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REVIEW

Assessing immune aging in HIV-infected patients

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ABSTRACT

Many of the alterations that affect innate and adaptive immune cell compartments in HIV-infected patients are reminiscent of the process of immune aging, characteristic of old age. These alterations define the immunological age of individuals and are likely to participate to the decline of immune competence with HIV disease progression. It is therefore important to characterize these changes, which point toward the accumulation of highly differentiated immunocompetent cells, associated with overall telomere length shortening, as well as understanding their etiology, especially related to the impact of chronic immune activation. Particular attention should be given to the exhaustion of primary immune resources, including haematopoietic progenitors and naïve cells, which holds the key for effective hematopoiesis and immune response induction, respectively. The alteration of these compartments during HIV infection certainly represents the foundation of the immune parallel with aging.

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Introduction

More than 30 y of research have taught us that the pathogenesis of HIV infection is highly complex. The infection of $CD4^+$ T cells, the primary target of the virus, represents the most fundamental feature of HIV pathogenesis. The depletion of these cells (in particular in mucosal lymphoid tissues like the gastrointestinal tract), necessary to maintain immune competence, eventually coincides with the onset of AIDS. The increased expression of a series of co-inhibitory receptors, nowadays referred to as immune check points, on chronically activated effector T and B cells play also an important role in dampening the functional efficacy of the anti-HIV response. However, we have come to realize that many other compartments of the immune system are actually affected during the course of HIV infection. Many of these immune alterations are reminiscent of the process of immune aging, that usually occurs with advanced age, and likely participates to the decline of immune competence in HIV-infected patients. We review below the multiple aging like alterations that have been reported in the different cellular compartments of the immune system, and how assessing these parameters gives us clues on the immunological age of patients infected by HIV.

Shortening of telomere length

Telomeres, which are special structures of tandem repeats at the end of chromosomes, are essential for chromosomal stability. In humans, telomeric DNA consists of TTAGGG repeat tracts of about 10 kb in length. In somatic cells, telomere length is shortened with each cell division due to the inability of DNA polymerase to replicate the extreme 5′ end of the lagging strand of DNA. Telomere length shortening is the classical marker of cellular senescence, and therefore commonly used as an indicator of the biological age of individuals.

In a longitudinal follow-up over 3–9 years, telomere length of total PBMCs from HIV-infected individuals was shown to shorten at an accelerated rate compared to age-matched seronegative controls.[1] In HIV-infected patients, the mean telomeric restriction fragment (TRF) length loss was greater in progressors (175 + 105 bp/year) than in asymptomatic individuals (114 + 100 bp/year), and both were significantly increased compared with healthy controls (4.7 + 71 bp/year). Telomere shortening was consistently observed in the $CD8^+$ T cells, with only minimal or no telomere shortening in the $CD4^+$ T cells.[1] TRF shortening in the $CD8^+$ T cell compartment accounted mainly for the expansion of cells lacking the expression of the co-receptor CD28, associated with short telomeres.[2] In fact, the telomere length of the $CD8^+$ $CD28^-$ T cells were the same size as those of uninfected centenarian lymphocytes. B cell telomere shortening was also documented in HIV-infected patients,[3] consistent with the well-documented hyperactivation observed during HIV infection. Changes in mean TRF length were also examined in HIV-infected patients

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initiating anti-retroviral therapy (ART). Increases in mean T cell TRF lengths were observed in most patients following therapy. However, the contribution of individual T cell subsets was complex. An elongation of $CD8^+$ T cell TRF was nearly uniformly observed, while changes in mean TRF length in $CD4^+$ T cells were heterogeneous, despite potent suppression of viral replication.[4]

Faster PBMC or T cell telomere erosion in HIV-infected patients is suggestive of accelerated immunological aging with HIV infection. However, a caveat in these studies is that telomere length was usually measured in total PBMC or in total T cell subsets (i.e. CD4 or CD8). Telomerase activity and telomere length indeed vary in distinct cell subsets according to the stage of differentiation (e.g. naïve, effector and memory cells). Since the distribution of such cell subsets is known to change during the course of HIV infection, the observation of overall TRF shortening may therefore reflect these cell distribution changes.

