

Cytomegalovirus, Aging, and HIV: A Perfect Storm

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Abstract

The success of highly active antiretroviral therapy in preventing progression of HIV-infected individuals to AIDS has greatly reduced the burden of opportunistic infections. Individuals with HIV infection are living longer, but as a group are at greater risk to develop age-related disorders, such as certain cancers, cardiovascular disease, type II diabetes, and cognitive impairment, at earlier ages than non-HIV-infected persons. This premature susceptibility to age-related morbidities reflects a syndrome referred to as accelerated aging, wherein deleterious features associated with aging emerge decades earlier in the setting of chronic HIV infection. A prominent immunological feature of accelerated aging in HIV infection is inflation of cytomegalovirus-specific memory T-cell responses to levels associated with an immune risk phenotype. In the absence of HIV infection, immune risk phenotypes develop in cytomegalovirus-infected octogenarians and signify some degree of immune senescence and an elevated risk for all-cause mortality. Chronic inflammation is a probable factor in health risks conveyed by the immune risk phenotype and in putative relationships between cytomegalovirus infection and the same set of age-related disorders arising in chronic HIV infection. Most HIV-infected individuals are cytomegalovirus-seropositive, both HIV and cytomegalovirus are associated with inflammation-related morbidities, and HIV infection accelerates the development of cytomegalovirus-dependent immunological abnormalities. Therefore, closer investigation of the relationship between cytomegalovirus and age-related morbidities emerging in chronic HIV infection appears warranted. This review summarizes evidence that cytomegalovirus could be an important cofactor in the development of age-related morbidities in HIV infection and discusses research to address underlying mechanisms. (AIDS Rev. 2012;14:159-67)

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Key words

HIV. CMV. Aging. Immune risk phenotype. Immune senescence. Cardiovascular disease. Cognitive impairment. Inflammation.

Introduction

Cytomegalovirus (CMV) infection is widespread, persistent, and increases in prevalence with age. Like other human herpes viruses, CMV coevolved with its host over an extended period to establish a mostly benign

or perhaps even symbiotic relationship¹. However, in settings of immune suppression, deficiency, or immaturity, CMV becomes a highly virulent, life-threatening pathogen^{2,3}. This striking dichotomy illustrates how through inter- and intra-generational adaptation, an immunological interface with CMV evolved to mitigate viral disease, while allowing persistence and transmission. By outstripping the pace of biological evolution, rapid socio-environmental changes are straining this generally benign relationship. The pervasive adoption of unhealthy lifestyles and, paradoxically, general increase in longevity are two underlying factors pressuring the host-CMV equilibrium. Recent studies indicate that CMV infection elevates the risk for all-cause mortality in the elderly population (> 80 years) and raises the risk for a number of age-related morbidities, reaching

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Table 1. Characteristics and significance of cytomegalovirus-related immune risk phenotype in HIV infection

Characteristic	Significance	Impact of HIV infection
Peripheral blood CD4 ⁺ /CD8 ⁺ T-cell ratio < 1	Numerical and functional deficit of helper T-cells	Exacerbation
Increased fraction of CD57 ⁺ CD8 ⁺ T-cells	Accumulation of CD8 ⁺ T-cells at stage of replicative senescence marked by shortened telomeres	
Decreased fraction of CD28 ⁺ CD8 ⁺ T-cells	Reduced vaccine responsiveness, immunosenescence	Exacerbation
Reduced <i>in vitro</i> response to T-cell mitogen concanavalin A	Reduced <i>in vivo</i> response to infection	
Resistance of CMV-specific CD8 ⁺ T-cells to apoptosis	Enrichment of CMV-specific CD8 ⁺ T-cells in T-cell repertoire	Unknown
Oligoclonal T-cell repertoire with > 10% of CD8 ⁺ T-cells specific for CMV	Reduced T-cell repertoire diversity Increased risk of all-cause mortality	Exacerbation Acceleration

CMV: cytomegalovirus.

