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REVIEW

T-cell immunity against cytomegalovirus in HIV infection and aging: relationships with inflammation, immune activation, and frailty

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Abstract

Both aging and treated human immunodeficiency virus (HIV) infection are characterized by low-level chronic inflammation and immune activation which contribute to the development of age-related diseases, frailty, and early mortality. Chronic cytomegalovirus (CMV) infection is highly prevalent in older adults and HIV-infected populations. A number of studies have shown that CMV induces broad and strong T-cell responses in CMV-seropositive older adults and HIV-infected individuals. CMV infection rarely develops into clinical disease in immunocompetent individuals. However, a large body of literature has shown adverse effects of chronic CMV infection on the health and longevity of these populations. It has been hypothesized that chronic CMV infection may be a driver of chronic inflammation and immune activation, and may further contribute to the development of frailty. Thus, there is a need to better understand the extent of the impact of chronic CMV infection on T-cell immunity and health in aging and HIV infection. In this review, we will address important considerations and challenges in the assessment of chronic CMV infection and CMV-specific T-cell responses. We will then review recent data on relationships between T-cell responses to CMV and levels of inflammatory markers and immune activation, as well as the onset of frailty.

Keywords Cytomegalovirus · Frailty · CLIP · Immune activation · HIV infection · Aging

Introduction

Aging is accompanied by a chronic low-grade inflammatory phenotype (CLIP) marked by elevated levels of circulating inflammatory mediators including C-reactive protein (CRP) and interleukin 6 (IL-6) [1], as well as chronic immune activation, both of which are believed to contribute significantly to most age-related diseases such as cardiovascular and neurodegenerative disease, frailty, and cancer [2–4]. While it is believed that HIV-infected (HIV+) individuals experience accelerated aging of their immune system, they differ from the age-related immune changes, or immunosenescence, in HIV-uninfected (HIV−) older adults. For example, HIV infection results in the depletion of CD4 T cells, and likely massive destruction of the gut barrier. Nevertheless, in parallel with what is observed in the geriatric population, well-treated HIV+ persons exhibit elevated levels of inflammatory mediators and chronic immune activation despite effective viral suppression [5, 6]. Although chronic inflammation in treated HIV infection is likely the result of residual HIV replication, co-infections, or increased microbial translocation due to damage to the gut mucosa, markers of inflammation and immune activation that are elevated as well as their associations with comorbidities are very much alike between HIV− and treated HIV+ aging populations [7]. Although difficult to quantify, HIV+ individuals manifest earlier onset and increased prevalence of age-related comorbidities and frailty compared to HIV− aging population

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[7]. Frailty is a state of increased vulnerability resulting from decline in physiological reserve and dysregulation of multiple organ systems. CLIP and chronic immune activation are thought to contribute to frailty in the elderly and in HIV+ individuals [2, 8]. The etiology of CLIP and immune activation in aging is unknown, but chronic cytomegalovirus (CMV) infection is common in the older adult and HIV+ populations and is suspected to contribute to chronic inflammation and immune activation.

CMV is a beta-herpesvirus, and is the largest virus known to cause human disease. Following primary infection, CMV can maintain a state of latency in myeloid progenitor cells and monocytes, and can be reactivated following inflammatory immune response or critical illness such as sepsis, differentiation of infected cells, or immunosuppression, although the exact mechanisms and conditions that trigger reactivation remain to be further elucidated. CMV seroprevalence increases with age and reaches 90% in those aged 80 years and over and is almost universal in HIV+ populations [9–11]. CMV is unique in its ability to drive clonal expansion of CMV-specific T-cells even in the absence of overt active infection. This results in skewing of the T-cell repertoire towards CMV antigens, often comprising more than 10% of T-cells [11–20]. While CMV infection rarely leads to clinical symptoms in immunocompetent persons and is even thought to have protective effects in youth [21], a large body of literature has associated CMV infection with adverse outcomes in health and longevity [22–26]. However, these observations are for the most part derived from cross-sectional studies and insight into the mechanisms and causality behind these associations are still lacking, and longitudinal and mechanistic studies to explore causality are needed. In people with advanced HIV infection, inhibition of CMV replication using valganciclovir significantly decreased the percentage of activated ($CD38^+HLADR^+$) CD8 T-cells, supporting the idea of a link between CMV infection and immune activation [27]. However, the relationships of T-cell responses to CMV with CLIP, immune activation and onset of frailty in the HIV+ aging population have just begun to be elucidated. In this article, we will first address important considerations and challenges the assessment of chronic CMV infection and CMV T-cell responses. We will then review recent data on correlations between T-cell responses to CMV and levels of inflammatory markers and immune activation, as well as the onset of frailty.

