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Herpesvirus-Specific CD8 T Cell Immunity in Old Age: Cytomegalovirus Impairs the Response to a Coresident EBV Infection

Naeem Khan,2* Andrew Hislop,* Nancy Gudgeon,* Mark Cobbold,* Rajiv Khanna,† Laxman Nayak,‡ Alan B. Rickinson,* and Paul A. H. Moss*

Aging in humans is associated with increased infections and the reduced proliferative capacity of T cells, part of the more global phenomenon termed immune senescence. The etiology of immune senescence is unknown but the accumulation of virus-specific memory T cells may be a contributory factor. We have examined CD8 T cell responses to two persistent herpesvirus infections, CMV and EBV, and to a recurrent virus infection, influenza, in different age cohorts of healthy donors using HLA-peptide tetramers and intracellular cytokine detection. Of these, CMV appears to be the most immunogenic, with the CD8 T cell response representing over 10% of the CD8 pool in many elderly donors. Interestingly, the effect of age upon EBV-specific responses depends upon donor CMV sero-status. In CMV seropositive donors, the magnitude of the EBV-specific immune response is stable with age, but in CMV seronegative donors, the response to EBV increases significantly with age. By contrast, the influenza-specific CD8 T cell immune response decreases with age, independent of CMV status. The functional activity of the herpesvirus-specific immune response decreases in elderly donors, although the characteristic phenotypes of CMV- and EBV-specific memory populations are retained. This demonstrates that aging is associated with a marked accumulation of CMV-specific CD8 T cells together with a decrease in immediate effector function. Moreover, infection with CMV can reduce prevailing levels of immunity to EBV, another persistent virus. These results suggest that carriage of CMV may be detrimental to the immunocompetent host by suppressing heterologous virus-specific immunity during aging. The Journal of Immunology, 2004, 173: 7481–7489.

The CD8 T cells play an important role in protection from viral infection and recognize viral Ags in the form of short peptides presented by MHC class I molecules at the surface of the infected cell. Primary infection leads to the activation of naive CD8+ T cells, which expand and differentiate into effector cells and ultimately give rise to a long-lived memory T cell population (1).

In elderly humans, notable changes are observed in several components of the immune system. One of the most striking observations is the accumulation of oligoclonal expansions of CD8 and CD4 T cells that together can comprise a significant component of the T cell repertoire (2). These expansions are believed to be memory T cells that have been repeatedly stimulated during the lifetime of the host and have accumulated to high frequency. Herpesviruses that elicit vigorous T cell responses, such as CMV and EBV (3–5), are never cleared from the host following infection, and in such cases the maintenance of latency is at least partly explained by persistent immune suppression of viral replication. The cellular immune response to such viruses is thus likely to contribute to memory T cell accumulation.

CMV is a ubiquitous β herpesvirus that usually causes an asymptomatic primary infection followed by subclinical persistent infection. The importance of the CMV-specific immune response is clearly demonstrated by the high incidence of viral reactivation that is observed in immunocompromised hosts such as allogeneic transplant recipients and HIV seropositive individuals. Experimental data from murine models and human transplantation studies have demonstrated that the CD8+ T cell response is of primary importance in control of CMV replication (6–9). The unusually high magnitude and differentiated phenotype of the CMV-specific CD8 T cell response has been documented in several studies (3, 10, 11).

CMV seropositivity is associated with significant changes in the immune repertoire such as an increase in the CD8+ T lymphocyte count and phenotypic alteration in lymphocyte subsets (12–14). These features appear to be more pronounced with aging, and an accumulation of CMV-specific CD8 T cells has been demonstrated in elderly donors (15). Such responses can measure up to 25% of the CD8+ T cell pool and are often clonally expanded from a single cell. This heavy investment in the CD8 T cell response against a single virus may compromise CD8 T cell repertoire diversity and the ability to respond to other pathogens. Indeed, CMV infection in the immunocompetent host may not be as benign as previously thought, and survival of CMV seropositive donors has been shown to be compromised in elderly individuals (16, 17).

