Aging and HIV Disease: Synergistic Immunological Effects?

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Abstract

The population of HIV-infected adults is progressively aging, due to more effective treatments that lower the viral load. Since aging and HIV disease each have major detrimental effects on the immune system, it is possible that in older persons who are infected with HIV-1, the immune changes due to the infection combined with those that occur with age may synergize to exacerbate the disease. Indeed, clinical studies have already documented older age as an independent risk factor for more rapid HIV disease progression. Moreover, immunological recovery in older individuals treated with antiretroviral drugs is less robust than in younger adults, even with equivalent levels of viral suppression. The challenge to future research will be to develop a detailed mechanistic understanding of the interplay between HIV-related and age-related immunological changes. This

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information will advance our theoretical understanding of the immune system and, at the same time, provide practical information regarding age-appropriate approaches to therapy and prophylactic vaccines.

Keywords
T cell · Aging · HIV/AIDS · Telomere · Telomerase · Immunosenescence · Cytomegalovirus

Introduction

Chronic infection of young individuals with human immunodeficiency virus (HIV-1) is associated with immunological changes reminiscent of those that occur during normal aging. Indeed, HIV disease has even been proposed as a model of premature immunosenescence (Appay and Rowland-Jones 2002). In young persons infected with HIV-1, the pace of immunological change is accelerated. Compounding this effect, the cohort of HIV-infected persons is actually aging chronologically as well. Recent data from the US Centers for Disease control and Prevention indicate that the cumulative number of AIDS cases in the USA in persons >50 years of age quintupled during the last decade, with similar trends reported in Europe (Grabar et al. 2006). In New York City, the epicenter of AIDS in the USA, 30% of HIV-infected persons are over age 50. Aging of the baby boomers, the increased sexual activity of elders in the era of erectile dysfunction drugs, and the prolonged survival of those infected with HIV-1 are among the contributory factors to the overall increase in age of the HIV-1-infected population.

HIV-1 infection and aging each have major effects on the immune system, raising the possibility that in older persons who are infected with HIV-1, the immune changes due to the infection combined with those that occur with age may synergize to exacerbate the disease. Indeed, age is an independent risk factor for more rapid disease progression, and immunological recovery after antiretroviral drug treatment in older individuals is less robust than in younger adults, even with equivalent levels of viral suppression (Rosenberg et al. 1994; Darby et al. 1996; Fordyce et al. 2002; Egger et al. 2002; Shah and Mildvan 2006). It therefore becomes essential to develop a detailed mechanistic understanding of the interplay between HIV-related and age-related immunological changes. Efforts in this direction may ultimately lead to novel age-appropriate therapies to enhance immune control over the virus. Immune-based approaches to therapy may, in turn, reduce the need for drugs that target the virus. This is important because one of the emerging issues with respect to the elderly is that many of the antiviral therapies are not tolerated well in this group (Casau 2005). Moreover, long term antiretroviral therapy (ART) may interfere with certain medications or exacerbate age-related pathologies.

This chapter will review immune system changes that are common to human aging and HIV disease, highlighting those areas that merit more detailed investigation. One of the fortuitous outcomes emerging from the confluence of research on aging and HIV disease is that the two fields are mutually benefiting each other.

Indeed, information on T cell changes that occur during normal aging, many of which are due to untreated persistent infections, has caused HIV biologists to focus on the immune consequences of the chronic antigenic stimulation. Conversely, detailed analysis of immune reconstitution dynamics following ART, which lowers the level of HIV-1, provides immunogerontologists with a unique model system to test the hypothesis that reducing chronic antigenic stimulation retards age-related deleterious changes within the human memory T cell compartment.

