Immune activation and inflammation in HIV-1 infection: causes and consequences

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Abstract
Thorough research on HIV is progressively enabling us to understand the intricate mechanisms that link HIV-1 infection to the onset of immunodeficiency. The infection and depletion of CD4+ T cells represent the most fundamental events in HIV-1 infection. However, in recent years, the role played by chronic immune activation and inflammation in HIV pathogenesis has become increasingly apparent: quite paradoxically, immune activation mechanisms that link HIV-1 infection to the onset of immunodeficiency. The infection and depletion of CD4+ T cells represent the most fundamental event in the pathogenesis of HIV-1 infection. The main cell target during established HIV-1 infection is the CCR5+CD4+ activated T lymphocyte. The majority of CD4+ T cells reside in lymphoid tissues, such as the lymph nodes, and in particular the mucosal lymphoid tissues, such as the gastrointestinal tract. It is noteworthy that mucosal CD4+ T cells consist predominantly of memory CD4+ T cells which express the HIV co-receptor CCR5 and present relatively activated status [3–5]; they are therefore ideal targets for the virus. Studies performed in primates infected with SIV (the simian equivalent of HIV) as well as in HIV-1-infected humans have actually revealed that massive CD4+ T cell depletion takes place in mucosal tissues throughout all stages of HIV infection [5–7].

HIV-1-infected individuals are also characterized by a gradual decline of peripheral blood CD4+ T cell counts during chronic infection. Although this decline is not as dramatic as the depletion of CD4+ T cells from mucosal sites, it is nonetheless critical in HIV pathogenesis, since it is directly associated with HIV disease progression. Low circulating CD4+ T cell count coincides best with the onset of AIDS, as minimum levels of circulating CD4+ T cells are required.

Introduction
Since its discovery in 1983 [1], HIV-1 has become the most extensively studied and notorious pathogen in history. Scientists had originally anticipated the rapid development of effective vaccines and cures against this rather small virus, consisting of only nine genes. However, the solution to the HIV-1 pandemic is still to come. In fact, the precise reasons for the onset of immunodeficiency that almost inevitably develops during HIV-1 infection have not yet been resolved. A multitude of factors, including immunological, genetic, viral and environmental, can potentially contribute to the rate of HIV disease progression. However, 25 years of intense research have not been futile: pieces of the puzzle are starting to come together and the whole picture of HIV-1 pathogenesis is being unravelled little by little. HIV harbours a number of mechanisms to escape its host immunity and establish successful persistence. However, this is not exclusive to HIV, as a range of other persisting viruses (eg herpes and hepatitis viruses) have also developed such mechanisms. What, then, makes HIV-1 different from other persisting viruses which do not lead to a general process of immunodeficiency?

HIV is unique in that it targets the CD4+ T cell pool (as well as, but to a lesser extent, macrophages and dendritic cells), which holds an essential role in immunity. The infection and depletion of CD4+ T cells represent the most fundamental event in the pathogenesis of HIV-1 infection. The main cell target during established HIV-1 infection is the CCR5+CD4+ activated T lymphocyte [2]. The majority of CD4+ T cells reside in lymphoid tissues, such as the lymph nodes, and in particular the mucosal lymphoid tissues, such as the gastrointestinal tract. It is noteworthy that mucosal CD4+ T cells consist predominantly of memory CD4+ T cells which express the HIV co-receptor CCR5 and present relatively activated status [3–5]; they are therefore ideal targets for the virus. Studies performed in primates infected with SIV (the simian equivalent of HIV) as well as in HIV-1-infected humans have actually revealed that massive CD4+ T cell depletion takes place in mucosal tissues throughout all stages of HIV infection [5–7].

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to maintain immune integrity. Massive depletion of mucosal CD4+ T cells and progressive decline of circulating CD4+ T cells are therefore hallmarks of HIV-1 infection. However, another phenomenon has become apparent in recent years—the association between HIV-1 infection and chronic immune activation and inflammation.

