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Immunosenescence and HIV

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Purpose of review

The present review discusses the interplay between HIV infection and other environmental factors (e.g. co-infection with CMV) in the acceleration of the aging process of the immune system, leading to 'immunosenescence.'

Recent findings

Basic studies in cell biology demonstrate that replicative senescence is a common pathway of many cell lineages, including those of the immune system, characterized by activation of a unique pro-inflammatory secretory program. In the setting of HIV disease, this process is accelerated, resulting in an immunosuppressed state that diminishes the ability of the immune system to contain virus while at the same time facilitating viral replication and spread. Clinically, these changes result in a lower capacity to respond to new infections as well as an increased frequency of age-associated end-organ disease (e.g. cardiovascular complications, cancer, and neurologic disease).

Summary

Accelerated immunosenescence in the setting of HIV disease is associated with increased morbidity and mortality, prompting the need for more investigation into its causes, diagnosis, and treatment.

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Introduction

The development of antiretroviral therapy for the treatment of HIV infection is one of greatest achievements of modern medicine. Within a relatively short period of time, the overall life expectancy for HIV-infected patients was extended from years to decades. Although the initial regimens were complex and associated with significant short-term and long-term toxicity, current regimens (constructed from amongst 25 unique antiretroviral drugs) are generally well tolerated, easy to administer, and effective. As a result, the epidemic has entered a phase in which HIV replication should be controllable indefinitely, at least within those with access to appropriate medical care.

Even still, combination antiretroviral therapy has its limits. For reasons that remain undefined, long-term treated HIV-infected individuals not only die at an earlier age than HIV-uninfected individuals, they also suffer a number of maladies that are usually only seen later in life [1,2]. Such non-AIDS complications surface as degenerative, dysfunctional, and/or malignant disease of multiple organ systems, including the heart, liver, kidney, bone, brain, and immune system [3]. Given the nature of these diseases, their negative impact on quality of life can be dramatic [4]. These observations suggest that HIV-infected individuals, including those who are completely compliant with the best-designed antiretroviral regimen, might suffer from premature 'aging' [4–6]. Here, we provide an overview of the accelerated aging process that occurs in the immune system, also known as 'immunosenescence,' and discuss its potential implications for health in these individuals.

Basic studies in immunosenescence

During normal aging, functional changes in the immune system contribute to increased susceptibility to infections, loss of protection from previous vaccinations, decreased responsiveness to new vaccinations, decreased surveillance against cancer, and increased autoimmunity. These age-associated changes in immune function occur as a consequence of alterations in both the innate and adaptive immune systems [7–10]. Thymus involution is a prominent manifestation of aging of the immune system and leads to decreased production of T cells [11]. A homeostatic process of memory T cell proliferation takes place to offset this production defect and results in an increasing shift over decades from naïve to memory T cells and to a relative decrease in T cell receptor repertoire diversity. The shift from naïve to terminally differentiated cells is associated with reduced capacity of these cells to proliferate ('replicative senescence') and/or function. This constellation of age-associated changes is referred to immunosenescence, although there is no real consensus on how to define this term [12].

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Replicative senescence is not unique to immune cells, can be caused either by repeated cell division or by oncogenic alteration, and is thought to represent a protective mechanism against dysfunctional cells, including cancer cells. During repeated cell division, a relative lack of telomerase activity leads to telomere shortening and the activation of the senescent phenotype. Senescent cells are characterized by shortened telomeres, lack of cell division (secondary to activation of tumor suppressor pathways regulated by Rb and p53), increased 'senescence-associated' β-galactosidase activity, and activation of a unique pro-inflammatory secretory program [13]. Senescent cells accumulate in various organs and tissues during aging, and have been proposed to play a direct causative role in the aging process via secretion of pro-inflammatory cytokines [13,14,15••,16]. Indeed, experimental elimination of $p16^{Ink\text{-}4a}$ positive senescent cells in a progeroid mouse strain (BubR1) delayed onset of aging-related phenotypes in tissues in which the action of $p16^{Ink\text{-}4a}$ contributes to pathology, including adipose tissue, skeletal muscle, and the eye [17••]. This selective removal of senescent cells with subsequent improvement in health is perhaps the strongest evidence yet that senescence contributes directly to the onset of age-associated disease.