Aging and HIV Disease Progression

There is an extensive body of research suggesting that age constitutes a significant risk factor for more rapid disease progression and a strong predictor of increased AIDS-related mortality, both in the presence and absence of ART (Ferro and Salit 1992; Phillips et al. 1991; Kalayjian et al. 2003; Rosenberg et al. 1994; Blatt et al. 1995; Darby et al. 1996; Fordyce et al. 2002; Egger et al. 2002). Moreover, even though virologic efficacy of ART may be equivalent in young and old persons, immunological recovery is, nevertheless, often slower and blunted in older HIV-infected adults (Shah and Mildvan 2006; Manfredi 2004). The negative effect of older age has been observed in persons infected via blood transfusion as well as intravenous drug use. A study on more than 6,000 HIV-infected persons documented that those who were older than age 50 had a significantly increased risk of contracting AIDS wasting syndrome and AIDS dementia and showed a shortened survival time after AIDS diagnosis (Balslev et al. 1997). Even after adjusting for patterns of complicating diseases, the effect of age persisted. Clearly, a more comprehensive understanding of the effect of age on immune reconstitution within multiple lymphoid compartments is critical in order to develop strategies to prevent the increased incidence/severity of opportunistic infections and the poor responses to vaccines.

Chronic HIV-1 infection is also associated with earlier onset of a number of age-related diseases/pathologies, many of which involve the immune system. Co-morbid conditions, such as cardiovascular disease and colon cancer, occur at younger ages in HIV-1-infected patients, an observation that is beginning to affect screening recommendations (Berretta and Tirelli 2006; Engels et al. 2006; Orlando et al. 2006; Palella et al. 1998, 2003); Murphy et al. 2001; Guy-Grand et al. 1991). Chronic immune activation, a signature feature of HIV-1 disease, is known to contribute to bone loss (Arron and Choi 2000), which is already accelerated with age. Indeed, one of the immune correlates of hip fracture in a group of uninfected elderly women is the increased proportion of $CD8^{+}CD57^{+}$ T lymphocytes (Pietschmann et al. 2001). This same cell subset, which has been shown to have telomere lengths consistent with replicative senescence, is significantly increased in HIV-infected persons (Brenchley et al. 2003).

It is well established that aging is associated with a dramatically increased risk of developing cancer. Indeed, old age carries a cancer risk exceeding that of smoking. The diminished immune surveillance associated with the general immune system

deterioration has been assumed to play a significant role in the age-associated cancer risk. Interestingly, chronic HIV infection is also associated with increased cancer incidence, further implicating immune deficiency. A recent meta-analysis compared cancers in HIV-infected with immunosuppressed transplant recipients (Grulich et al. 2007). Both populations showed increases in cancers with a known infectious cause, such as EBV lymphomas, liver cancer, and human papilloma virus (HPV)-associated cancers, including those of the mouth, penis, anus, liver, stomach, esophagus, larynx, and eye. In cancers that are associated with persistent infections, such as EBV, exhaustion of the relevant virus-specific CD8 T cell response is believed to be one of the contributing factors (Effros 2004). Overall, the similarity in the patterns of increased cancer risk in the elderly and in HIV-infected younger persons is consistent with the notion that the immune deficiency, rather than other risk factors, is responsible for the increased cancer incidence associated with chronic HIV disease. These and other data predict that the combination of aging and HIV disease will further increase the cancer risk, which would be consistent with the notion of synergy between the immune effects of each separate condition.

In considering the combined effect of HIV and aging on immunosenescence, it should be emphasized that there are two categories of older HIV-infected persons – those who become infected during youth, but survive to old age due to successful treatment, and those individuals who first become infected during old age. Most of the data on aging and HIV are derived from the first category, with minimal information on persons who become infected when they are already old. This latter group of elderly persons may be at a distinct disadvantage, given that the initial control over HIV-1 during the primary infection is so critical in terms of the long term effect on the rate of disease progression. Since aging itself is associated with suboptimal responses to acute infections, from this standpoint alone, the newly infected elderly would be predicted to be at greater risk of more rapid progression to AIDS. A second issue that affects disease progression in newly infected elderly persons relates to the initial diagnosis. It is rare that physicians discuss sexual activity or safe-sex with elderly persons, and even in the face of symptoms suggestive of HIV, blood tests for the virus are rarely advised. Thus, HIV disease may be diagnosed later in older persons, which will have an additional impact on the rate of progression to AIDS.