**Immune activation in HIV-1-infected individuals**

The paradoxical immune activation

Immune activation in HIV infection is a rather broad expression that covers a large range of events or observations involved in active molecular and cellular processes (eg related to cell activation, proliferation and death, secretion of soluble molecules) and their consequences. HIV-infected individuals display elevated markers of activation and/or apoptosis on CD8+ and CD4+ T cells [8–11], as well as B cells, NK cells and monocytes. High levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β) in both plasma and lymph nodes, are also observed from the early stages of HIV-1 infection [12–16]. The secretion of chemokines such as MIP-1α, MIP-1β and RANTES is increased in these patients [17,18]. Immune activation, which usually reflects the mounting of antiviral immunity, may be seen as a normal and positive observation in the case of an infection with any pathogen, including HIV. However, in the 1990s, Giorgi and colleagues reported a rather counter-intuitive observation: T cell activation levels, as measured with the expression of the activation marker CD38 on CD8+ T cells, were predictive of an adverse prognosis for the infected patients [19–21]. Several investigators have then confirmed that there is indeed a direct correlation between HIV-1 disease progression and CD8+ T cell activation levels [22–24].

Further evidence of the paradoxical role of immune activation in HIV infection was brought by studies of SIV-infected primates. Rhesus macaques which, like HIV-infected humans, suffer progressive CD4+ T cell depletion and progression to AIDS upon SIV infection, are characterized by strong T cell activation. In contrast, SIV-infected sooty mangabeys and African green monkeys, the natural hosts of SIV, do not develop any immunodeficiency, exhibit minimal T cell activation despite evident viral replication [25]. Another interesting observation comes from the study of HIV-2 infection. Most HIV-2-infected individuals experience a mild or slow disease progression and will die from HIV-2-unrelated causes. In addition to low viral load and robust immune responses [26], they usually display significantly less immune activation compared to HIV-1-infected individuals [27]. The adverse effect of immune activation in HIV pathogenesis may also account for the observations linking more rapid disease progression in Kenyan prostitutes with frequent intercurrent infections and related immune activation [28], or for the accelerated SIV-induced disease progression reported in SIV-infected macaques that were subjected to repeated SIV-independent immune stimulus to mimic chronic activation [29].

The causes of immune activation and inflammation in HIV-1 infection

During HIV-1 infection, the establishment of immune activation and inflammation involve several mechanisms that are either directly or indirectly related to viral replication. The common cause of T cell activation during an infection is antigenic stimulation by the virus, which is the foundation of the adaptive immune response. During primary infection, HIV-1 induces strong T cell responses, in particular CD8+ T cells, which can persist during the chronic infection phase due to the continuous replication of the virus: up to 20% of circulating CD8+ T cells can be HIV-specific in untreated chronically infected patients [30,31]. HIV-specific CD4+ T cell responses are usually present at a lower magnitude (ie up to 3% of circulating CD4+ T cells) [30], which may be related to their preferential depletion by the virus [32].

Nonetheless, the extent of activation during the course of HIV-1 infection is such that stimulation with HIV antigens solely cannot account for the complete phenomenon of immune activation observed. Although the physiological impact is not yet known, in vitro studies suggest that HIV gene products can induce directly the activation of lymphocytes and macrophages, and the production of proinflammatory cytokines and chemokines. For instance, the envelope protein gp120 may be able to activate cells or to enhance their responsiveness to activation, even in absence of direct infection, through binding to CD4 or co-receptors [33–35]. The accessory protein Nef is also able to lead to lymphocyte activation either directly [36,37] or through the infection of macrophages [38].

HIV-1 also causes immune activation and inflammation through indirect means. Antigenic stimulation during HIV-1 infection may be induced by other viruses, such as CMV and EBV. CMV reactivation appears to occur recurrently in healthy donors, as evidenced by the presence of a large population of CD69+ CMV-specific cells indicative of recent in vivo activation [39]. During HIV-1 infection, the depletion of CD4+ T cells may result in suboptimal immune control of these persistent viruses and thus permits their reactivation and replication. In addition, inflammatory conditions occurring during HIV infection (eg release of proinflammatory cytokines) may also participate in the reactivation of latent forms of CMV and EBV. Recent studies have shown significant activation of EBV- and CMV-specific CD8+ T cells during HIV-1 acute infection [40,41]. Hence, sustained antigen-mediated immune activation occurs in HIV-1-infected
patients, which is due to HIV-1, but also to other viruses (and may be restricted to CMV and EBV).