Aging of the adaptive immune compartment

Accumulation of $CD28^-/CD57^+$ $CD8^+$ T cells

Following their maturation and production in the thymus, both $CD8^+$ and $CD4^+$ T cells can be divided into multiple subsets of naïve and effector/memory cells, which are identified according to the expression of a variety of cell surface receptors (e.g., CD45RA, CCR7, CD27, CD28, CD57, CD95) and present distinct functions and properties.[5]

The first immune parallel drawn between aging and HIV infection has been the accumulation of $CD8^+$ T lymphocytes lacking expression of the co-receptor CD28.[2,6] These cells represent a population of differentiated memory T cells, which are characterized by a reduced capacity to produce IL-2 and to proliferate, short telomere lengths, as well as altered metabolism.[7,8] In this population, $CD57^+$ cells, considered as end-stage senescent cells (with the shortest telomeres) also accumulate.[9,10] A similar process occurs for $CD4^+$ T cells, although the raise of $CD28^-$ cells is less obvious in this compartment compared to $CD8^+$ T cells. Highly differentiated T cells accumulate as a consequence of chronic cellular activation, often associated with chronic replication of HIV, as well as other persistent viruses, in particular cytomegalovirus (CMV), co-infecting patients. Immune activation indeed drives the proliferation and differentiation of virus specific T lymphocytes, that eventually loose expression of CD28, and display CD57.[9-13] The accumulation of $CD28^-/CD57^+$ T cells is commonly used as a marker of "immunosenescence" in HIV-infected patients.

Interestingly, this marker, together with a marker of T cell activation (HLA-DR expression) was recently used to generate a score of immune activation and senescence. This immune score was correlated with the clinical state of HIV-infected patients and was significantly associated with the raise of non-AIDS related multi-morbidities (e.g. kidney disease, diabetes, dyslipidemia, cardiovascular events, hypertension, degenerative central nervous system disorders, and cancer) in treated patients younger than 60 y.[14] Moreover, increased frequencies of $CD28^-/CD57^+$ $CD8^+$ T cells have been associated with the presence of Kaposi's sarcoma among successfully treated patients.[15] However, the frequency of these cells does not decrease in HIV-infected patients upon initiation of antiretroviral therapy (ART), even with good $CD4^+$ T cell recovery.[16] In addition, ART naïve HIV controllers can display high levels of these cells.[16] This indicates that the accumulation of $CD28^-/CD57^+$ $CD8^+$ T cells is not necessarily a strict marker of HIV disease progression and decline of immune competence. Of note, the accumulation of $CD28^-/CD57^+$ $CD8^+$ T cells is independent and unrelated to the increased expression of co-inhibitory receptors (such as PD-1) on $CD8^+$ T cells, that is not a characteristic of old age, and not a marker of immunological aging.[17]

Quantitative and qualitative alterations of naïve T cells

Another important immune parallel between aging and HIV infection is the reduction in $CD4^+$ and $CD8^+$ naïve T cell frequencies. As it is observed with advanced age, the capacity of the thymus to produce new T cells, or thymic output, decreases significantly during the course of HIV infection,[18-20] which may in part explain the decline of naïve T cells. In a human model of premature immune aging (i.e., thymectomized young adults), decreased naïve T cell frequency was indeed shown to be the consequence of inadequate T cell renewal capacity due to reduced thymic output, together with their consumption upon chronic activation due to a persistent virus infection.[21,22] Interestingly, perinatally HIV-infected subjects displayed preserved naïve T cell counts associated with high recent thymic immigrant levels even 15 y after infection, highlighting the role of persistent thymic activity to compensate for the loss and consumption of this compartment.[23] Moreover, HIV-2 infected patients, who usually control the virus and do not progress toward AIDS, maintain a robust thymic out and good naïve T cell counts.[24] In HIV-infected patients, the pool of naïve T cells is usually partially restored upon initiation of ART, except in the case of immunological failure, when patients fail to reconstitute their immune system despite the treatment.[25] Overall, the frequency of naïve T cells represents a good marker of immunological age in humans, and its

progressive decrease in HIV-infected adults is usually directly associated with HIV disease progression.[16,26] Of note, as patients progress toward the disease, the decline in naïve T cell counts is correlated with evidence of homeostatic proliferation (i.e. Ki67 expression), likely as a mean to maintain adequate levels of these cells, similarly as with advanced age.[27]