greater prominence in the general population. This suggests emerging links between CMV infection, the ill effects of unhealthy diet and lifestyle, and age-related health deterioration. In HIV infection, development of the same age-related morbidities is accelerated, as is a striking tumescence of the immunological interface with CMV⁴. Most age-related morbidities emerging prematurely in HIV infection are associated with inflammation, a feature that also potentially links CMV infection to cardiovascular disease (CVD) in the general population and to all-cause mortality in the elderly⁵. Therefore, accelerated aging and chronic inflammation, factors continuing to challenge clinical management of HIV infection despite the success of HAART, may synergize dangerously with CMV infection and other risk factors to fuel the pathogenesis of disorders with an inflammatory component or etiology⁶. Despite the success of HAART in suppressing HIV replication itself, conditions disposing to the acceleration and aggravation of the negative effects of CMV infection persist in HIV-infected individuals, as illustrated by CMV-specific CD8⁺ T-cell memory inflation to levels associated with the immune risk phenotype (IRP) at much younger ages⁴. This makes understanding the relationship between CMV infection and age-related morbidities an urgent priority for HIV research, with the potential for the acceleration of effects associated with the IRP a prominent feature for investigation.

The IRP manifests in elderly CMV-seropositive individuals as levels of immunological parameters in peripheral blood cross a threshold beyond which a number of negative health outcomes increase in likelihood.

Phenotypic changes symptomatic of an IRP are associated with reduced immune function, and IRP development in the elderly population clearly signifies increased risk for a number of morbidities and all cause mortality. Conversely, absence of an IRP is associated with longevity. Although these markers, described in greater detail in the immune risk phenotype section and summarized in table 1, generally increase with age, they do not reach levels associated with increased risk in all elderly individuals or even in all elderly CMV-seropositive individuals. The absolute magnitude of T-cell responses against CMV largely determines IRP development in the non-HIV-infected population. Markers associated with the IRP are also elevated by HIV infection, partially due to the immune response against HIV itself and partially due to accelerated CMV-specific CD8⁺ T-cell memory inflation. This magnified impact of CMV across shorter timeframes in HIV infection is an area of growing concern for the aging HIV-infected population. In addition, mechanisms by which CMV and other risk factors promote the pathogenesis of age-related morbidities in the general population may burn more brightly under investigation within the context of accelerated aging in HIV infection.

Immune risk phenotype

The IRP was originally identified as a predictor of non-survival over various lengths of follow-up in a large Swedish study of determinants of longevity in the elderly⁷. Cluster analysis of immunological parameters defined the IRP as CD4⁺/CD8⁺ T-cell ratios < 1 (normal is ~2),

increased fractions of CD8⁺ T-cells that don't express CD28, and low *in vitro* T-cell responses to the mitogen concanavalin A (Con A). Subsequent analysis found that just a CD4⁺/CD8⁺ T-cell ratio < 1 alone was sufficient to signify an IRP⁷⁻⁹. Since the IRP is defined by immunological parameters, increased mortality associated with the IRP likely reflects a level of immune dysfunction predisposing to multiple age-associated morbidities. The features diagnostic of an IRP primarily reflect aberrant accumulation of CMV-specific CD8⁺ T-cells with a restricted TCR repertoire and distinct phenotype¹⁰⁻¹². The predominant phenotype of CD8⁺ T-cells comprising the IRP, with an absence of CD28 and expression of CD57, has important functional implications¹³. For naive T-cells, CD28 is an accessory molecule that delivers a co-stimulatory signal critical for activation and proliferation¹⁴. Expression of CD28 also reflects the capacity to produce interleukin-2 (IL-2), a central autocrine and paracrine T-cell growth factor¹⁵. Once T-cells undergo initial activation and proliferation, CD28 co-stimulation is dispensable for effector function, and therefore, T-cells lacking CD28 include effector cells and effector memory cells, both with limited regenerative capacity^{16,17}. While the function of CD57 itself is unclear, its expression can denote terminal differentiation of CD8⁺ T-cells towards cytotoxic effector function, replicative senescence, and shortened telomeres^{18,19}. Thus, the CD28-CD57⁺ phenotype of CMV-specific CD8⁺ T-cells accumulating in later life matches their function in that they are generally characterized as cytotoxic effector memory cells that proliferate poorly and produce interferon- γ (IFN- γ), but not IL-2, when stimulated with antigen^{20,21}. Relative resistance to apoptosis is another functional abnormality of these cells that may contribute to their prevalence in the aging T-cell repertoire²². Their aberrant features and inordinate levels of expansion notwithstanding, CMV-specific memory T-cells do provide protection against direct CMV disease. However, this expanded oligoclonal CD8⁺CD28-CD57⁺ T-cell population, which depresses the CD4⁺/CD8⁺ T-cell ratio, reduces T-cell repertoire diversity, lowers the fraction of naive T-cells, and portrays immune senescence, is associated with potentially destructive immunological tendencies and undeniably negative outcomes. In the absence of CMV infection, or if CMV-specific T-cells comprise only a small fraction of the CD8⁺ T-cell repertoire, an IRP does not develop²³. Therefore, bringing CMV under lifelong control with fewer CD8⁺ T-cells may ultimately reduce a number of health risks.