Challenges in assessing chronic CMV infection

CMV is a complex virus whose infection presents a diagnostic challenge. CMV infection is considered a smoldering infection as the virus establishes latency, but may periodically reactivate in some cells or tissues, resulting in low-level viral replication. Traditionally, the most common method is the measurement of CMV-reactive antibodies, anti-CMV IgG for chronic infection and IgM primary or re-infection. Based on anti-CMV IgG serology, individuals are routinely classified as CMV-seropositive or negative, and some may use absolute anti-CMV IgG titers to assess CMV burden. Therefore, anti-CMV IgG serology is the current diagnostic paradigm for chronic CMV infection both in older adults and in HIV+ aging individuals. However, anti-CMV IgG serology is a crude measure that merely indicates prior exposure to the virus. It does not allow to assess the degree or frequency of reactivation and low-level viral replication. A longitudinal analysis of a subset of participants from the Women's Health and Aging Studies (WHAS) II showed essentially no change in absolute anti-CMV IgG titers over a 12-year follow-up period, indicating limited utility, if any, of this measure for monitoring of chronic CMV infection [18]. Other diagnostic evaluation tools include different PCR methods including nested PCR and droplet digital PCR (ddPCR) for the detection of cell-associated CMV DNA which may allow more accurate evaluation of the current state of CMV infection and reactivation [28]. We have shown that the presence of CMV UL123 and UL93 DNA in monocyte-enriched peripheral blood mononuclear cells (PBMCs) rather than anti-CMV IgG titers was associated with high frequencies of CMV pp65-specific CD8 T-cells in older adults [17]. This may explain why some studies reported no significant association between anti-CMV IgG titers and adverse health outcomes [28–30]. Although highly sensitive, nested PCR is a qualitative assay. On the other hand, ddPCR allows accurate quantification of low numbers of target DNA copies. One study reports that CMV prevalence and viral load in the peripheral monocytes increases with age in a cohort of healthy donors [31]. Future studies should validate these novel diagnostic tools and further investigate the relationship between chronic CMV infection as defined by these novel methods and T-cell responses to CMV.

Assessing T-cell responses to CMV has also proven to be a complex matter. A vast majority of studies assess T-cell responses to CMV by only measuring responses to the CMV phosphoprotein 65, pp65 (encoded by UL83) and immediate early-1, IE1 (UL123) epitopes through tetramer, pentamer or dextramer analysis, as it was assumed that these represented the dominant responses [12–15, 23, 32–35]. However, using ribosome profiling and transcript analysis, Stern-Ginossar et al. observed over 700 open reading frames (ORFs) in human CMV genome that are translated to protein in CMV-infected fibroblasts [36]. Although many of these proteins may only be short lived and non-functional, the antigenic potential of CMV is likely much greater than previously anticipated. In a study of 33 healthy CMV-seropositive

donors, peptide pools from 213 CMV ORFs (a total of over 13,000 peptides) were tested for immunogenicity, and 151 of these ORFs were recognized by either CD4 T-cells (44 ORFs), CD8 T-cells (26 ORFs), or both (81 ORFs) [19]. The ORFs recognized by CD4 and CD8 T-cells were different, but 8 of the 15 most recognized ORFs were common to both CD4 and CD8 T-cells including UL83 and UL123. In addition to the broad range of recognized CMV epitopes, the T-cell responses to CMV are highly heterogeneous. The number of CMV ORFs recognized by T-cells from healthy donors varied greatly from 5 to 55 ORFs. Thus, to accurately assess the overall CMV-specific T-cell responses, one or a few ORFs are not sufficient, at least the 19 top ORFs should be used to obtain an acceptable approximation of the overall T-cell response to CMV [19]. In 12 virologically suppressed HIV+ and 10 HIV− CMV-seropositive men from the Multicenter AIDS Cohort Study (MACS) of men who have sex with men (MSM), we evaluated CD4 and CD8 T-cell responses to the previously described 19 most recognized ORFs [37]. We found that only < 12% and < 40% of total CMV-specific CD4 and CD8 T-cells, respectively, responded to pp65 or IE1 peptide pools, and there was no difference between HIV+ and HIV− individuals. This supports the notion that data restricted to these two epitopes do not represent the overall CMV-specific T-cell immunity.

