue, which damages the lymph node architecture and prevents normal T cell homeostasis[29,30]. Moreover, a vicious cycle is established in which HIV-1 replication promotes immune activation and immune activation promotes HIV-1 replication. Pro-inflammatory cytokines are released and participate in this mechanism. The synergic action of IL-1β, TNF-α and IL-6 can lead to T cell activation. In addition, IL-1β and TNF-α may decrease trans-epithelial resistance in mucosal tissues[31,32]. cART has been considered the best "deactivator" of the immune system in HIV-1-infected patients. cART usually results in a marked reduction in T cell activation and apoptosis[33,34] and a decrease in pro-inflammatory cytokine levels. In addition, antigen-specific stimulation is strongly diminished due to the rapid decline in the number of HIV-1-specific CD8+ T cells[35,36]. cART reduces the depletion of naïve T cells and induces immune recovery. However, even when a decrease in inflammation and the down-regulation of immune activation markers is observed in patients on cART, more inflammatory parameters remain at higher levels than those in healthy individuals and a significant imbalance in the cytokine profiles persists.

MT

The HIV-1-induced disruption of MALT results in the translocation of microbial products across the intestinal mucosa into the peripheral circulation, which produces high levels of plasma LPS and bacterial DNA that persist over time (Table 1). MT is correlated with markers of systemic immune activation[37]. LPS is a component of the cell wall of gram-negative bacteria, and the majority of authors suggest that LPS is a marker of MT throughout chronic HIV-1 infection[38].

Mucosal damage and the dysfunctional phagocytic clearance of microbial products are responsible for MT in the bloodstream. The translocation of bacterial

Table 1 Main dynamics involved in the development of immune dysfunction during human immunodeficiency virus-1 infection

Microbial translocation	Residual viremia	Immune senescence
HIV-1 invasion of the gut mucosa	MT is enhanced in patients presenting residual viremia	High frequency of CD4+CD38+ and CD8+CD38+ T cells
Disruption of mucosal integrity and depletion of local Th-17 cells	Stochastic antigen stimulation of long-lived latency infected cells	Accumulation of senescent antigen -experienced memory T
LPS, CpG DNA in blood stream with aspecific and polyclonal immune-activation *via* LPS	Viral replication in anatomical sanctuaries	Inefficient T cell renewal
Pro-inflammatory cytokines secretion (TNF-α; IL-1; IL-6)	Incomplete viral suppression during cART	Fibrosis of lymphopoietic organs cells (CD28-CD57+)

HIV-1: Human immunodeficiency virus-1; Th-17: T helper-17; LPS: Lipopolysaccharide; CpG: --C--phosphate--G--; TNF-α: Tumor necrosis factor-alpha; IL-1: Interleukin-1; MT: Microbial translocation; cART: Combined antiretroviral therapy.

products results in the profound activation of the innate immune response. LPS, flagellin and CpG DNA, which are toll-like receptor (TLR) ligands, can directly stimulate peripheral macrophages and dendritic cells to produce a range of pro-inflammatory cytokines. Several investigations have demonstrated that LPS is biologically active *in vivo* and its interaction with CD14/TLR-4 on monocyte/macrophages is one of the mechanisms that leads to the secretion of soluble CD14 (sCD14) and pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1. SCD14 is produced by monocyte/macrophages in response to stimulation by LPS. LPS stimulation in vitro has been demonstrated to promote T lymphocyte activation and death[39,40].

The correlation between plasma LPS levels and the frequency of circulating CD8+ T cells with an activated CD38+ HLA-DR+ phenotype suggests that MT may directly or indirectly generate polyclonal T cell activation *via* the production of cytokines and chemokines[41].

Consistent with these observations, subjects with HIV-1 infection and high levels of LPS have an increased risk of disease progression to full-blown AIDS or death, irrespective of their CD4+ T cell counts and HIV-1 RNA levels viral load (VL). Moreover, this marker has been demonstrated to be a strong predictor of mortality, independent of the CD4+ T cell count and the VL[42,43].