T Lymphocyte Changes During Aging

Changes in cellular immunity are considered to be the main factors responsible for the well-documented increases in infection-related morbidity and mortality in the elderly. CD4 T lymphocytes are key players in the immune response to pathogens and vaccines, and during aging, the requisite helper functions with respect to both B lymphocytes and CD8 T lymphocytes are diminished (Haynes and Swain 2006; Haynes et al. 2002). In addition to the reduced number of recent thymic emigrants, as determined by T cell excision circle (TREC) analysis (Douek et al. 1998), the naïve CD4 T lymphocytes that are produced show specific functional decrements. For

example, defective T cell help is responsible for the delay, reduced size, and diminished number of B cell germinal centers in old mice (Zheng et al. 1997). Similarly, alterations in CD4 T lymphocyte function have also been implicated in the reduced level of B cell hypermutation (Yang et al. 1996) and in the failure to produce high titer antibody in response to influenza vaccination (Swenson and Thorbecke 1997). CD4 T lymphocytes also provide help for CD8 T lymphocyte responses, most notably in chronic diseases, and are required for the maintenance of CD8 T lymphocyte memory after acute infections (Sun et al. 2004). Therefore, the age-associated reduced numbers and quality within the naïve T cell pool affect multiple facets of immunity.

The progressive reduction of naïve T lymphocytes with age is due to the combined effects of thymic involution and the homeostatic pressure of the expanded memory T cell population. The lower numbers of naïve T cells are associated with blunted capacity to respond to neoantigens, such as those present in vaccines. The reduced proportion of naïve T cells also has an impact on cancer, which, as noted above, increases with age and during HIV disease. Interestingly, thymic output is related not only the development of cancer, but also to tumor progression. Specifically, in the most deadly form of brain tumor, glioblastoma multiforme, the number of recent thymic emigrants within the CD8 T cell subset influences both tumor antigen recognition and age-dependent mortality (Wheeler et al. 2003). Thus, a variety of age-associated defects have been identified for the naïve T lymphocyte subset, all of which may contribute to the phenomenon of immunosenescence, but arguably to a lesser extent than changes that occur within the memory T lymphocyte population, as will be discussed below.

Aging in humans is associated with significant changes within the memory CD8 T lymphocyte compartment, particularly in the cytotoxic T lymphocyte (CTL) responses to viruses, where both delayed and diminished responses have been documented (Deng et al. 2004; Po et al. 2002; Zhang et al. 2002). Within the memory pool of elderly humans, there are clonal expansions of CD8 T lymphocytes that often occupy a large proportion of "immunological space" and which are also associated with a constriction of the available T cell repertoire (Ouyang et al. 2003). A large proportion of the lymphocytes within the clonally expanded populations lack expression of the CD28 costimulatory molecule.

Based on extensive cell cultures studies, it appears that the increased proportions of CD28-negative ($CD28^-$)T lymphocytes in the elderly may be the in vivo correlates of cells that reach the end stage of irreversible cell cycle arrest in vitro following multiple rounds of antigen-driven proliferation. These cells show permanent and irreversible loss of CD28 expression (Effros et al. 1994). Similar to lymphocytes in senescent culture, $CD8^+CD28^-$ T lymphocytes tested ex vivo are resistant to apoptosis (Spaulding et al. 1999; Posnett et al. 1999), show minimal proliferative potential (Effros et al. 1996; Almanzar et al. 2005), and have shortened telomeres (Monteiro et al. 1996; Effros et al. 1996). CD8 T lymphocytes that reach replicative senescence in culture also produced high levels of two pro-inflammatory cytokines (TNFα and IL-6) that are associated with a variety of age-related pathologies, and whose concentration is increased in the serum of frail elderly individuals.

Another modulatory effect on the process of replicative senescence is exerted by adenosine deaminase (ADA), the enzyme that converts immunosuppressive adenosine to inosine (Gessi et al. 2007; Hovi et al. 1976). Most of the research on ADA is focused on its critical function in lymphoid development, where its absence results in severe combined immunodeficiency disease (Hershfield 2005). As it happens, ADA also plays a key role in the optimal function of mature T cells. It is present both intracellularly and on the surface, as ecto-ADA that is bound to CD26 on antigen-presenting cells (Kameoka et al. 1993). Recent studies in our lab have been the first to document that ADA is key to upregulation of telomerase activity and that both intracellular and ecto-ADA decrease with increasing population doublings in cell culture. In addition, if exogenous adenosine is added to long term cell cultures, a scenario mimicking the in vivo environment, the progression of CD8 T cells to replicative senescence is accelerated, with more rapid loss of CD28 expression and telomerase activity, ultimately reducing the overall proliferative potential (Parish et al. 2010).