The T-cell receptor repertoire

The T-cell receptor (TCR) repertoire of young healthy persons includes well over 1×10^6 different clonotypes, none of which individually occupies a sizable fraction of the repertoire. In contrast, octogenarians often have oligoclonal TCR populations with individual clones occupying > 10% of the repertoire²⁴. This substantial clonal outgrowth within normally diverse repertoires was once considered completely benign, in that it did not portend lymphoma or leukemia. It also did not initially appear to reflect any overt health risk over that of octogenarians without oligoclonal T-cell populations. Like benign oligoclonal gammopathy, oligoclonal T-cell expansions were viewed as a cumulative effect of adaptive immune responses across a long lifespan and not as risk factors for complications likely to lower octogenarian life expectancy. However, for a variety of reasons, the number and fraction of individuals living past 80 years of age is rapidly increasing and recent studies addressing factors associated with living to 90, or even 100, have revealed the salience of abnormal TCR repertoires²⁵. Oligoclonal TCR expansions were found to underlie the CD8⁺ T-cell changes producing the IRP that signifies increased risk for all-cause mortality in the elderly⁷. The changing demographics of our population and the growing burden of age-related morbidities make understanding the relationship between oligoclonal T-cell populations, IRP, and healthy aging a priority for public health research in general.

The role of CD8⁺ T-cells

Most of the oligoclonal T-cell populations that arise in octogenarians express CD8, a coreceptor identifying T-cells with clonotypic receptors specific for peptides presented by class I human histocompatibility-linked leukocyte antigens (HLA)²⁴. Class I HLA-restricted T-cells are critical for recognition, suppression, and clearance of intracellular pathogens, especially viruses, which are the primary source of antigenic peptides presented by class I HLA. In an unexposed individual, naive virus-specific CD8⁺ T-cells are generally present at frequencies below $1/10^4$ T-cells. During acute infection, these relatively rare precursors are selectively activated to proliferate and acquire effector functions that enable viral suppression. Once the virus is eliminated or effectively controlled, the T-cell population relaxes towards a new resting state, with TCR representation only subtly altered by an increased frequency of now antigen-experienced, memory T-cells specific for

that virus²⁶. Viruses that avoid elimination to establish chronic infection continue to recruit and activate CD8⁺ T-cells, which progressively skews the T-cell repertoire towards higher frequencies of virus-specific cells with activated or memory phenotypes²⁷. Virus-specific T-cells that fail to eliminate or effectively suppress the virus acquire a phenotype distinct from effector or stable memory T-cells, become dysfunctional, and often undergo apoptosis²⁸. Thus, ongoing recruitment, activation, and frustration of virus-specific T-cells in chronic infections creates a CD8⁺ T-cell population markedly distinct from the relatively quiescent populations of young, healthy, uninfected individuals^{27,29}. Phenotypic analysis of the oligoclonal CD8⁺ T-cell populations in elderly individuals implies they are immunological imprints from protracted exposure to particular intracellular pathogens. As the fraction of the TCR repertoire occupied in this way grows with age, it influences the CD4⁺/CD8⁺ T-cell ratio, as well as functional and phenotypic characteristics of CD8⁺ T-cells in a way that manifests in the elderly as an IRP, and signifies increased risk for all-cause mortality^{10,30,31}.

The role of cytomegalovirus

Some viruses, most notably herpes viruses, effect an acute infection, become latent, and then reactivate at unpredictable intervals. This leads to cycles of virus-specific T-cell expansion, viral latency, cessation of T-cell recruitment, and population of the memory cell compartment. Such recurrent viral reactivations conceivably create the IRP of aged individuals by enlarging virus-specific memory T-cell pools with each cycle³¹. Of the common human herpes viruses, CMV or human herpes virus-5 (HHV-5) creates the most notable imprint on the CD8⁺ T-cell repertoire. Acute CMV infection triggers massive CD8⁺ T-cell expansion and activation that, in the vast majority of cases, effectively contains the virus³². Although the activated CD8⁺ T-cell population then contracts, the small fraction preserved as memory cells increases the frequency of CMV-specific T-cells in the TCR repertoire²⁶. In most immunocompetent individuals, the response is sufficient for effective lifelong control of CMV disease. However, freedom from symptomatic CMV infection appears highly dependent upon ongoing immune surveillance against viral reactivation, as without treatment, severe CMV disease frequently occurs in the settings of transplant-associated immune suppression or immune deficiency, AIDS, and other immune disorders^{2,3}. Due to serial occult CMV reactivation throughout life and/or