Recently, Douek and Brenchley have brought to light another potential mechanism that could be central in HIV pathogenesis and involves the activation of the innate immune system [42]. The massive depletion of CD4+ T cells (and possibly macrophages and dendritic cells) by HIV-1 in mucosal lymphoid tissues can result in disrupting the different immune components that constitute the mucosal barrier in the gut, this barrier usually prevents the translocation of the flora that inhabits the intestinal tract and restricts these pathogens to the lamina propria and the mesenteric lymph nodes. Compromising its integrity may therefore results in microbial translocation from the gut to the systemic immune system [43]. Interestingly, HIV-1 infection is associated with a significant increase of plasma LPS levels, an indicator of microbial translocation, which is directly correlated with measures of immune activation [42]. Translocation of bacterial products is highly likely to result in a profound activation of the innate immune response: for instance, lipopolysaccharide (LPS), flagellin and CpG DNA, which are toll-like receptor (TLR) ligands, are known to directly stimulate peripheral macrophages and dendritic cells to produce a range of proinflammatory cytokines (e.g., TNFα, IL-6 and IL-1β). The eventual outcome may be systemic activation and differentiation of lymphocytes and monocytes and the establishment of a proinflammatory state.

The consequences of immune activation and inflammation in HIV-1 infection

The initiation of this state of immune activation and inflammation and its long-term establishment due to persistence of the virus have extensive and detrimental effects on the immune system and human health.

The vicious cycle of immune activation and HIV-1 spreading

A direct consequence of T cell activation is the increase of intracellular nuclear factor kappa B (NF-kB) levels, which enhances the transcription of integrated virus and therefore the production of new virus that will infect new targets [44]. A vicious cycle is therefore established, during which HIV-1 replication promotes immune activation (ie T cell activation) and immune activation promotes HIV-1 replication. Released proinflammatory cytokines participate also to this refueling cascade: the synergic action of IL-1β, TNFα and IL-6 can lead to T cell activation [45]; In addition, IL-1β and TNFα may also decrease transepithelial resistance in mucosal tissues [46], therefore promoting microbial translation and further activation.

The activation of T cells implies also their turnover, differentiation from naïve to antigen experienced cells, and apoptosis. While a large number of T cells ends up dying upon activation, dynamics of activation, expansion and apoptosis seem to differ between CD4+ and CD8+ T cells [47–49]. CD8+ T cells experience extensive expansion upon activation and can establish a stable pool of resting memory cells. In contrast, the capacity of CD4+ T cells to expand and survive seems to be lower, so that the vast majority of activated CD4+ T cells apoptose rapidly, hence a further burden with regard to the renewal of the CD4+ T cell pool. During chronic infection, the frequency of infected circulating CD4+ T cells is too low (0.01–1%) to account solely for the decline of peripheral blood CD4+ T cells [32,50,51]. While infection and depletion of T cells in mucosal site may eventually account for this decline, activation-induced apoptosis is also considered as a major cause of peripheral CD4+ T cell loss in HIV-infected patients. Overall, the immune system of HIV-1-infected individuals faces major difficulties: it has to cope with a massive cellular destruction, in particular CD4+ T cells (through apoptosis or direct infection), and to contain HIV-1 replication, as well as associated pathogens. Dealing with such overwhelming and enduring challenge has a cost.

The limited regenerative capacity of the immune system

Despite the plasticity and efficacy of the immune system are prodigious, its regenerate capacity may have boundaries. Accumulating evidence suggests that the so-called Hayflick limit (ie the irreversible state of growth arrest indicative of replicative senescence, initially observed with cultured human fibroblasts) applies to cells of the immune system [52], so that their replicative life span in vivo is limited. The occurrence of replicative senescence is primarily related to the number of cell divisions. A commonly used marker of replicative history is the length of the telomeres (repeated hexameric DNA sequences found at the ends of the chromosomes), which is reduced with each cell division. Important telomere shortening can result in chromosome instability and eventually in growth arrest and/or apoptosis of the cells. During primary viral infection, up-regulation of telomerase (the enzyme involved in the maintenance of telomere length) occurs, in order that activated virus-specific T cells maintain telomere length despite the considerable clonal expansion that takes place at that moment [53,54]. However, such capacity to up-regulate telomerase seems to decrease after repeated stimulation [55], so that memory T cells specific for persisting viruses will eventually present shorter telomere length, as exemplified in EBV infection [56,57], and reach stages of replicative senescence. The immune system deals with this irreversible exhaustion of T cells by continuously providing new cells.