In addition to these quantitative alterations, the naïve T cell compartment is also characterized by functionally impairments during HIV infection. Naïve $CD8^+$ T cells from HIV-infected patients present signaling defects and a lower capacity to be activated upon T cell receptor stimulation.[28] Although its exact cause remained to be determined, this impairment is similar to observations in elderly subjects.[29] Since the induction of *de novo* adaptive immune responses relies on the activation of naïve T cells specific for a given neoantigen, quantitative and qualitative alterations of this compartment are likely to impact on the ability of HIV-infected patients to mount new effective immune responses. Ineffective capacity to mount immunity against emerging HIV mutants and therefore to control new viral variants will certainly contribute to the onset immunodeficiency and HIV disease. Likewise, vaccine efficacy against HIV or other pathogens is also at stake. In fact, HIV-infected patients, like the uninfected elderly, show poorer responses to influenza vaccination.[30,31]

Unbalanced B-cell memory subset distribution

In healthy humans, B cells develop and convert into transitional cells in the bone marrow, then migrate into the periphery, where they finally mature in naïve B cells. After contacting the antigen, naïve B cells activate and differentiate into plasma cells, able to secrete specific antibodies. When immune responses end, only a minority of specific B cells survives and constitutes the pool of resting memory B cells.[32] These B cell subpopulations are identified in most studies by different expression of IgD, IgM, CD10, CD19, CD27, CD10, CD24, CD38 and CD21.[33]

The number of circulating B cells significantly decreases with age and the diversity of B cell repertoire is reduced.[34] Furthermore, the relative frequencies of the different B cell subsets are altered: it has been shown that naïve B cells (IgD^+ $CD27^-$) and switched memory B cells (IgD^- $CD27^+$), predicting optimal antibody responses,[12] decrease with age.[35] Conversely, the antigen-experienced late/exhausted memory B cells (IgD^- $CD27^-$) increase with age.[36]

Like in older individuals, B-cell lymphopenia is described in HIV-infected individuals as well as a reduced frequency of resting memory B cells (IgD^- $CD27^+$); this reduction was paralleled by increased levels of exhausted B cells ($CD20^+$, CD21low, $CD27^-$, referred in aging as IgD^- $CD27^-$), which correlated with viremia and a reduced immunosurveillance.[37-41] Another common feature of B cell alteration is their hyperactivation, characterized by an hypergammaglobulinaemia[42-45]; and an increased expression of activation markers, including CD70, CD71, CD80 and CD86. Potent antiretroviral therapy normalizes B cell counts and the relative percentages of the main B lymphocyte subsets[46] as well as gammaglobulinaemia.[47] Moreover, ART can normalize CD70, CD71, CD80, and CD86 expression.[48] However, even potent treatments are not able to fully revert the loss of memory B cells and their function during chronic infection at the level observed in healthy individuals.[38,46,49-51]

Aging of the innate immune compartment

Preferential expansion of mature NK cells

Based on surface CD56 density, NK cells are categorized into 3 distinct subsets: the cytokine producing $CD56^{++}CD16^-$ subset, the cytotoxic $CD56^+CD16^+$ subset, and a minor $CD56^-CD16^+$ NK cell subset with poor antiviral activity. With aging or HIV infection, the distribution of NK cell subsets and their functions are altered.[52] Gradual loss of the $CD56^{++}$ NK cell subset is observed in both contexts, probably due to limited production of its precursors, while an expansion of dysfunctional $CD56^-CD16^+$ NK cells is described.[53,54] The expansion of this $CD56^-$ $CD16^+$ NK cell population has been suggested to be a mechanism to compensate for the loss of $CD56^+$ NK cells in order to maintain overall NK cell homeostasis in HIV-infected individuals.[52] Moreover, the rapid $CD56^-$ NK cell expansion has also been argued as a consequence of high viremia, since both parameters strongly correlate with each other but not in virally suppressed LTNPs.[55]

Concerning the predominant $CD56^+$ NK cells, their properties are also modified with age or during the course of HIV infection. Indeed, highly differentiated mature $CD57^+CD56^+CD16^+$ NK cells accumulated with aging (in particular in CMV seropositive donors).[56-58] In HIV patients, it is their functionality which is modified: these cells display a decreased ability to kill virus-infected target cells and to interact with other cellular components of the adaptive immune system.[59,60] During chronic HIV infection, there is an impairment of NK cell cytotoxicity and cytokine secretion as well as a reduced capacity to respond to IFN-α and to produce high amounts of IFN-γ and TNF α along with low amounts of perforin.[61] Similarly, NK cell repertoire diversity, that might influence immune surveillance, is differentially impacted during aging and HIV infection.[62-65] However, a direct comparison between

HIV infected patients and elderly individuals is difficult to establish since their respective $CD56^+$ cell subsets have been characterized according to different criteria (phenotype, function or repertoire). Further studies of the various attributes of $CD56^+$ NK cells are needed to understand this parallel between HIV infection and aging.