other unknown factors, CMV-specific CD8⁺ T-cell numbers increase with age to a point that in a subset of aged individuals, they confer an IRP^{11,20,30,33}. Most of the CMV-specific CD8⁺ T-cells are reactive against one of two immunodominant CMV proteins, pp65 tegument or immediate early protein (IE)-1. While similar memory inflation could be rationally envisioned for other herpes viruses, only Epstein-Barr virus (EBV)-specific CD8⁺ T-cells occasionally combine with CMV-specific T-cells to contribute in any meaningful fashion to the IRP found in the elderly³⁴.

Systemic outcomes associated with immune risk phenotype

Numerous studies have documented an elevated risk of negative health outcomes stemming from CMV infection itself or from the IRP produced when a large fraction of the CD8⁺ T-cell repertoire is focused against CMV. Longitudinal studies of Swedish octogenarians first identified IRP as a major predictor of all-cause mortality^{7,35}. While the mortality rate from CVD levels off after age 80, the mortality rate due to infectious disease rises, indicating that immune function is an important determinant of longevity. The reduced *in vitro* proliferative responses to Con A described in subjects with an IRP possibly translates into reduced T-cell response capacity *in vivo* and increased susceptibility to infection³⁶⁻³⁸. Later follow-up studies of the same Swedish cohort showed 100% concordance between survival to 100 years of age and avoiding IRP development, reinforcing the idea of a pivotal role for effective immune function in survival²³. Negative effects from chronic CMV infection are also suspected in the less elderly, where CVD is the most common cause of death. A cross-sectional study of American subjects ≥ 45 years of age revealed an association between CMV seropositivity and history of CVD, defined as stroke, heart attack, and/or congestive heart failure³⁹. Longitudinal follow-up revealed CMV seropositivity *per se* was associated with all-cause mortality, while CMV seropositivity compounded by elevated levels of C-reactive protein, an acute-phase protein induced by proinflammatory cytokines, signaled increased risk for CVD-related mortality⁴⁰. These results suggest that subsets of CMV-seropositive subjects at greater risk for negative health outcomes can be distinguished by IRP, levels of proinflammatory cytokines, or by other markers of inflammation. Defining markers that reliably identify those at greatest risk may be an important step for proactive health care and a crucial step towards elucidating the pathological mechanisms in play.

Immunological outcomes associated with immune risk phenotype

Different components of the IRP can be interpreted as reflecting a tendency towards either immune atrophy or hyperactivity, both of which invite negative health outcomes. In terms of immune atrophy, the IRP includes poor proliferative responses to the T-cell mitogen Con A^{7,41}. If this *in vitro* manifestation reflects reduced T-cell responsiveness against pathogens *in vivo*, this could increase the risk of many infections. Another illustration of immune atrophy in the elderly is poor responsiveness to influenza vaccination, a feature independently associated with CMV seropositivity⁴²⁻⁴⁵. Reduced *in vitro* lymphocyte responses, increased susceptibility to infection, and poor vaccine responsiveness are functional correlates of immune senescence, which is implied directly by the preeminent phenotype of CD8⁺ T-cells comprising the IRP¹⁷. An inverted CD4⁺/CD8⁺ T-cell ratio generally confers poor immune responsiveness, while lack of CD28 and expression of CD57 on T-cells can signify an extensive replication history, culminating in short telomeres and replicative senescence^{16,17,35,46,47}. Thus, multiple elements of the IRP imply reduced immune function.

At the other end of the spectrum, elevated levels of the proinflammatory cytokine interleukin-6 (IL-6) also predict mortality in the old elderly⁴⁸. This, and the finding that elevated levels of C-reactive protein identify CMV-seropositive individuals at increased risk for CVD, suggests that a pathological link between CMV infection and inflammation or immune hyperactivity operates in a subset of individuals⁴⁰. Inflammation could be a major factor relating CMV infection to CVD in the general population and IRP to mortality in the elderly population. The pathogenesis of other morbidities associated with CMV seropositivity, such as type II diabetes in the general population, cognitive deterioration in the elderly, and pre-eclampsia in pregnant women, may also involve inflammatory processes⁴⁹⁻⁵⁴.