Pioneering work conducted by Effros and colleagues have defined the role of chronic inflammation as one of the mechanisms of $CD8^+$ T cell aging [18,19]. Following repeated cycles of activation and cell division *in vitro*, normal human $CD8^+$ T cells undergo replicative senescence and progressively lose expression of the CD28 marker. Increasing proportions of T cells lacking CD28 expression have been observed in normal human aging, particularly within the $CD8^+$ T cell subset. Further study of humans of different ages has shown that, at birth, the vast majority of the $CD8^+$ T cells express CD28 and that there is a progressive increase with age in the proportion of T cells that lack CD28 expression in humans [20,21]. A striking association between high proportions of $CD28^-$ T cells and chronic viral infection, both by HIV and by CMV, has also been observed, suggesting that persistent viruses induce a state of replicative senescence *in vivo* [22].

Replicative senescence of T cells probably represents a normal end-stage state of human memory T cell differentiation and proliferation, and may also exert deleterious influences through the release of pro-inflammatory cytokines. The abundance of potentially senescent cells (as defined by the lack of CD28 expression or the presence of CD57 on lymphocytes) correlates with a variety of negative outcomes, such as decreased vaccine responsiveness in the elderly, autoimmunity, frailty, reduction in overall TCR repertoire, cardiovascular disease, poor antigen responsiveness and, particularly relevant to this review, more rapid progression to AIDS [23–27,28•,29]. As discussed below, the increased number of senescent cells may enhance disease pathogenesis where inflammation represents an important risk factor, such as neurodegeneration, atherosclerosis, and cancer.

The impact of HIV on immunosenescence

The ontogeny of the immune system encompasses a carefully orchestrated series of events that enable multilineage hematopoietic stem cells and lineage-restricted progenitor cells to differentiate through and function within specialized hematolymphoid microenvironments such as the fetal liver, the bone marrow, and the various compartments of the peripheral lymphoid system. Discrete subpopulations of B, T, and myeloid cells interact with one another and with exogenous environmental factors to confer tolerance of self and antigen-specific effector functions against non-self. During the course of a normal lifespan, the hematopoietic system progresses from one that is fetal in nature (and capable of conferring tolerance to antigens from the mother) [30,31] to another that is more immunogenic during childhood and adulthood and, finally, to one that eventually senesces to a point of relative dysfunction.

In the setting of HIV infection, the above physiologic steps are accelerated and then subverted [32–34,35•,36–40]. The immune response to persistently replicating HIV is associated with abnormally high levels of activation [41,42•], leading to a cascade of continued viral spread and cell death. Concomitantly, the thymus and, probably, elements of the supportive liver and bone marrow microenvironments are destroyed, rendering the system less able to replace those mature cells that are lost [43,44••]. The end result is disruption of normal immune homeostasis and collapse of the important, multi-functional $CD4^+$ T cell compartment. These events are observed irrespective of when during life HIV infection may occur, converting even the immune system of young HIV-infected subjects to one more similar to that of an individual who is 40 years older [45].

During this inexorable decline of immune system function, persistent replication of HIV (as well as of other viruses such as HCV and CMV) [41,46•] leads to antigen-specific and non-specific differentiation and proliferation of T cell subsets and, ultimately, to replicative senescence (Figure 1). As in the case of uninfected individuals of a much older age, such senescent cells are characterized by a lack of CD28 expression, an increase in the expression of CD57 [29,47], loss of expression of CD100 (an immune semaphorin that improves antigen-specific priming by antigen presenting cells and that serves as a co-stimulatory molecule on T cells) [36], reduced ability to proliferate, shortened telomeres, and the propensity to secrete pro-inflammatory cytokines such as IL-1, TNF-α and IL-6 [13,15••]. The emergence of such cells augments the immunosuppressed state in several ways: not