Primary resources may also be limited. The thymus (the organ on which depends the generation of naïve T cells and the maintenance of TCR diversity [58]),

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is known to undergo significant involution with time, so that it has almost completely disappeared by the age of 60 in humans [59,60], and the rate of naive T cell output from the thymus dramatically declines with age [60–62]. In addition, limitation of T cell regenerative capacity may happen even further upstream in the development of lymphocytes; emerging data suggest that deregulation of haematopoiesis can occur over time (eg with age). Progenitor cells in elderly individuals present shorter telomeres than in cord blood of newborns [63]. Poor results of bone marrow transplantation in elderly individuals [64] suggest also that the aged bone marrow microenvironment has a significantly reduced ability to support haematopoietic regeneration. Moreover, granulocytes and/or naïve T cells show a shortening in telomere length associated with age [65] or after bone marrow transplantation [66], suggesting that this applies also to haematopoietic stem cells. Although it is unclear whether this phenomenon has a real consequence on the immune function in ageing, these data support the idea that the regenerative capacity of the progenitor pool may not be unlimited and could reach exhaustion over time. The overall deterioration of the immune system with time may be referred to as immunosenescence. A number of alterations that characterize HIV-infected individuals may actually be related to immunosenescence, and may be the likely consequence of immune activation, manifested at two distinct levels.

**Senescence/exhaustion of HIV-specific T cell responses**

Levels and/or recurrency of cellular activation is a major driving factor of proliferation and T cell differentiation resulting in the generation of antigen-experienced cells, which eventually lack expression of CD28 and show increasing expression of CD57 [40,67]. These subpopulations tend to lose the capacity to produce IL-2 and present a decline of their proliferative capacity, associated with a shortening of telomere lengths, so that highly differentiated cells (CD28+/CD57+) have been considered as approaching end-stage senescent cells [40,68]. HIV-specific CD8+ T cell populations play a major role in holding back HIV spreading. These populations are heterogeneous and consist of cells which can vary in their antiviral efficacy. For instance, long-term non-progressing HIV-infected patients [89,90], which may relate to the decreased proliferative capacity reported in this population [91]. These changes, together with alterations in cytokine secretion (eg decreased IL-2 production).

HIV-specific CD8+ T cells may be gradually driven towards an irreversible exhaustion of their replicative capacities, to become worn-out cells, even resulting in the loss of important anti-HIV T cell subpopulations. Due to their sensitivity for the antigen, high-avidity T cells may be particularly sensitive to such stimulation-driven depletion [73]. The exhaustion and loss of these important T cells can play a significant role in the onset of HIV disease progression, despite other HIV-specific CD8+ T cells, still functionally active but less effective (of lower avidity/efficacy), remaining present in the patients [73]. It is important to make the distinction between this irreversible loss of cells and the recently reported exhaustion of HIV-specific CD8+ T cells, based on the expression of PD-1 [74,75]. The latter may actually be more regarded as a reversible decrease of T cell functions, related to T cell activation due to high viral load rather than to exhaustion [76].