HIV infection

The impact of CMV infection and the associated IRP on morbidity and mortality is potentially aggravated in settings where the relevant risk factors are reinforced. In HIV infection, CD4⁺/CD8⁺ T-cell ratios < 1 often persist despite HAART, oligoclonal T-cell expansions are common, more CD8⁺ T-cells bear markers of chronic activation and frustration, an elevated fraction of the CD8⁺ T-cell population is CD28⁻CD57⁺, and

coinfection with CMV is almost universal⁵⁵⁻⁵⁸. Inflammation is considered a key component of HIV pathogenesis and, most notably, CMV-specific CD8⁺ T-cell memory inflation to levels associated with the IRP occurs decades earlier than in non-HIV-infected persons^{4,6,59}. Now that HAART, where available, controls HIV replication itself, comorbidities have become the major clinical challenges of chronic HIV infection. The most prominent comorbidities are the same morbidities associated with aging and inflammation in the general population, such as cancer, CVD, type II diabetes, and neurocognitive impairment^{5,6,60,61}. While chronological aging of the HIV-infected population is one factor in the emergence of these comorbidities, the importance of accelerated aging as a complication of HIV infection and of synergy between HIV and CMV in driving precipitous IRP development and immune senescence warrants investigation^{59,62}. The “perfect storm” of IRP-related risk factors coalescing in a prematurely aging HIV-infected population and its imminent impact on the health of HIV-infected persons emphasizes the need for expanded research on mechanisms linking asymptomatic CMV infection and IRP to morbidity and mortality (Fig. 1). If negative synergy between CMV and HIV increases with age, comorbid conditions complicating the HAART-extended lifespan in HIV infection could rapidly reinstate the importance of CMV coinfection, while foretelling an even broader emerging impact of CMV as more people live well past 80 years. In coinfecting individuals, the effects of CMV versus HIV in terms of contribution to IRP and the impact of IRP versus other factors related to chronic HIV infection and long-term antiretroviral therapy on health outcomes may be difficult to untangle. Subgroups of HIV-infected individuals with well controlled HIV replication need to be stratified by levels of inflammatory markers and by the fractional representation and phenotype of their CMV-specific CD8⁺ T-cells to assess relationships with comorbidities and to begin addressing the pathogenesis of comorbidities. Ongoing biomedical interest in inflammatory markers, CMV status, and age-related comorbidities, together with the well established interdisciplinary nature of HIV clinical care, extensive study cohorts, broad infrastructure, and other resources already in place, constitute a solid framework for conducting this research. Thus, the potential to expeditiously resolve pathological relationships relevant to both the aging HIV-infected and general population within this setting represents a compelling opportunity for productive collaboration between interdisciplinary teams of researchers and healthcare providers.