The translocation of bacterial products into the systemic circulation through the damaged gastrointestinal barrier has been described as a pivotal driver of immune activation in the course of chronic HIV-1 infection[44-47]. MT is the result of CD4+ T cell depletion in the gut mucosa and increased gut permeability; however, MT has been observed in other diseases, such as idiopathic CD4+ T cell lymphocytopenia[48]. High levels of MT have been observed in many HIV-1-naïve patients. Several studies suggested that cART induces a progressive decrease in the plasma levels of microbial DNA, which tends to stabilize after several weeks of treatment but never normalizes[44]. A reduction in MT and inflammatory markers is broadly associated with a decrease in HIV-1 load. Moreover, recent findings have indicated that the presence of MT is associated with residual viral replication in HIV-1-infected subjects who receive effective cART. Those subjects with higher viral suppression (*i.e.*, VL < 2.5

copies/mL) presented the same LPS levels as HIV-1-uninfected subjects, which suggests that cART may have reverted HIV-1-induced mucosal damage[49]. However, other authors found that MT is strongly associated with higher levels of inflammation markers, independent of HIV-1 VL levels. Despite the findings that cART can reduce MT levels, inflammatory marker levels remain higher than those observed among uninfected subjects[50]. Recent findings in cART-treated subjects revealed that HIV-1 DNA levels in the gut mucosa were strictly correlated with LPS levels and the number of CD8+CD38+ T cells[51].

Long-term cART is associated with reduced plasma LPS levels and the down-regulation of immune activation markers. However, LPS plasma levels often remain detectable in patients who are successfully treated with cART[44]. This phenomenon may be explained by the ongoing partial repair of the mucosal barrier during cART. The LPS levels in subjects with maximal viral suppression are comparable to those observed in healthy donors. However, the mechanisms of LPS reduction after starting cART are not well understood because these mechanisms do not depend on VL but come into play soon after treatment initiation. However, the lack of an association between reduced MT and increased CD4+ T cells during the first weeks of cART suggests that MT is more influenced by the cellular turnover of latently infected cells than from circulating CD4+ T-cells.

The following questions regarding the role of MT in HIV-1 pathogenesis remain unsolved: (1) During the natural course of HIV-1 disease, does MT contribute to immune system activation or is MT a consequence of immune system activation? (2) Is MT the sole cause of immune activation in HIV-1-infected patients or does residual viremia play a pivotal role? If yes, what is the importance of these two mechanisms? (3) Is gut mucosal damage completely reversible after starting cART? and (4) Moreover, does LPS play a key role in virologically controlled patients with blunted CD4+ T cell gain?

RESIDUAL VIREMIA

The objective of cART is to maintain plasma virologi-

cal suppression below the limits of detection, which are generally less than 50 copies/mL depending on the assay that is used[52]. Several studies have demonstrated that maintaining viral load levels < 50 copies/mL leads to long-term virological success and immunological and clinical benefits in HIV-1-infected subjects. However, the main methods that are used to evaluate HIV-1 RNA load during HIV-1 infection have various detection limits. The polymerase chain reaction (PCR) assay has a detection limit of 400 copies/mL. The ultrasensitive PCR assay has a detection limit of 50 copies/mL, and the real-time PCR assay has a lower limit of detection that ranges from 20-48 copies/mL[53]. The lower limits of detection of the new real-time assays may result in increased measurements of transient and intermittent detectable viral RNA (blips) in patients with virological suppression. There is controversy about the significance and consequences of viral blips. Several authors suggest an association between blips and the development of mutations that confer resistance to cART and an increased risk of virological failure[54-56]. In contrast, other authors did not find any relationship between isolated blips and virological failure[57,58]. Intermittent viremia increases T cell activation and facilitates the extension of HIV-1 infection. Subjects with intermittent viremia present higher levels of total specific CD8^{+} and CD4^{+} T cell responses compared with patients who have persistently undetectable HIV-1 RNA levels. These CD8^{+} and CD4^{+} T cell responses may block viral replication, thereby reducing the risk of virological failure[59]. The discrepancies in the findings may be due to inconsistencies in the definitions of blips and virological failure and to differences in the testing methods for the detection of HIV-1 RNA levels[60].

Recent studies have used a laboratory-based real-time PCR assay that was capable of detecting single HIV-1 RNA copies/mL. These studies demonstrated that several patients who received cART had persistent low-level viremia that ranged from 1-49 copies/mL. The source and dynamics of persistent viremia in treated patients are currently under investigation. It has been proposed that low-level viremia may be the result of ongoing viral replication in patients, which is caused by incomplete viral suppression during cART[61]. Therefore, several studies have investigated whether intensification with raltegravir, an integrase inhibitor that blocks viral DNA integration into host cell DNA, would further decrease the persistent low-level residual plasma viremia in patients on effective cART[62]. In subjects who were treated during chronic infection, the intensification of cART with raltegravir for 48 wk was associated with a significant decrease in CD8^{+} T cell activation and a transient increase in episomal HIV-1 DNA, which suggests that raltegravir intensification may positively impact residual HIV-1 replication[63].