We and others have also demonstrated the heterogeneity in the magnitude and breadth of T-cell responses to CMV within older adults and within HIV+ individuals [37–39]. In several studies, although the mean number of CMV-specific T-cells was elevated in CMV-seropositive older age group, there was a large variation between individuals. Many of the individuals in the older age group had similar number of CMV-specific T-cells as seronegative or young individuals [20, 23, 28]. It remains unclear whether broader and greater T-cell responses are required for protection against CMV. Given the rarity of CMV-related disease in immunocompetent individuals, it is possible that very low and restricted T-cell responses are sufficient to protect from CMV disease. This raises the question of whether broader and greater T-cell responses are excessive and may prove to be detrimental by leading to immunosenescence, increased chronic inflammation and immune activation, and thereby contributing to frailty and other age-related chronic conditions.

T-cell responses to CMV, CLIP, immune activation, and frailty

The accumulation of CMV-specific T-cells as well as extensive T-cell responses to CMV likely contributes to CLIP and immune activation as these cells produce large amounts of inflammatory mediators such as interferon-γ, tumor necrosis factor-α (TNF-α) and IL-6. In the WHAS II cohort, the presence of CMV UL123 DNA was associated with elevated IL-6 levels [18]. In another study of community-dwelling older adults, the presence of CMV UL123 DNA in monocytes, but not anti-CMV IgG serology, was associated with elevated levels of neopterin, a marker of monocyte and macrophage activation which has also been associated with frailty in older adults [29, 40].

More recent data from 22 virologically suppressed HIV+ and 20 HIV− men from the MACS show that T-cell responses to 19 CMV ORFs are correlated with serum levels of inflammatory mediators [41]. Although CMV titers were not measured in these participants, all men exhibited positive T-cell responses to CMV. Generally speaking, T-cell responses to CMV were broad with high inter-person variation. Strong correlations between both CD8 and CD4 T-cell responses and inflammatory and immune activation markers in the HIV+ non-frail as well as HIV− frail and non-frail participants. Correlations with cytokines and activated CD4 and CD8 T-cells were positive, while correlations with chemokines were generally negative [41]. Furthermore, in these same individuals, CD4 T-cell IL-2 responses to UL83 or UL123 alone were not correlated with elevated levels of CPR, but the total CD4 T-cell IL-2 response to all 19 CMV ORFs was (Fig. 1). In another study of HIV+ individuals, CMV-specific CD4 T-cells responses were associated with CD8 and CD4 T-cell activation, but not with inflammatory markers [42]. However, only T-cell responses to CMV-pp65 and glycoprotein B (gB) were assessed. Once again, this supports the need to investigate the responses to more than a few antigenic epitopes when assessing responses to CMV infection. While these new data support a role for T-cell responses to CMV in chronic inflammation and immune activation, it is important to note that an age-related increase in levels of inflammatory mediators CPR, IL-6, TNF-α is also observed in CMV-seronegative individuals [43]. Thus, other mechanisms may contribute to CLIP and immune activation in older adults.

It has been hypothesized that CMV infection could contribute to frailty through chronic inflammation or CLIP [44]. In the WHAS I and II cohorts, chronic CMV infection assessed by positive CMV IgG serology has been associated with frailty, the association was particularly strong in participants with high IL-6 levels suggesting a possible link between CMV infection and frailty through increased inflammation [24]. We were also able to show that a high CD4 T-cell IL-2 response to CMV was predictive for the onset of frailty in HIV- non-frail men. However, this was not the case for HIV+ non-frail men [41]. Whether HIV infection modifies T-cell response to CMV and/or its relationship with CLIP in aging MSM or general aging population deserves further investigation.