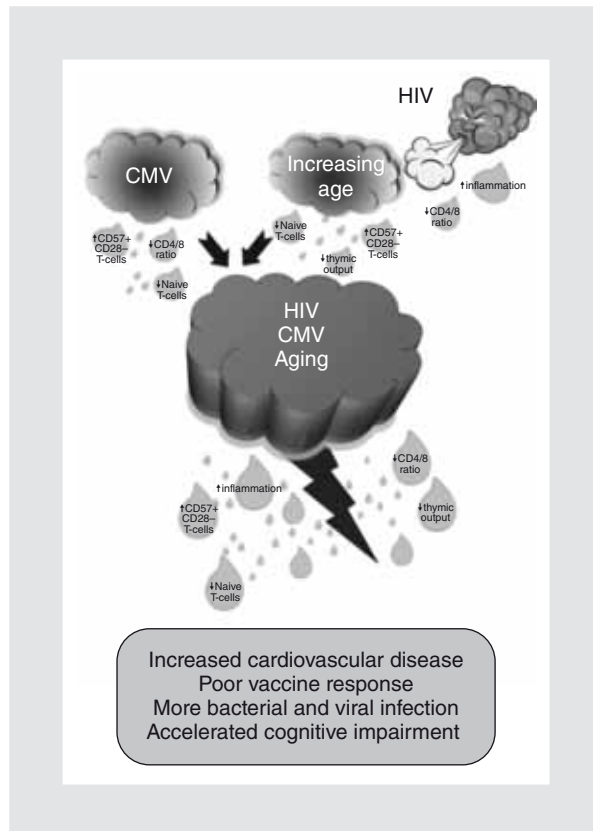


Figure 1. HIV and CMV coinfection accelerate and exacerbate development of the immune risk phenotype and associated morbidity. With aging, the immune system changes in a number of ways that reduce its ability to respond well to infectious insults. Naive T-cell frequencies decrease, thymic output is diminished, and a higher percentage of circulating T-cells appear terminally differentiated. Adding CMV infection to aging promotes oligoclonal expansion of CMV-specific T-cells and a decrease in the CD4⁺/CD8⁺ T-cell ratio. The downpour of immunologic decay associated with CMV and aging is swept forward by HIV infection, which exacerbates these changes within a setting further challenged by increased inflammation. The combination of factors has the potential to coalesce into the maelstrom depicted, with aggravated immune senescence and increased inflammation fueling an elevated risk for cardiovascular disease, cognitive impairment, and other age-related morbidities.

Etiology of cytomegalovirus associations with negative health outcomes

Atherosclerosis

The core mechanistic question raised by epidemiological associations between CMV infection and increased risk for multiple morbidities is how symptomatically latent infection manifests this increased risk. With regard to CVD, both CMV replication itself and the immune response against CMV can promote changes in endothelial cells that correspond to abnormal growth

and the pathogenesis of atherosclerosis. The secretome of CMV-infected endothelial cells contains proangiogenic factors including IL-6 and granulocyte macrophage colony stimulating factor (GM-CSF)^{63,64}. Interleukin-6 induces expression of survivin, a chemokine that promotes endothelial cell survival to compound the abnormal growth of vascular endothelium⁶³. Interleukin-8 (IL-8), a chemokine produced by CMV-infected endothelial cells, attracts neutrophils, which conceivably mediate endothelial cell damage to initiate cycles of cell damage, cell death, and cell growth⁶³. Immune cells responding to CMV infection can both independently activate cascades resulting in endothelial cell destruction and can aggravate the effects of the CMV secretome. When peripheral blood mononuclear cells (PBMC) from persons with strong anti-CMV T-cell responses were incubated with CMV antigens, IFN- γ and tumor necrosis factor released from the CMV-specific T-cells stimulated endothelial cell destruction with production of the chemokines fractalkine (CX3CL1), RANTES, and macrophage inflammatory protein-1- α (MIP-1 α)⁶⁵. While RANTES and MIP-1 α may perpetuate inflammation *in vivo* by recruiting leukocytes to the site, fractalkine appears to be a key mediator as its neutralization almost completely abrogated endothelial cell destruction⁶⁶. A recent study demonstrated an association between carotid artery intima-media thickness and frequency of CD4⁺ T-cells expressing the fractalkine receptor⁶⁷. This subset of T-cells could be localized to the coronary arterial wall, produced high levels of proinflammatory cytokines, and was comprised mostly of CMV-specific CD4⁺ T-cells⁶⁷. In light of these findings, the arterial wall thickening associated with CMV infection could plausibly involve direct effects of CMV replication, CMV replication with consequent activation of immune cells, or even latent CMV infection and residual immune activation with elevated levels of IFN- γ and IL-6^{63,64,68-70}. Thus, the link between CMV and atherosclerosis may reflect a complex constellation of viral, immunological, and interactive insults, culminating in cyclical growth, damage, and repair of endothelial cells. Similar immuno-viral collaboration might also underlie increased levels of proinflammatory agents linking CMV infection to other disorders.

Immune senescence

The cause or causes of functional immune senescence accompanying the IRP in later life are not clear. Chronic inflammation or immune activation may impair *de novo* immune responses, CD8⁺ T-cells comprising