CD8 T Cell Replicative Senescence in HIV Disease

As in most viral infections, HLA class I-restricted CTL are a critical component of immunological response to HIV-1. The decline in plasma viral RNA after the appearance of HIV-specific CTL during acute infection (Koup 1994; Borrow et al. 1994) and the prognostic significance of vigorous CTL responses in disease progression (Carmichael et al. 1993; Connor et al. 1993) highlight the key role of CTL. These observations in humans are further bolstered by experiments in rhesus macaques, where depletion of CD8 T lymphocytes led to striking increases in plasma SIV RNA (Schmitz et al. 1999; Jin et al. 1999). Thus, there is strong indication that CTL are critical in HIV-1 immunopathogenesis, and it follows that viral persistence and disease progression are due, at least in part, to the eventual failure of CTL.

Similar to aging, chronic infection with HIV-1 is associated with reduced thymic function. In HIV disease, the number of recent thymic emigrants, as determined by TCR excision circle (TREC) analysis of both CD4 and CD8 naïve T cells, is reduced (Nobile et al. 2004). There is also evidence suggesting that naïve T cells generated during aging and/or HIV infection may be qualitatively different from those generated during youth. Telomere measurements on two populations of naïve CD4 T lymphocytes, one that represents the most recent thymic emigrants and the other that has lost expression of CD31 due to homeostatic proliferation (defined by the CD31 marker), show that both types of naïve cells undergo telomere shortening with age. Indeed, the naïve CD4 T cells in young HIV-infected persons were shown to have telomere lengths that were similar to uninfected persons 30 years their senior (Rickabaugh et al. 2007). These cells also had reduced levels of telomerase activity compared to uninfected controls.

Even the most antiretroviral successful treatment strategy does not eradicate the virus, resulting in ongoing stimulation/replication of HIV-1-specific CD8 T

lymphocytes over many years. Indeed, it is likely that the persistence of suboptimal (i.e., low perforin) HIV-1-specific CD8 T cell responses despite prolonged therapeutic viral suppression is associated with continuous proliferation and telomere shortening, which can eventually lead to the end stage cell cycle arrest known as replicative senescence. Telomere shortening within the CD8 T cell subset in HIV-1-infected persons has, in fact, been documented by several investigators (Palmer et al. 1997; Effros et al. 1996; Wolthers et al. 1996). Conversely, robust, continuous proliferation and CTL function of HIV-specific CD8 T lymphocytes has been identified as a key biomarker of long-term nonprogressors (Migueles et al. 2002).

The importance of telomere maintenance in retarding the process of replicative senescence is underscored by studies demonstrating that gene transduction of HIV-specific CD8 T lymphocytes from infected donors with the human catalytic component of telomerase leads to indefinite proliferation, increased suppression of viral production by acutely infected CD4 T lymphocytes, and enhanced HIV-specific IFN-γ secretion, consistent with the importance of telomere length maintenance in anti-viral CTL (Dagarag et al. 2004). Gene transduction with hTERT also retards loss of CD28 expression, which is important, since chronic infection with HIV is associated with increased proportions of $CD28^-$ T cells (Appay et al. 2002; Effros et al. 1996; Brinchmann et al. 1994).