ART does not significantly influence the recovery of NK cell function, as IFN-γ production[66] and repertoire (e.g., NKp46, NKp30, NKp44 and KIRs) expression may be persistently impaired even after successful therapy.[65,67] NK cells from treated HIV-infected patients have reduced expression of key signaling proteins that are required for antibody-dependent cellular cytotoxicity; however, the factors causing this phenomenon are unknown.[68] Moreover, virologically suppressed HIV patients show activation of NK cells and persistent innate immune activation.[69] It remains to elucidate if NK cells from elderly people exhibit a similar activation pattern.

Over-representation of $CD16^+$ monocytes

Monocytes play an important role in defense against microbial pathogens and inflammation. Three main subpopulations of monocytes are described: classical ($CD14^{++}$ $CD16^-$) that expresses CD62L, CCR2 and low levels of CX3CR1, intermediate ($CD14^{++}CD16^+$) that lacks CD62L or CCR2 but expresses CX3CR1 and secretes high level of TNF-α in response to Toll-like receptors (pro-inflammatory monocytes), and non-classical ($CD14^+CD16^{++}$), CCR2low CX3CR1high.

Several phenotypic and functional changes observed in monocytes from HIV seropositive patients are similar to those observed in elderly uninfected individuals. Indeed, monocytes from HIV-infected patients or old subjects possess characteristics of activated cells, such as spontaneous production of proinflammatory cytokines, expression of CD38, CD69, CD11b, HLA-DR, and CD86, and decreased CD62L (reviewed in[70]). In HIV-infected patients, CD69 and HLA-DR expression correlates well with plasma levels of lipopolysaccharide, which is an indicator of microbial translocation.[71] Despite relatively few changes in the absolute numbers of monocytes, the distribution of the different subsets is changed, characterized by a marked reduction in classical monocytes and an increased frequency of intermediate and non-classical monocytes in older or HIV infected patients.[72-74] These $CD16^+$ monocytes are increased during the infection and are correlated with viremia, T cell activation, and with plasma levels of IL-6. They are expanded in patients who do not take therapy or discontinue treatment. On the contrary, in patients under effective ART, the expression of CD16 is similar to that of uninfected controls.[75] Moreover, plasma levels of soluble CD163 and CXCL10, both markers associated with monocyte activation, also increase with both age and HIV.[72,76] These biomarkers of monocyte activation are only partially normalized upon ART mediated viral suppression,[77] suggesting that these changes may contribute to the increased risk of inflammatory age-related diseases in treated HIV-positive individuals.[76]

Biased frequency of plasmacytoid DC

Two major subsets of circulating DCs have been described, that are, myeloid DC (mDC) and plasmacytoid DC (pDC), which differ in ontogeny, phenotype, and function. pDCs ($BDCA\text{-}2^+$ $BDCA\text{-}4^+$ $CD123^+$) are involved in antiviral immunity and predominantly produce Type I IFNs. Conversely, mDCs ($BDCA\text{-}1^+$ $CD11c^+$) sense both bacterial and viral pattern motifs through a broader range of TLRs and are involved in the induction of Th1- and Th2-type responses. Both subsets exhibit a functional plasticity in directing T-cell responses.[78] Alterations in DC numbers, phenotype, and function exist in the elderly, where reduced pDC numbers and increased expression of CD40 and CD86 have also been described.[79-81] The DC changes described during the course of HIV infection are reminiscent of the situation observed in elderly subjects[82-84]: in particular peripheral pDC numbers are decreased.[85] This loss correlated with high viral load and the occurrence of opportunistic infections.[82,84,86] Costimulatory or activation markers (such as CD40, CD80, CD83, CD86, CD38, HLA-DR, and PD-L1) of both mDC and pDC have also been investigated in HIV-infected subjects and revealed an activated phenotype.[87] Primary dendritic cell function in aging generally shows decreased TLR-dependent cytokine production in both mDC and pDC populations. Notably, basal cytokine production was markedly elevated in mDCs and pDCs from older, but not young subjects, reflecting the heightened pro-inflammatory environment of aging (another similarity to HIV). So far, studies in HIV patients have not reached a consensus with regards to this point.[88,89] Further efforts should address if DCs from HIV patients show altered functional patterns as in the elderly.