The absence of any detectable effects of drug intensification on HIV-1 residual viremia in patients on therapy suggests that viremia is not due to ongoing replication but may arise from different sources. An alternative hypothesis is that the residual amount of HIV-1 RNA may be the result of virus release from long-lived latently infected cells that are activated by stochastic antigen stimulation (Table 1). Several papers have reported that genetically homogeneous viral subpopulations can often be observed in patients on long-term treatment and in the viral population that rebounds during treatment interruptions. These findings further support the concept that persistent low-level viremia arises from long-lived cells rather than ongoing viral replication[64,65].

A further line of investigation has focused on anatomical compartments that may serve as "sanctuary sites", such as the central nervous system and the genital tract, in which HIV-1 replication can occur unhindered by poorly penetrating antiretroviral agents. However, the role of ongoing HIV-1 replication in tissue compartments and cellular reservoirs remains to be defined. Several findings suggest that the reservoir is mainly established and maintained in tissue and that infected cells that are circulating in the blood may not be representative of the much larger population of infected cells in tissue. Sequences of persistent HIV-1 populations in plasma are often not found in peripheral blood resting memory CD4^{+} T cells[61-65]. Understanding the relationship between residual low-level viremia and the size of the reservoir will help guide future attempts at HIV-1 eradication; however, further prospective studies are required to determine the cause-and-effect relationship between these parameters.

Several studies that have used conventional HIV-1 RNA assays suggest that a chronic inflammation status may persist in patients with undetectable HIV-1 RNA loads[53,66]. The persistency of low-level residual viremia represents a continuous pro-inflammatory stimulus for the immune system, which underlies chronic immune activation and inflammation. Chronic inflammation and immune system dysfunction are important contributors to the increased risk of non-AIDS comorbidities that are often observed in HIV-1 patients, such as cardiovascular events, renal impairment and non-AIDS cancers[41,67]. Moreover, increased levels of inflammation have been associated with an increased risk of progression to AIDS and mortality in HIV-1 patients. In contrast, viremia control is accompanied by a decrease in MT, chronic inflammation and immune system activation parameters[68]. Whether residual low-level viremia plays a key role in increasing the inflammatory status in patients is unclear, and different results have been reported. In the SMART trial, markers of inflammation, coagulation and renal function were elevated in HIV-1 participants and remained elevated even after HIV-1 RNA levels were suppressed with cART[69].

Elite controllers have higher levels of the inflammatory marker C-reactive protein (CRP) than uninfected controls. This finding may be explained by the presence of infected CD4^{+} T cells that carry replication-competent HIV-1 particles, which suggests that low levels of

ongoing viral replication contribute to the maintenance of HIV-1 reservoirs in the absence of detectable plasma viremia[70]. However, no association has been found between low-level viremia and CRP, fibrinogen and IL-6 levels, which suggests that CRP may not be a reliable marker of inflammation due to ongoing viral replication or viral persistence. In addition, no correlation has been found between immune activation markers and residual viremia[61,66,68]. HIV-1-infected patients with high levels of LPS have an increased risk of progression to AIDS. Plasma LPS levels are correlated with the persistence of HIV-1 in the gut mucosa. Furthermore, HIV-1 DNA levels are correlated with the levels of the activation marker CD38 and CD8+ T cell numbers. Recent studies found that HIV-1-infected patients on cART who had negative HIV-1 RNA plasma levels (< 20 copies/mL) presented less frequently with MT and had lower levels of inflammation markers than patients with low-level viremia (20-200 copies/mL), which suggests that inflammation is induced by MT and not by HIV-1 viremia[50].

These contrasting data indicate that the mechanisms by which residual viremia and chronic inflammation increase the risk of morbidities and mortality in HIV-1-infected subjects on cART are complex, and further studies are needed.

HIV-1 AND IMMUNE SENESCENCE

The association between HIV-1 infection and inflammation is similar to that between advanced age and inflammation, which has been well described. HIV-1 infection shares several similarities with aging, including an increased incidence of cardiovascular diseases, malignancies, infections, chronic viral reactivations, osteoporosis, neurocognitive decline, and frailty[1,71].

Similar to aging, HIV-1 infection is characterized by a general decline in T cell renewal, and an altered capability to regenerate T lymphocytes has been observed in both conditions. Therefore, the naïve T cell pool cannot be efficiently replenished and old, exhausted CD8+ T cell clones and depleted CD4+ T cells cannot be continuously replaced. The double insult of aging and HIV-1 infection impacts the functions of both the hematopoietic stem cell compartment and the thymus and may contribute to many of the changes that are associated with immune senescence, including reduced naïve T cell production, reduced T cell proliferation, and an impaired immune system response to vaccines and infections. The direct infection of the thymic stroma and thymocytes by HIV-1[72-74] and the thymic atrophy that is observed in HIV-1-infected subjects may account for this immune decline, which is similar to age-related thymic involution[75] and may be the result of the suppressive effects of pro-inflammatory cytokines on the thymus[76].