As with aging, in chronic HIV infection, the presence of CD8 T cells that are $CD28^-$ is associated with deleterious outcomes. A recent study compared the predictive value of CD28 on CD8 T cells between two carefully matched HIV-infected cohorts: one that progressed to AIDS within 4 years and the second that progressed more slowly (i.e., > 8 years). The data show that the fast progressors had significantly greater proportions of $CD8^+CD28^-$ T lymphocytes at the start of the study (Cao et al. 2009). Moreover, the telomere length of the $CD8^+CD28^-$ T cells in young (mean age 43) HIV-infected persons is the same as that of PBMC from centenarians (Effros et al. 1996), consistent with the notion that HIV disease may represent premature immunological aging (Appay and Rowland-Jones 2002). Interestingly, CMV, which plays a key role in aging, is also important in HIV disease. It has been shown that in HIV-infected persons who have progressed to AIDS, detectible plasma CMV DNA was an independent predictor of death even after adjusting for HIV-1 level and CD4 T cell counts (Wohl et al. 2005).

Chronic Antigenic Stimulation by CMV: Impacts on Aging and HIV/AIDS

The clinical relevance of age-related changes within the T cell compartment is underscored by data from longitudinal studies in humans, which have identified a cluster of T cell parameters, the so-called "immune risk phenotype" (IRP) that is predictive of early mortality in the very old. These include an inverted CD4/CD8 ratio, poor proliferative responses, and high proportions of $CD8^+CD28^-$ T lymphocytes. The IRP is significantly associated with latent viral infections, particularly

CMV, and to lesser extent with Epstein-Barr virus (EBV) and varicella zoster (Ouyang et al. 2002). Interestingly, immune control over CMV is also relevant with respect to HIV-1 disease: in patients with AIDS, detectible plasma CMV viremia is an independent predictor of death even after adjusting for HIV-1 level and CD4 T cell counts (Wohl et al. 2005). The above mortality data from both aging and HIV-1 disease suggest that the continuous antigenic stimulation of CD8 T cells involved in maintaining the latent status of persistent viruses plays a major role in the accumulation of dysfunctional virus-specific lymphocytes, resulting in the reconfiguration of the aging immune system (Pawelec et al. 2004; Effros 2016).

Although the total number of T cells in the peripheral blood remains stable throughout life in the very healthy elderly (Pawelec et al. 2005), there are marked changes in the relative distribution of T lymphocyte subsets. In particular, there is a significant decrease in the proportion of naïve CD8 T lymphocytes, which is accompanied by increased proportions of memory CD8 T lymphocytes. Most of these memory cells are part of clonal expansions that are specific for persistent viruses, mainly CMV, but also EBV and VZV (Pawelec et al. 2005). Although these viruses do not necessarily re-emerge or cause disease, it is becoming increasingly evident that maintaining control over persistent infections over many decades is "costly" in terms of overall immune function (Pawelec et al. 2004). Thus, it seems that chronic antigenic stimulation of CD8 T lymphocytes plays a central role in age-related reconfiguration of the human immune system.

In the elderly, replicative senescence within the CD8 T lymphocyte population is associated with a variety of deleterious clinical outcomes. For example, one of the key immune correlates of reduced vaccine responses is the presence of high proportions of CD8 T cells that lack CD28 expression. Furthermore, clonal expansions of CD8 T cells that are $CD28^-$ are part of a so-called "immune risk phenotype" (IRP), which is predictive or early mortality in the very old (Wikby et al. 2002). As mentioned above, the IRP is significantly associated with latent viral infections, particularly CMV. High proportions of senescent CD8 T lymphocytes are also associated with osteoporotic fractures in older women (Pietschmann et al. 2001), and with accelerated disease progression in the autoimmune disease, ankylosing spondylitis (Schirmer et al. 2002). Finally, in patients with head and neck tumors, the $CD8^+CD28^-$ T cell subset undergoes expansion during the period of tumor growth, but is reduced following tumor resection (Tsukishiro et al. 2003), underscoring the putative role of chronic antigenic stimulation in the generation of senescent CD8 T cells.

It has been proposed that persistent herpes virus infection may cause CD8 T lymphocyte replicative senescence in vivo. The persistent nature of these infections is believed to periodically stimulate T cell responses, resulting in considerable proliferation and clonal expansion of virus-specific CD8 T cells over time (Appay et al. 2002). Most of these infections are acquired during youth and establish chronic infection with latency and reactivation, so that by old age there is a cumulative effect of chronic periodic antigenic stimulation of CD8 T cells causing accumulation of senescent cells (Pawelec et al. 2004). Chronic infection with CMV seems to be important with respect to HIV disease as well. During the primary (acute) phase of

HIV infection, CMV-specific CD8 T cells in the blood become activated (Doisne et al. 2004), and once the infection becomes chronic, a large proportion of the CD8 T cell pool is directed at CMV.