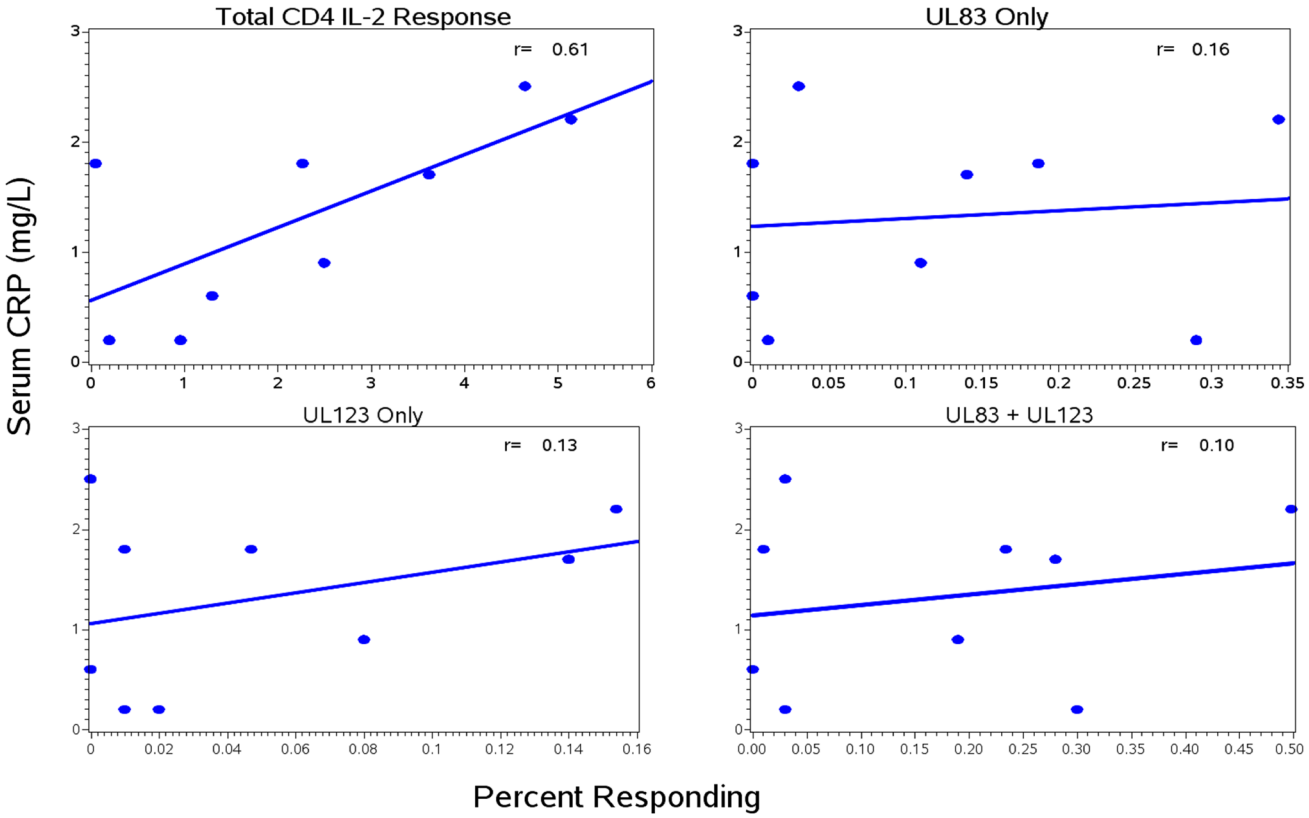

Fig. 1 Correlations between cytomegalovirus-induced CD4 IL-2 responses and serum C-reactive protein (CRP). CD4 T-cell IL-2 responses to CMV-pp65 (encoded by) UL83 or IE1 (UL123) alone or together are only poorly correlated with serum CRP while the total CD4 T-cell IL-2 response to peptide pools encoded by all 19 CMV open reading frames is strongly correlated with elevated serum CRP levels

Concluding remarks

Recent data support the hypothesis that T-cell responses to CMV could explain much of CLIP and immune activation in people with treated HIV infection and in older adults. However, it remains challenging to distinguish the direct effect of CMV on CLIP and immune activation from other potential etiologic mechanisms. To this end, the role of CMV reactivation should also be further investigated. Additional investigations including longitudinal and treatment studies are needed. These studies should take frailty status into account. Recently developed novel evaluation tools, especially T-cell responses to a broad range of epitopes and diagnostic methods of chronic CMV infection such as nested PCR and ddPCR should facilitate more accurate assessment of the immunological burden of CMV and its impact on CLIP and immune activation, and possibly its role in the pathogenesis of frailty and other age-related chronic conditions.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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