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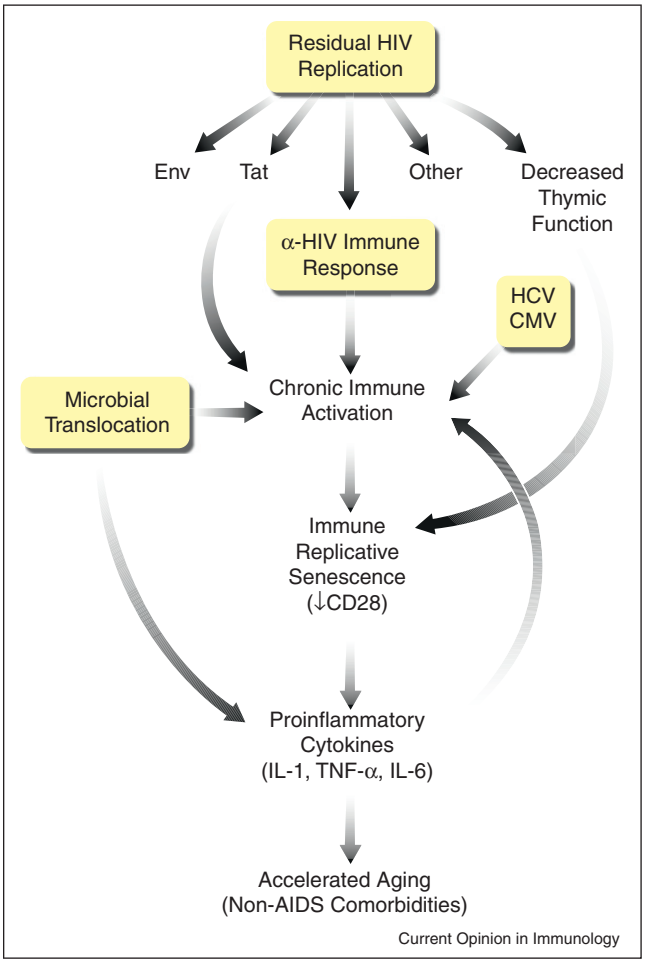
Figure 1



The relationship between HIV replication and accelerated aging.

only are they less functional than normal cells but they also drive pro-inflammatory forces that can drive viral spread.

Antiretroviral therapy generally improves all aspects of immune function, including those related to immunosenescence. Long-term effective therapy results in reduction of $CD28^-$ T cells and possibly improves the function and proliferative capacity of those cells that remain $CD28^-$ [48••,49]. Despite clear improvements associated with effective antiretroviral therapy, some subjects (and, in particular, those with low levels of $CD4^+$ T cell recovery) show persistent alterations in T cell homeostasis, with lower levels of naïve $CD4^+$ and $CD8^+$ T cells and a higher frequency of effector memory T cells [48••,39,50] that express CD57 [37]. Such constraints on $CD4^+$ T cell recovery after HAART are further exacerbated in the setting of co-infection with CMV and increasing age [35•,48••,51]. It is possible that continued perturbation in immune system homeostasis and function leads to some of the non-AIDS sequelae of 'effective' antiretroviral therapy, many of which are end-organ manifestations of chronic inflammation.

The clinical implications of HIV-induced immunosenescence

As outlined above, age has a complex and often highly variable effect on immune function, resulting in the peripheral accumulation of senescent T cells that are well differentiated, pro-inflammatory, and less likely to proliferate. The clinical implications of such immunologic changes were first demonstrated in elderly Swedish individuals [52,53]: a reduced CD4/CD8 ratio, a reduced naïve/memory ratio, an increased proportion of $CD8^+CD28^-$ cells, and/or a reduced capacity of T cells to proliferate were associated with early mortality. Subsequent studies of older adults found that many of these markers also predicted a lower capacity to respond to new infections, environmental exposures, and vaccines [54–57]. These age-associated changes may also contribute directly to end-organ disease [58–62]. It should be emphasized that there have not been any large, well-conducted studies of humans in which a well-characterized functional measure of immunosenescence has been associated with poor outcome. Thus, it is expected that many of the currently accepted conclusions about the complex association between immunosenescence (or a surrogate for this syndrome, such as the presence of a chronic viral infection) will be challenged once such studies are performed. For instance, a recent analysis of a large well-characterized cohort of 731 elderly people failed to confirm that CMV co-infection predicts influenza vaccine responsiveness (as defined by antibody production) [63•].