Exhausted hematopoiesis

The alteration of many major compartments of innate and adaptive immune cells during the course of HIV infection points toward a possible defect of hematopoiesis (i.e., the generation of immunocompetent cells). A number of studies have indeed shown that hematopoietic stem cells from HIV-infected patient bone marrows present functional alterations, suggesting impaired hematopoiesis in HIV infection.[90-93] Compared to healthy donors or HIV-infected

non-progressors, patients progressing toward AIDS, like uninfected elderly people, have decreased numbers of circulating hematopoietic progenitor cells (HPCs), and their remaining $CD34^+$ cells present functional alterations (e.g. reduced clonogenic potential).[25] $CD34^+$ HPCs from these individuals display a preferential reduction in cells with lymphoid precursor capacity, along with an impaired capacity to generate T lymphocytes in *in vitro* culture assays.[94-96] Deterioration of the hematopoietic system with advanced age is certainly thought to be a key issue in the overall decline of immune competence of the old person, and is a likely cause of the accelerated immune aging profile in HIV-infected individuals. In the latter, ART restores partially the HPC compartment and a normal hematopoiesis, associated with the reconstitution of all immunocompetent cell pools.[25] A recent study reveals that, upon ART initiation, $CD4^+$ T cell recovery was correlated with the ability of HPCs to proliferate, showing the importance of bone marrow derived HPCs to reconstitute the immune system during HIV infection.[97] Of note, in treated patients presenting immunological failure despite effective suppression of viral replication, ART failed to re-establish hematopoietic resources, which seemed fully exhausted.[25]

Deterioration of the hematopoietic system with advanced age is thought to result from life-long mobilization of resources and intrinsic cellular impairments (of both HPCs and stromal cells). The fine mechanisms underlying the exhaustion of hematopoiesis during untreated HIV infection still need to be addressed. Altered lymphopoiesis in HIV-infected patients probably results from the combination of multiple factors. Evidence for the infection by HIV and apoptosis of hematopoietic progenitors has been reported.[98] However, HIV infection mediated depletion of $CD34^+$ cells remains debated.[99-102] Nef was shown to have inhibitory effects on HPC multipotent potential.[103,104] HIV may also infect and deplete bone marrow stromal auxiliary cells, which has been suggested as a potential cause of disrupted hematopoiesis.[105] In addition, elevated systemic immune activation may have a major effect on HPC activity and hematopoiesis. The lack of correlation between viral replication and $CD34^+$ cell levels suggests that a direct effect of the virus on hematopoiesis disruption may only be secondary, in comparison with the effect of immune activation.[25] The association between plasma sCD14 levels and $CD34^+$ cell counts in untreated patients suggests that high levels of microbial products such as lipopolysaccharide (LPS; associated with bacterial translocation), or IFN-α (associated with activation of plasmacytoid dendritic cells), which result in monocyte activation and are both associated with disease progression in HIV or SIV infection[106,107] might participate in disrupting lymphopoiesis.

Concluding remarks

Among the constellation of immunological alterations observed during the course of HIV infection, many highlight a clear immune parallel between HIV disease progression and aging. HIV-infected patients can display innate and adaptive immunosenescence like attributes, sometimes decades before uninfected people. Elevated chronic immune activation is the most likely drivers of this phenomenon, although the precise mechanisms (e.g., systemic inflammation related damages or viral antigen driven consumption of immunocompetent cells) still need to be determined in details. The majority of these immune aging alterations points toward the accumulation of more mature and differentiated innate and adaptive immune cells. The increased proportion of these cells accounts, to a great extent, for the reduced telomere length observed in PBMCs of HIV-infected patients. However, comprehensive analyses of telomere length and telomerase activity in the different subsets of T, B, NK cells, according to their stage of differentiation, may be required. In particular, it will be important to assess telomere length directly in primary immune cell compartments, such as HPCs and naïve cells, which embody the source of hematopoiesis and immune response induction respectively. The alteration of these compartments during HIV infection certainly represents the foundation of the immune parallel with aging, and the decline of the immune system fitness. Their fine characterization is necessary to draw a complete picture of the immunological age according to HIV disease progression and chronological age, and of the remaining hematopoietic potential of HIV-infected patients.

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