**Global exhaustion of immune resources in HIV-1 infection**

It is important to appreciate that the consequence of immune activation in HIV infection may go far beyond the simple loss of virus-specific CD8+ T cells, but extend to a global decline of the immune resources. Although data are still emerging and reasons unclear, HIV infection appears to result in a deregulation of haematopoiesis (lower numbers of progenitor cells and decline in their ability to generate new cells) [77–79]. The capacity of the thymus to produce new cells is also significantly reduced in HIV-infected individuals [80]. Several reasons may account for this decline of thymic output: the direct infection of the thymic stroma and thymocytes by HIV [81,82]; and the atrophy of the thymus in HIV-infected subjects, which is similar to age-related ‘thymic involution’ [83] and may be related to thymosuppressive effects of proinflammatory cytokines (such as IL-6; eg by inducing apoptosis of immature thymocytes) [84,85]. In addition, immune activation and inflammation are thought to cause fibrosis of the lymphatic tissue (ie collagen deposition), therefore damaging its architecture and preventing normal T cell homeostasis [86,87]. HIV-infected subjects are therefore characterized by a general decline of T cell renewal capacities. As a consequence, the naïve T cell pool cannot be replenished efficiently, and is therefore unable to continually replace old exhausted CD8+ T cell clones and depleted CD4+ T cells in HIV-infected individuals. CD28−/CD57+ cells accumulate in the CD4+ and particularly CD8+ T cell compartments during HIV-1 infection [40,88]. In addition, telomere length is significantly shortened in the whole CD8+ lymphocyte population of HIV-1-infected patients [89,90], which may relate to the decreased proliferative capacity reported in this population [91].
Parallel with age: beyond immunosenescence

Several immunological alterations that characterize HIV-1-infected individuals are remarkably similar to those accumulated with age in the HIV-1-uninfected elderly [93]. During ageing, a reduction in T cell renewal, together with a progressive enrichment of terminally differentiated T cells with shortened telomeres, thought to be the consequence of immune activation over a lifetime, translate into a general decline of the immune system, gradually leading to immunosenescence [99]. This may be, at least in part, responsible for the increased incidence and/or rapid progression of many infectious diseases (eg influenza, pneumonia, meningitis, sepsis, varicella zoster virus, HIV) and possibly cancers, observed in individuals of old age, which leads to increased morbidity and mortality [100,101]. The onset of a process of immunosenescence may not be the only similarity between HIV-1 infection and human ageing [93]. This represents the maintenance of homeostasis in the context of inadequate regenerative capacity and is the likely consequence of HIV-mediated systemic immune activation. It is noteworthy that CMV infection may hold a particular role in this process. CMV has been associated with strong and persistent expansions of T cell subsets that show characteristics of late differentiation and replicative exhaustion [94–96]. The anti-CMV response appears to monopolize a significant fraction of the whole T cell repertoire [97], so that it might compromise the response to other antigens by shrinking the remaining T cell repertoire and reducing T cell diversity. CMV infection is actually extremely common in HIV-1-infected individuals and its recurrent reactivation may put further stress on their immune resources. Interestingly, CMV-seropositive subjects generally experience more rapid HIV disease progression than CMV-seronegative subjects [98].

A model of HIV pathogenesis

In this section we summarize the links between the different parts described above and propose a simplified model of HIV pathogenesis, which integrates three main aspects: the massive depletion of CD4+ T cells; the paradoxical immune activation; and the exhaustion of immune resources (see Figure 1).
A primary event in HIV-1 pathogenesis is the infection of the CD4+ T cell pool. During primary infection, HIV-1 is able to infect a large number of CD4+ T cells, in particular activated memory cells expressing CCR5. At this stage anti-HIV immunity is not yet mounted, so that viral replication and spreading remain mostly uncontrolled. Viraemia shoots up to reach peak levels, until the appearance of the adaptive immune response, in particular HIV-specific CD8+ T cells, that sees the end of the acute phase. However, the damage has been done: HIV-1 has been able to establish the premise of its latent reservoir, rooting itself in its host, and extensive viral replication has resulted in the massive depletion of CD4+ T cells, particularly in mucosal lymphoid tissues. This has immediate consequences on the integrity of the mucosal surfaces, and microbial translocation ensues.

Considerable immune activation then takes place, which is multicausal and lasts throughout the course of the infection. First, the immune response against HIV-1 itself is activated, and aims at controlling the virus, despite persisting replication and emergence of variants that can escape both cellular and humoral responses. The immune system has also to cope with

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**Figure 1.** A model of HIV pathogenesis. Causes and consequences of immune activation are in yellow or red, respectively. Hypothetical consequences of immune activation that make a parallel with human ageing are in italic.
other persisting pathogens (such as CMV), whose reactivation is enhanced by the substantial loss of CD4+ T cells. HIV proteins can directly induce cellular activation. Last but not least, translocation of microbial products leads to systemic activation of lymphocytes and monocytes. As a consequence, levels of proinflammatory cytokines increase notably. In addition, immune activation promotes HIV replication, thus establishing a vicious cycle.