The herpesviruses CMV/EBV/VZV establish latency with intermittent reactivation causing chronic intermittent antigenic stimulation leading to replicative senescence. The effect is even more dramatic effect during chronic infection with HIV-1, which persists with exuberant ongoing viral replication and therefore vigorous chronic antigenic stimulation of the CD8 T lymphocyte pool. This accelerated process of stimulation and senescence would therefore be an ideal model to study, in a short time frame, the aging-associated immune dysfunction caused by ongoing significant antigenic stimulation. HIV-1 provides an additional experimental advantage in that it is a chronic viral infection for which viral replication is easily quantitated and blunted by antiviral treatment. Asymptomatic chronic CMV/EBV/HSV infections, in contrast, are not typically monitored for viral replication or treated due to their predominantly latent state. Thus, studies comparing age-matched treated and untreated HIV-1-infected persons might provide novel insights into the role of chronic antigenic stimulation on the process of replicative senescence.

Why CMV?

Cytomegalovirus (CMV) is a member of the *herpesviridae* family, which contains more than 100 viruses. Vertebrate species, including humans, have been infected by various *herpesviridae* family members for millions of years. Due to the intricate strategies developed by these viruses that allow them to escape the immune system, once infected, humans develop lifelong persistent infections, starting early in life (Gianella et al. 2015). Seroprevalence varies according to the geographic locale, but it has been estimated to range from 45–100%. CMV is notable for having the largest genome of all viruses that infect humans. Studies using over 200 protein-spanning peptide pools tested on a human cohort of mixed HLA backgrounds suggest that at least 150 proteins of the virus can be recognized. This may actually be an underestimate, since the CMV genome actually provides more than 700 protein open reading frames (Terrazzini and Kern 2014; Stern-Ginossar et al. 2012; Holtappels et al. 2009). Although there is some genetic and antigenic heterogeneity among CMV isolates, the persistence of CMV within the human population is generally assumed to be due to its complex strategies of immune evasion, rather than rapid mutation of target proteins (Sijmons et al. 2015).

The interactions between and CMV and humans have occurred over millions of years, suggesting possible beneficial effects, given the overall high presence of the virus worldwide. This notion is based on evolutionary theory, which posits that certain beneficial effects during youth are positively selected, since this is the period associated with the need for reproductive success. Indeed, studies comparing CMV infection in different age groups have documented several positive immunological effects during youth, including elevated circulating levels of IFN

gamma, increased antibody response to influenza vaccination, and increased CD8 T cell sensitivity (Furman et al. 2015). Mouse studies accord with the human observations, showing such beneficial effects as cross-protection against a bacterial infection in young, but not old, animals (Barton et al. 2007). An interesting suggestion regarding the fact that the humans harbor CMV and other latent herpesvirus infections is that the term "normal" immune system be refined to take into account these persistent infection modulatory effects on the immune system (White et al. 2012).

The Ying-Yang of CMV beneficial effects during youth versus its deleterious effects during old age is consistent with one of the major theories of aging, namely, antagonistic pleiotropy. This theory posits that certain biological features are positively selected during youth due to certain favorable effects, but turn out to be harmful in old age, i.e., during a stage of life that is neutral in terms of evolutionary natural selection. There are numerous examples of how this notion is consistent with biological observations. For instance, high levels of estrogen favor reproductive success early in life, but may enhance the growth of breast tumors in older women. The process of replicative (cellular) senescence – which suppresses tumor formation during youth, but plays a key role in many-age-related pathologies – is a second example of antagonistic pleiotropy.

Gut-Associated Lymphoid Tissue (GALT): The Missing Link in Aging Research

In humans, essentially all the information on the immune system has been derived from studies on peripheral blood, which contains approximately 2% of total body lymphocytes. As noted above, a salient finding from those studies is the profound alteration in function and composition of the memory CD8 T lymphocyte pool, due, in large part, to the progressive accumulation of cells with features of replicative senescence. There are no data on the age-related changes in CD8 T lymphocytes in the human gastrointestinal tract, the major reservoir of lymphocytes, and an anatomical region of high antigenic exposure.