Previous studies have documented the CMV-specific CD8 T cell response to a limited number of peptides derived from the immunodominant pp65 and IE-1 proteins, but functional analysis of such populations has been limited. Moreover, the magnitude and phenotypic profile of the CD8+ T cell response to other viruses in the same donors has not been determined. Here we have taken advantage of a number of recently described CMV epitopes (18, 19) to...
determine the magnitude, phenotype, and functional activity of CMV-specific CTL in healthy donors of three different age groups. In addition, an analysis of CTL specific for EBV or influenza has been performed in the same donors and the immune response compared between CMV seropositive and seronegative donors. The results demonstrate that CMV seropositivity affects the immune response to heterologous viruses and imply that carriage of CMV may not be without cost to an immunocompetent host.

Materials and Methods

Donors

Ethical permission was obtained for this study. All donors were healthy volunteers aged between 21 and 85 years that gave formal written consent to donate 50 ml of blood for the study. Blood was collected by venepuncture in heparinized tubes and separated immediately. CMV status was determined using the CMVscan test kit (BD Biosciences, Oxford, U.K.). DNA was extracted, from 5 ml of blood using a DNA blood kit (Qiagen, Crawley, U.K.), for molecular class I HLA typing conducted by the Blood Transfusion Service in Birmingham, U.K.

Peptides

All peptides were synthesized commercially by Invitrogen (Paisley, U.K.). Peptides used are listed in Table I. Hereafter, an abbreviated reference to each peptide is made, according to the first three amino acids. For example, the peptides GLCTLVAML and NLVPMVATV are referred to as GLC and NLV, respectively. The HLA-B8-restricted influenza peptide is designated as ELRS to avoid confusion with the HLA-B8-restricted CMV and NLV, respectively. The HLA-B8-restricted influenza peptide is designated as ELRS to avoid confusion with the HLA-B8-restricted CMV and NLV, respectively. The HLA-B8-restricted influenza peptide is designated as ELRS to avoid confusion with the HLA-B8-restricted CMV and NLV, respectively.

HLA-peptide tetramer synthesis

Tetramers were made as described elsewhere (20) with minor modifications. Tetramers incorporating the HLA-B7-restricted IE1-1-encoded peptide CRVLCYYVL could not be synthesized. This was because of our inability to successfully refold this HLA-B7 CRV complex (probably attributed to the highly reactive nature of the peptide), and so responses were inability to successfully refold this HLA-B7 CRV complex (probably at-

Results

High frequencies of CD8 T cells against multiple CMV Ags in old age

An initial study described enhanced CD8 T cell responses in old age against pp65-derived peptides that were restricted through HLA-A2 and HLA-B7 (15). It is now becoming clear that a number of other CMV proteins are strong targets for the CD8 T cell response, and it was therefore necessary to expand the analysis to include several Ags and also a broader range of HLA types. A total of 156 donors that were involved in this study were grouped into three categories based on age. These were designated as young (20–40 year), middle-aged (40–60 years), and elderly (60 years and over). Donors were further split into CMV seropositive/seronegative groups and HLA typed to determine eligibility for study (expression of one or more of HLA-A1/A2/A68/B7/B8/B35 alleles). Using HLA class I tetramer complexes, we stained PBMC from the group of donors involved and quantified them as a proportion of CD8 T cells.

Staining experiments with novel tetramer reagents revealed that high frequencies of CTL against peptides derived from IE1 and pp50 were seen in several donors. The highest IE1-specific responses measured 32% against a single HLA-B8-restricted epitope (ELK), and combined IE1 responses were over 20% in another four donors (Fig. 1A). Overall, these responses were significantly higher in elderly donors than in both middle-aged (p = 0.0159) and younger age groups (p = 0.003). For analysis of the response against the HLA-B7-restricted CRV peptide IFN-γ responses were measured after 6-h peptide stimulation. This was because of technical problems involved in generating a HLA-B7 CRV tetramer. Again there were significantly higher responses in the older age group to this IE1-derived peptide with some cases where the IFN-γ-producing CD8 T cells were nearly 10% of the CD8 subset (see Table II).