Immune activation causes considerable cellular turnover, senescence and apoptosis, which represent a massive task for the immune system in terms of cellular renewal in order to maintain homeostasis. Over time, the consequence may be a progressive decline of regenerative capacities and the development of immunosenescence. In parallel, the elevated production of proinflammatory cytokines leads to the deterioration of a series of physiological functions. With the exhaustion of primary resources, naïve T cells disappear and highly differentiated oligoclonal populations accumulate. The fragile balance between functional HIV-specific CD8+ T cell activity and ongoing HIV-1 replication is broken. Uncontrolled viral replication rapidly depletes the rest of the CD4+ T cell pool, which cannot be replenished, resulting in the collapse of the immune system’s ability to control pathogens, characterizing AIDS. The pace of this process may vary, depending on the intrinsic pathogenicity of the virus, host genetic factors and also environmental factors. For instance, less pathogenic viruses (such as those with attenuating Nef mutations) are more readily controlled and are associated with clinical non-progression [127]. Age seems be an important positive factor of HIV disease progression among HIV-infected individuals [128,129], possibly reflecting the impact of HIV-1 on an already ageing immune system.

Conclusions

Normal life is characterized by low-grade, recurrent immune activation and inflammatory activity, which eventually leads to immunosenescence. Through the induction of persistent, sustained immune activation and inflammation, it is possible that HIV-1 infection induces an accelerated process of immunosenescence and systemic ageing. During this process, the immune system burns itself quickly, as the source of its combustion (ie the virus) cannot be put off. Taking into consideration the pivotal role of immune activation in HIV pathogenesis opens several possibilities of action to counteract the adverse effect of HIV-1 infection.

Antiretroviral therapy (ART) remains the most successful therapy against AIDS to date. Unexpected inflammatory disorders, known as immune restoration inflammatory syndrome, can sometimes accompany the beginning of ART (due to increased inflammation during immune reconstitution in immunocompromised HIV-infected patients) [130]. However, through its potent and prolonged inhibition of HIV replication, ART represents somehow the best ‘deactivator’ of the immune system for HIV-infected patients, usually resulting in a marked reduction of T cell activation and apoptosis [131–133], along the decrease of proinflammatory cytokine levels. Antigen-specific stimulation is also strongly diminished, as seen with the rapid decline in the numbers of HIV-specific CD8+ T cells [134–136]. Eventually, ART enables the reduction of naïve T cell consumption and helps to restore their numbers. Other strategies may be developed to block or minimize immune activation and inflammation. These could include the use of immunosuppressive drugs (eg cyclosporine A [137,138]), inhibitors of bacterial product-mediated effects (eg antagonists of TLR-4, the receptor for LPS [139,140]), or inhibitors of proinflammatory cytokines (eg anti-IL-1β, -IL-6 or -TNFα [141]). Lowering inflammatory and oxidative stress responses may indeed help delaying immunosenescence, as suggested by a recent study showing that long-term caloric restriction could delay the process of immunosenescence in primates [142]. Strategies to restore or rejuvenate the regenerative capacity of the immune system are also being explored. These includes the use of cytokines such as IL-2 (to expand circulating CD4+ T cells [143]), or IL-7 (to reverse thymic atrophy and induce thymopoiesis [60,144,145]), or hormones such as the growth hormone (to reconstitute the thymic microenvironment and the production of naïve T cells [146–148]). The potential of HSC transplantation may also be considered for therapy in HIV infection, since this can lead to the total reconstitution of the immune system. Last, investigating the mechanisms of virus-host adaptation (eg that prevent systemic immune activation) in SIV-infected sooty mangabeys and African green monkeys could certainly help the design of effective strategies to fight HIV-1. A recent study has actually revealed that the Nef protein from non-pathogenic SIV strains as well as HIV-2 harbours a T cell activation-suppressing function (through down-modulation of the TCR complex), which was lost by HIV-1 [149].

Teaching materials

Power Point slides of the figures from this Review may be found at the web address http://www.interscience.wiley.com/jpages/0022-3417/suppmat/path.2276.html

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