The data from animal studies suggest that aging is associated with significant alterations within the GALT, underscoring the need for similar studies in humans. Significantly, changes in the distribution of CD8 T lymphocytes in the GALT have been observed in aged rats (Daniels et al. 1993). Mucosal immune system studies in mice have documented age-related reduced frequencies of naïve CD4 T lymphocytes and dendritic cells in Peyer's patches (Fujihashi and McGhee 2004). Defects in mucosal IgA secretion (Taylor et al. 1992) as well as in helper T cells, CTL function, and mucosal vaccine responses have been described for old mice (Fayad et al. 2004). Finally, the reported age-associated reduction in immune responses to cholera toxin and *E. coli* enterotoxin, which are adjuvants frequently used in mucosally delivered vaccine preparations, may have broad implications for vaccine success in the elderly (Schmucker et al. 1996). Based on these animal studies, it has been proposed that age-associated alterations arise in the mucosal immune system of the gastrointestinal

tract earlier than in the peripheral immune compartment (Koga et al. 2000). These data underscore the need for detailed characterization of the effect of aging on the human GALT.

HIV disease, which, as noted above, shows many immunological parallels with aging, provides a unique opportunity to elucidate changes within the GALT that are due to chronic antigenic stimulation. In fact, it is becoming increasingly recognized that most of the immunological "action" during HIV-1 infection occurs in the gut. Regardless of the route of transmission, the HIV-1 virus selects CD4 T lymphocytes that also express CCR5 receptors, most of which reside in the gut, with enhanced per-cell CCR5 expression as compared to the blood (Anton et al. 2000). Indeed, treatment strategies based on peripheral blood measurements of CD4 T lymphocytes or level of viremia have been described as "misguided," since these values are often an underestimate of the profound and continuous loss of CD4 T lymphocytes in the gut (Veazey and Lackner 2005).

The importance of early and persistent immune responses within the gut mucosa is highlighted in comparisons between long-term nonprogressors and those with high levels of viremia, in which the former show prolonged maintenance of mucosal T lymphocytes, enhanced virus-specific responses and distinct gene expression profiles (Sankaran et al. 2005). Once the infection has become chronic, the CD8 T cell response in the gut is "too little, too late," with a magnitude that is $<5\%$ of that seen in any other lymphoid organ (Reynolds et al. 2005). Indeed, the ultimate failure of the immune system has been suggested to occur when CD4 and CD8 T lymphocytes are unable to sustain sufficient frequencies of effectors in both lymphoid and extra-lymphoid tissues, particularly the gut (Grossman et al. 2006).

There is accumulating evidence that HIV-1 may continue to replicate in mucosal tissues, despite being undetectable in the blood. A recent study, which compared the viral burden of DNA and RNA in lymphocytes from the gastrointestinal tract to lymphocytes from the blood, concluded that the GI mucosal lining carries a disproportionately high viral burden (Comi et al. 2001). In fact, quantifiable levels of HIV-1 can be detected in rectal mucosa-associated tissue despite years of undetectable levels of plasma HIV-1 RNA (Anton et al. 2003). Also, in some women, levels of HIV-RNA are higher in the genital mucosa compared to the blood (Neely et al. 2006).

Peripheral blood studies may also fail to reflect the level of immune reconstitution in the gut. In a 7-year study of HIV-1-infected individuals who began ART shortly after infection, it was observed that although the blood population of CD4 T lymphocytes rebounded to normal levels, a subset of lymphocytes within the gut remained depleted in 70% of the subjects. After 3 years of intensive drug therapy that suppresses HIV-1 replication very effectively, most patients still had only half the normal number of CD4 effector memory T lymphocytes in their gastrointestinal tracts (Mehandru et al. 2006). All of these data from studies on HIV disease underscore the need for increased research on the human gut mucosal immune compartment, which has, for various reasons, heretofore been ignored in human immunological studies.