CTL responses against pp50 were studied using the novel HLA-A1-restricted peptide VTE. Donors in the elderly age group had significantly higher frequencies of CTL against this peptide than donors in the young age group (p = 0.0059). Two donors had very
high responses at 32 and 21% of CD8 T cells, and several others had responses between 5 and 10% of the CD8 T cell repertoire (Fig. 1B).

pp65-specific responses were significantly higher in both the elderly age \( (p < 0.0001) \) and middle-aged \( (p = 0.0046) \) groups than the youngest age group (Table II). At least three elderly donors had responses above 10% of the CD8 subset, with the highest measured at 18% of the CD8 T cell pool (Fig. 1C) for the HLA-A*0201-restricted epitope (NLV). There were also strong CTL responses detected against both HLA-B*0702-restricted peptides (TPR and RPH) in elderly donors (Table II).

It appears that donor HLA type is strongly associated with target Ag choice. This is supported by the finding that all HLA-A1+ donors displayed a strong response against the pp50-encoded VTE peptide, whereas all HLA-A*0201+ donors had detectable levels of CD8 T cells specific for the pp65-derived NLV peptide. Furthermore, HLA-B8+ CMV seropositive donors showed bias toward making IE-1-specific CD8 T cell responses, as we did not observe any detectable response against the pp65-derived HLA-B80-restricted peptide (DAN).

Where possible, responses to the above CMV Ags were combined in individual donors to give a profile of the “global” CMV response (Fig. 1D). Interestingly, the increase in frequency observed between middle-aged and younger donors was statistically more significant \( (p = 0.0067) \) than the increase between elderly and middle-aged \( (p = 0.0352) \).

Comparison between CMV-, EBV-, and influenza A-specific CD8 T cell responses

An important question that arises from these observations is what happens to CD8 T cell immunity to other viruses with aging, in particular to another persistent herpesvirus such as EBV and to a nonpersistent (but occasionally recurrent) virus infection such as influenza? Donors were stained with tetramers refolded with influenza A proteins (see Table I). We observed little difference in the magnitude of CMV- or EBV-specific CD8 T cell frequencies in young and middle-aged donors; responses detected against most EBV peptides were quite comparable with those against CMV ranging from 0.1 to 6.5% of CD8 T cells (Fig. 1E). In elderly donors, EBV tetramer binding frequencies were significantly lower than the massive frequencies detected with CMV tetramers \( (p < 0.0001) \), although staining with EBV tetramers did reveal two cases where binding exceeded 10% of CD8 T cells. This difference was interesting given that both viruses are persistent and may present a similar constant challenge to the immune system.

These responses were compared with those against a nonpersistent virus, influenza A. The HLA-A*0201-restricted GIL epitope and the HLA-B8-restricted ELRS epitope were chosen on the basis of their immunogenicity in healthy young donors. CD8 T cell responses against influenza A were often undetectable in our elderly population using GIL and ELRS tetramers refolded with influenza peptides. Interestingly, these responses were far lower and often not detectable using tetramers (Fig. 1F). This represented a significant fall in the response when compared with younger \( (p = 0.0002) \) and middle-aged groups \( (p = 0.0018) \) and is probably explained by the nonpersistent nature of the virus.

Functional measurements of CMV- and EBV-specific CD8 T cells

Previous work in younger donors has shown that a large proportion of CMV-specific CD8 T cells were indeed functional. This was demonstrated by their ability to secrete cytokines and lyse peptide-loaded target cells in cytotoxicity assays (15). Recent reports have suggested a decline in the number of IFN-γ-producing CMV-specific T cells with aging (21). In this study, we compared the proportion of functional cells (IFN-γ-producing cells/tetramer-binding cells) with increasing age. This was calculated by dividing the number of CD8+ IFN-γ+ T cells, detected following peptide stimulation, by the number of CD8+ tetramer+ T cells. Representative plots of CMV and EBV peptide-specific responses are shown in Fig. 2, A and B. The collated results indicate that although the
proportion of IFN-γ-producing cells is quite high in young and middle-aged donors (69 and 74%, respectively; Fig. 2C), there is a fall in the proportion of functional CMV-specific CD8 T cells with age later on in donors aged over 60 years ($p = 0.0001$). In parallel, we also performed IFN-γ assays using EBV peptides in a subset of donors. We observed that the proportion of functional cells was lower than for CMV-specific CD8 T cells within each age group, and this ratio declined with advancing age ($p = 0.0104$).