The impact of immunosenescence on clinical outcomes in HIV disease is now being addressed in a number of studies. In a large cohort involving over 1291 HIV infected adults initiating antiretroviral therapy, the frequency of $CD28^-CD8^+$ (and, to a lesser degree, $CD28^-CD4^+$ T cells) before therapy predicted who would exhibit robust versus blunted $CD4^+$ T cell gains over the following two years [48••]. In terms of clinical outcomes, a limited case-control type longitudinal study suggested that classical markers of immunosenescence during HIV infection predict subsequent disease progression [64••] and another well-performed study found that the frequency of $CD28^-CD4^+$ T cells during treatment independently predicts vaccine responsiveness [65]. More recent evidence supporting a role of immunosenescence in disease progression, including data from a cohort of HIV infected women linking $CD28^-CD57^+$ 'senescent' T cells with markers of atherosclerosis [28•] and vascular dysfunction [38], has been cross-sectional in nature. Of note, there is a wealth of data indicating that, independent of other factors, measures of T cell activation (e.g. co-expression of CD38 and HLA-DR) and

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inflammation predict morbidity and mortality in both untreated and treated HIV disease. Similarly, the $CD4^+$ T cell count during treatment is a strong predictor of disease progression. Since immune activation and $CD4^+$ T cell function tend to be strong correlates of immunosenescence (and, indeed, are often included in the definition of this syndrome) [66–68], it seems likely that these markers will continue to emerge as potentially important predictors of disease in HIV-infected adults.

The observational nature of these studies makes it impossible to rule out the impact of potential confounding issues, including the presence of certain co-infections that could be causally associated with both immunosenescence and with end-organ dysfunction via independent mechanisms. Without a precise intervention aimed at preventing or reversing immunosenescence in humans, it will be difficult to generate definitive proof that the immune senescent profile is causally responsible for morbidity and mortality. For these reasons, most of the more mechanistic work is carried out in animal models. As discussed above, gene-mediated depletion of senescent cells in mice delayed the onset of age-associated complications [17••]. Also, immune-mediated clearance of senescent hepatocytes was found to prevent development of liver cancer in mice [69].

The next task at hand will be to translate studies such as these to humans so that 'effectively' treated subjects with HIV disease might lead a life as long and as healthy as their age-matched HIV-uninfected peers. Prospective interventional studies are now focusing on the more readily targeted causes of immunosenescence, including inflammation. For example, a small short-term pilot study of valganciclovir (an anti-CMV drug) among HIV-infected adults [46•] suggests that some measures of T cell dysfunction can be reversed if CMV replication is contained. Also, a study of growth hormone found that thymic function could be enhanced in older individuals with treated HIV disease [70]. It is hoped that clinical trials can eventually use immunosenescence biomarkers as outcomes, as has been done in non-human primates [71], although the lack of strong links between these markers and disease progression might limit interest in such studies designs.

Conclusion

The observation that markers of immunosenescence might predict morbidity and mortality in HIV-infected adults as well as in the general population has raised a number of unresolved questions. Should we routinely categorize all of the age associated-changes to T cell function as 'immunosenescence,' even though this term formally refers to cells that exhibit cell-cycle arrest? Does immunosenescence predict disease progression independent of other factors? Which of the many commonly used markers of immunosenescence is the strongest predictor of progression and do these markers differ for various types of endpoints (e.g. infectious complications, vaccine responsiveness, cardiovascular disease, or death)? Can markers of immunosenescence measured earlier in life (when presumably interventions to prevent immune progression might be considered) predict long-term disease outcomes? If immunosenescence is indeed a causal factor in disease progression, what is the mechanism for this effect? Can knowledge about these issues be used to identify therapeutic interventions? Finally, can any of the currently used biomarkers for immunosenescence be validated as surrogate markers for disease and, hence, also be used as endpoints in clinical trials? Given the complexity and costs associated with measuring immune cell function retrospectively as well as the costs associated with constructing well-powered prospective studies with clinical endpoints, answering these questions will require substantial investment in rigorously performed longitudinal cohort studies.

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- •• of outstanding interest

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