Translational Implications

One of the shared features of immunosenescence and AIDS is the accumulation of memory CD8 T lymphocytes with features of replicative senescence. In both aging and HIV disease, the driving force seems to be chronic antigenic stimulation by persistent viruses. Clearly, prevention of primary infection with these viruses would be the most efficient strategy to prevent replicative senescence. However, it is highly unlikely that prophylactic vaccines against CMV and HIV-1 will be developed in the foreseeable future. Another possible approach is to reduce the antigenic burden by treatments directed against the virus itself. Anti-CMV therapy is usually reserved for situations of extreme immunosuppression, such as in organ transplant patients or the final stages of HIV disease, but it is possible that expanding the criteria for treatment to include all CMV seropositive individuals may lead to improved immune function during aging and AIDS. Antiretroviral therapy (ART) against HIV does, in fact, reduce the antigenic burden and should theoretically also retard the generation of senescent HIV-specific CD8 T cells, but no studies have actually addressed this question.

An alternative to reducing the antigenic burden is to augment the function of the virus-specific CD8 T cells by retarding replicative senescence. For example, since senescent CD8 T cells no longer express the CD28 co-stimulatory molecule, one approach that has been used is gene transduction with CD28. Indeed, the re-expression of an intact signaling CD28 molecule in CMV- or HIV-specific CD8 T cells that had lost CD28 expression led to the restoration of IL-2 production and autocrine-induced proliferation in response to antigen recognition (Topp et al. 2003). Another approach to modulating replicative senescence is based on the enzyme telomerase, which is upregulated in T cells during primary and secondary antigenic stimulation, but becomes undetectable by the third and all subsequent stimulations. Transduction of HIV-specific CD8 T cells isolated from HIV-infected persons with the gene for hTERT (the catalytic telomerase component) results in increased proliferative potential, telomere length stabilization, and enhanced ability to control viral replication (Dagarag et al. 2003, 2004). These proof-of-principles demonstrate that telomerase-based immunomodulatory strategies may be practical approaches to enhancing antiviral CD8 T cell function in both aging and AIDS. Indeed, preliminary studies show that exposure of CD8 T cells to certain small molecule telomerase activators leads to increased proliferation and antiviral function (Fauce et al. 2005).

If replicative senescence can be retarded, the result would be a reduction in the proportion of senescent T cells, and presumably the associated deleterious clinical effects noted above. Thus, more detailed studies on the process of T lymphocyte replicative senescence may lead to improved prognosis for both aging and HIV disease. An additional benefit of immune-based approaches to therapy may be a reduced need for drugs that target HIV-1. Many of the current drug treatments are associated with metabolic changes normally associated with aging, including lipodystrophy, dyslipidemia, and insulin resistance, all of which increase the risk of cardiovascular disease (Morse and Kovacs 2006). Thus, HIV disease is associated

not only with premature immunosenescence, but also in treatment-associated acceleration in the appearance of many other physiological features of aging (Morse et al. 2007).

Concluding Remarks

Treatment advances have resulted in increased life expectancy for persons infected with HIV, which is leading to the "graying" of this cohort (Hinkin et al. 2001). In addition, the age of primary infection with HIV-1 is increasing, due to the greater levels of high risk behavior in older adults. The question of whether the immunological changes associated with HIV-1 infection synergize with those that occur during chronological aging has not been addressed. Elucidation of the underlying immune system basis for the relationship between age and HIV-1 disease progression will have far-reaching translational/treatment implications for the progressively increasing elderly population of HIV-1-infected persons. If it turns out that older HIV-infected persons have less immunological reserve, the timing of treatment initiation may require modification. Indeed, many of the current guidelines have been derived from correlations between CD4 T cell counts and opportunistic infection incidence in younger persons. In addition, since HIV-1 persists with exuberant ongoing viral replication and therefore vigorous chronic antigenic stimulation, particularly of the CD8 T cell pool, this infection constitutes an ideal model to study the effects of chronic antigenic stimulation on immune dysfunction. It is anticipated that the convergence of immunological studies in the areas of HIV disease and aging will undoubtedly lead to new paradigms for medical care and vaccine strategies for both situations.

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