**Phenotypic analysis of CMV- and EBV-specific CD8 T cell responses**

CMV-specific CD8 T cells typically exhibit a highly differentiated membrane phenotype (3, 10) that is commonly associated with effector memory T cells (22). A comparison of the membrane phenotype of CD8 T cells specific for a range of viruses has shown that CMV-specific CD8 T cells are driven toward a more differentiated state than EBV-specific CD8 T cells (11). We thus compared the phenotype of T cells specific for both CMV and EBV in our donors. The analysis was performed in donors with detectable responses to either of the three CMV Ags described above and to both EBV lytic and latent cycle Ags. Fig. 3 shows an example of such staining, and the summarized data from all donors studied is displayed in Fig. 4. CD8 T cells directed against CMV Ags are highly differentiated, as indicated by extremely low levels of CD28 and CCR7. There is more diversity in CD27 and CD45 isoform expression, although the trend is for low levels of CD27 and high levels of the CD45RA marker. We did not observe a hierarchy in differentiation patterns between the three CMV Ags studied. In contrast, EBV-specific CD8 T cells were much less differentiated. This was manifested in the maintenance of CD27 and CD28 on a significant proportion of cells, as well as less reversion to the CD45RA isoform than observed with CMV-specific CD8 T cells. In addition, CMV-specific CD8 T cells expressed high levels of CD57 and perforin but very little CD62L. This contrasted with EBV-specific CD8 T cells, which expressed low to intermediate levels of CD57 and perforin and low levels of CD62L (data not shown). However, despite the phenotypic difference between CMV-specific and EBV-specific CD8 T cells within individuals, there did not appear to be any significant difference in phenotype of virus-specific CD8 T cells between young and elderly donors (Fig. 4).

**Influence of CMV status on EBV-specific immunity**

Given the very significant impact that CMV infection can have on the memory T-cell repertoire, we asked whether CMV status might influence prevailing levels of immunity to EBV. We thus proceeded to compare EBV-specific responses in CMV-seropositive vs CMV-seropositive donors in the different age groups.

Fig. 5 illustrates some typical examples of the levels of EBV tetramer staining observed when comparing between CMV seropositive and CMV seronegative elderly donors using our tetramer

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**Table II. Virus-specific CD8 T cell responses in healthy elderly donors**

<table>
<thead>
<tr>
<th>Ag</th>
<th>HLA Restriction</th>
<th>Peptide</th>
<th>Donors/ Mean</th>
<th>Range of</th>
<th>Donors Tested</th>
<th>Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV A1</td>
<td>VTE</td>
<td>19/19</td>
<td>3.4</td>
<td>0.2–32.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE-1 pp50</td>
<td>A1</td>
<td>8/19</td>
<td>0.24</td>
<td>0–1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV pp65</td>
<td>B8</td>
<td>7/13</td>
<td>2</td>
<td>0–13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV A1</td>
<td>VLE</td>
<td>14/26</td>
<td>1.25</td>
<td>0–22.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE-1 pp50</td>
<td>A2</td>
<td>26/26</td>
<td>3.5</td>
<td>0.1–18.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV A1</td>
<td>VLE</td>
<td>14/26</td>
<td>1.25</td>
<td>0–22.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE-1 pp50</td>
<td>A2</td>
<td>26/26</td>
<td>3.5</td>
<td>0.1–18.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values indicate tetramer binding frequencies of CD8 T cells.

* Frequencies for the CMV-specific CD8 T cells were derived by detection of peptide-induced IFN-γ (B7-CRV monomers could not be refolded).