the IRP may themselves be immunoregulatory, or the dedication of large fractions of the T-cell repertoire against CMV may erode the capacity to respond against other agents. In transgenic mice where senescent cells are flagged and made sensitive to elimination, removal of senescent cells from certain settings invigorated the function of those remaining, and delayed or even attenuated the ongoing development of age-related disorders⁷¹. Both CD57-expressing and CD28⁻ CD8⁺ T-cell subsets, which are enriched for senescent cells, were attributed immunosuppressive properties in previous studies of immune regulation⁷²⁻⁷⁵. More recently, substantial fractions of CMV-specific CD4⁺ and CD8⁺ T-cells have been categorized as regulatory T-cells, revealing another potential link between CMV and reduced immune function⁷⁶⁻⁷⁸. While the anti-CMV response seems to hold CMV in check, it is important to determine whether commitment of a large fraction of the T-cell repertoire against CMV reflects smoldering CMV replication or whether CMV-specific memory T-cell inflation occurs through an intrinsic immunological pathway. The decrease in inflammatory markers reported in HIV-infected individuals treated with valganciclovir suggests that in this population, some level of CMV replication underlies the relationship with increased inflammation⁷⁹. Likewise in the elderly population, higher levels of neopterin, a marker of monocyte activation, and stronger anti-CMV T-cell responses were found in subjects with detectable CMV DNA in their circulating monocytes^{80,81}. However, detectable CMV DNA in plasma has so far mostly been associated with clinical risk in HIV-infected individuals with CD4⁺ T-cell counts below 100/ μ l peripheral blood⁸². Longitudinal studies tracking the evolution of the CMV-specific T-cell response in concert with sensitive, multigene assessment of CMV transcription and translation are needed to address the relationships between CMV activation, inflation of the CMV-specific T-cell response, and immune dysregulation.

Immune risk phenotype development

An intriguing question for basic immunology is why CMV, uniquely among the herpes viruses, drives memory inflation to the extent seen. Reactivation of herpes simplex virus (HSV)-1 and HSV-2 is relatively common, and EBV persists at some level in circulating B-cells for life. Even in the setting of chronic active HIV replication with abundant HIV-specific T-cell responses, CMV-specific T-cells against several epitopes in just two of many CMV proteins can grow to dominate the CD8⁺

T-cell repertoire. Most remarkable is that this memory inflation occurs without overt evidence of CMV reactivation. The process leading to plentiful CMV-specific effector memory T-cells was effectively exploited with a CMV-based recombinant vaccine against simian immunodeficiency virus (SIV)⁸³. In this setting, the exceptionally strong response induced by the CMV-based vaccine effectively controls SIV replication in the absence of any short-term adverse effects. There is no obvious reason why CMV-specific T-cells would be uniquely poised to proliferate excessively or selectively acquire resistance to apoptosis. Therefore, the key to their inordinate accumulation may lie somewhere in the assembly of a unique interface between the immune system and CMV during acute infection. Under the influence of smoldering CMV activation, inherent immunoregulatory processes, or something else not yet suggested, this interface undergoes periodic renovation to eventually take shape as an IRP. Stratifying CMV-infected and CMV/HIV-coinfected populations into groups with different degrees of CD8⁺ T-cell repertoire commitment against CMV will be important for dissecting out whether aspects of CMV infection itself or aspects of the immune response against CMV underlie associations with increased inflammation and its many sequelae. Such stratification will also enable longitudinal research to discern the contribution of viral versus immunological mechanisms to the inordinate expansion and accumulation of CMV-specific T-cells. This will be key both for harnessing the benefits of this process towards vaccination and for intervening against a rising stream of negative health outcomes confronting the HIV-infected, elderly, and general populations.

Conclusion

Through many years of coexistence, the immune system and CMV have achieved a form of symbiosis, with hosts enjoying enhanced protection against certain collateral infections and CMV spreading through the population. However, in modern societies, diseases of affluence, such as type II diabetes and some forms of CVD, influence survival more than infections, thereby threatening the value of this symbiosis. The extended lifespan provided by medical and other advances has revealed a set of CMV-associated changes in the CD8⁺ T-cell repertoire that signify increased risk for short-term mortality. These changes are literally harbingers of death in the elderly, and are potentially markers of increased risk for multiple age-related disorders in the general population. The surfacing relationship between

CMV and morbidity is predicated on features especially prominent in HIV-infected persons, who, as a group, prematurely suffer a number of age-related morbidities. Therefore, mechanisms by which CMV infection raises the risk for age-related morbidities may operate earlier and with greater intensity in the setting of HIV infection. Investigating the accelerant effect of CMV on the development of immune senescence and other age-related morbidities in an aging HIV-infected population could expedite understanding of the more insidious, but potentially widespread, role of CMV in morbidity and mortality elsewhere. Ironically, together with the increase in lifestyle-associated diseases, extending longevity in general and the life expectancy of HIV-infected individuals in particular are key factors flushing apparently asymptomatic CMV infection into the foreground to draw reevaluation of its pathological potential.

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