In both aging and HIV-1 infection, the increased expression of the activation marker CD38, which is expressed on the surface of CD4+ and CD8+ T cells, has been observed[77,78]. Moreover, positive correlations have been observed among the proportion of CD8+ T cells that share the HLA-DR+/CD38+ phenotype, the rate of CD4+ T cell decay and the development of opportunistic diseases[79,80]. In addition, persistent T cell activation leads to T cell proliferation and T cell differentiation, which results in the accumulation of senescent, antigen-experienced memory T cells, the reduced expression of CD28 and an increased expression of CD57[81].

The expression of the surface marker CD57 has been correlated with greater resistance to apoptosis in CD8+ T lymphocytes during HIV-1 infection, which facilitates T cell accumulation[82]. CD28 is a co-stimulatory molecule, and the loss of this marker on CD4+ and CD8+ T cells results in reduced B cell function and restricted T cell diversity. A high proportion of CD8+ T cells that express CD57 has been observed in both aging and HIV-1 infection, and this senescent CD28-/CD57+ phenotype is characterized by a reduced capacity to produce IL-2 and a shortened telomere[83,84]. A higher frequency of senescent CD8+ T cells (CD45RO+CD57+CD28-) and a lower frequency of naïve CD4+ and CD8+ T cells (CD45RA+CD28+CCR7+) were found both in cART-treated patients with undetectable viremia and high CD4+ T cell counts and in older HIV-negative individuals when compared with HIV-1-negative younger controls. The expression of CD8+ T cell activation markers (HLA-DR+CD38+) was higher in HIV-1-infected individuals than in older or younger seronegative individuals[85] (Table 1).

The disproportionate production and accumulation of cytokines, such as TNF-α, IL-1β and IL-6, may lead to several adverse effects. Pro-inflammatory cytokines share a pivotal role in the process of aging and are present at higher concentrations in the blood of the elderly[86,87]. IL-6 is directly associated with the development of age-related disorders, including osteoporosis, cognitive decline and frailty symptoms, whereas increased plasma levels of TNF-α and IL-1β have been observed in the elderly with atherosclerosis[88-90]. In addition, these cytokines may have a role in neurocognitive impairment and neuronal[91-93] pathologies most likely through the induction of large amounts of nitric oxide[94-96], which is conducive to oxidative stress-related damage. This overall process can be referred to as "inflammaging", which is the up-regulation of anti-stress responses and inflammatory cytokines[97]. During the chronic phase of HIV-1 infection, both the accelerated process of immune senescence and inflammaging may contribute to the development of the progressive immunodeficiency.

CONCLUSION

Many questions remain unanswered about the mechanisms that underlie HIV-1 pathogenesis and the role of microbial product translocation, residual viremia and immune senescence in the development of persistent

immune activation and chronic inflammation, which is present at different degrees in all HIV-1-infected subjects. Moreover, despite effective cART-mediated viral suppression, persistent immune activation and inflammation have emerged as a major problem in the current HIV-1 era. Chronic inflammation and persistent immune activation remain abnormally elevated in many HIV-1-infected individuals and can be used to predict disease progression, subsequent mortality and non-AIDS-related morbidities, including cardiovascular diseases.

Different studies have linked inflammatory indexes, cytokine networks, and immune activation markers to clinical outcomes, which validate persistent immune activation as a possible therapeutic target. Other recent investigations have helped to elucidate the role of residual viremia, MT, and immune senescence in driving this persistent inflammatory state. These findings may contribute to the identification of new targets for novel intervention strategies that are aimed at minimizing immune activation and inflammation, such as anti-inflammatory molecules, *i.e.*, corticosteroids, cyclosporine, hydroxychloroquine, aspirin, omega-3 fatty acids, vitamin D and statins. Other interventions, such as IL-2 and IL-7 treatments, may be useful to restore the regenerative capacities of the immune system and to reconstitute the thymic microenvironment and the production of naïve T cells. Experimental strategies that have demonstrated promising anti-aging effects include the use of resveratrol, rapamycin, acetyl-L-carnitine, alpha-lipoic acid, telomerase activators, caloric restriction and stem cell therapy[98].

The effective monitoring of HIV-1-infected patients requires the evaluation of activation biomarkers in clinical practice, which may help guide treatment decisions and may be used to better characterize the infection stage and the risk of disease progression.

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