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**FIGURE 2.** Comparison of IFN-γ production by herpesvirus-specific CD8 T cells. PBMC were either stained with tetramers or stimulated for 6 h with viral peptides and stained for intracellular IFN-γ. For each donor a ratio of IFN-γ- tetramer binding was derived and plotted for each age group. Representative flow cytometric plots of both tetramer staining and IFN-γ staining are shown of two young donors in the left and EBV-specific responses on the right. Frequencies shown within each plot represent the tetramer-binding/IFN-γ-producing cells (boxed) of the total CD8 subset. The summarized data from all donors tested is shown in C, with donors shown in A and B marked accordingly.
FIGURE 3. Phenotype of herpesvirus-specific CD8 T cells in young and elderly donors. Representative phenotypes are shown for one young (A) and one elderly donor (B). PBMC were stained with tetramers, anti-CD8, and for a third marker. Frequencies shown indicate the percentage of tetramer-binding cells that express the marker as shown on the x-axis.
panel. Quite clearly there appear to be higher frequencies of EBV-specific CD8 T cells in the CMV seronegative subgroup. Statistical analyses (Fig. 6A) revealed no difference in EBV-specific CD8 T cell frequencies in the two groups of younger donors. However, there does appear to be an increase in EBV responses in CMV seronegative donors in middle age \((p = 0.0341)\), and a clearly significantly difference was seen between CMV seronegative and CMV seropositive elderly hosts \((p = 0.0002)\). This is also evident when examining absolute numbers of EBV-specific CD8 T cells (Fig. 6B). Thus EBV-specific CD8 T cell frequencies in CMV seronegative elderly donors could be quite high, with up to 14% detected in one individual against a lytic epitope and a latent epitope, whereas in CMV seropositive donors the response detected never exceeded 3% of CD8 T cells.

EBV-specific CD8 T cells were then compared for phenotypic differences in CMV seropositive and seronegative donors (Fig. 7). A difference in membrane phenotype was observed between EBV lytic and EBV latent responses, as documented previously (23). Lytic responses displayed more reversion to the CD45RA\(^+\) phenotype and significant loss of CD28 and CCR7. In contrast, the latent responses were predominantly CD45RO\(^+\) and maintained CD28 and CCR7. However, we did not observe any significant differences in phenotype between the CMV seropositive and CMV seronegative groups for either latent or lytic EBV responses.

Discussion

The human immune system shows a functional decline during aging with major alterations such as thymic involution, changes in lymphocyte counts, impaired responses to mitogens and Ags in vitro, clonal expansions, and immune senescence (12, 24, 25). One characteristic of immune senescence is an accumulation of CD28\(^-\) CD57\(^+\) CD8 T cells in elderly individuals, which has been linked directly with reduced immune responsiveness. This population of cells has reduced proliferative potential and is often clonally expanded (26).

CMV is now appreciated as a potent immunogen that may trigger a very large CMV-specific CD8\(^+\) T cell response. An increase in the number of CD57\(^+\) CD8 T cells within peripheral blood has been correlated with CMV seropositivity, and this subset may be...
The disparity in frequency may be explained by a number of mechanisms. Despite both viruses being immunogenic in their own right, there are fundamental differences in their biology that could tilt the balance of immune responses more toward CMV. Whereas EBV undergoes latency in B cells (29), CMV targets cells of the myeloid lineage such as CD34+ stem cell progenitor cells (30). These cells become latently infected by CMV and through differentiation into monocytes or dendritic cells allow CMV reactivation to occur. Such events of CMV reactivation may occur more repeatedly in life than for EBV, resulting in more frequent presentation of CMV peptides to CD8 T cells. Further complexity is added when we consider that CMV encodes for several proteins that function to block MHC processing and presentation (reviewed by Reddehase in Ref. 31). Nonetheless, highly differentiated CD8 T cell responses are present in many CMV seropositive donors against Ags expressed across the virus replicative cycle, suggesting that immune evasion is overcome in vivo. In addition to direct recognition of endogenous Ag in virally infected cells, CD8 T cell responses can be primed and stimulated by the indirect presentation of exogenous Ag captured by dendritic cells as shown for CMV recently (32).

Another explanation may be that some CMV-specific T cells are more cross-reactive than EBV-specific T cells with self or other pathogen-derived Ags. This has been reported in murine heterologous infection (33) and may be true in humans, as shown for CD4 responses to CMV (34). To date, there are no data illustrating cross-reactivity of CMV-specific CD8 T cell responses for other Ags, although there are for an EBV-specific response (35).

Although making conclusions, we must also note that we do not have any information regarding the time of primary virus infection in the donors analyzed. This may vary between individuals considerably and be an important factor in determining the size of the response. Heterologous virus infection has been well studied in mice, where it appears that attrition of T cell responses occur to previously encountered virus Ags upon infection with a second and then third virus (36). To date, a longitudinal study of the maturation of CMV-specific immunity from primary infection has not been conducted largely due to the asymptomatic nature of primary CMV infection and consequent difficulty in identifying cases for study.

Of the relatively few reports on primary CMV infection, there has been one interesting recent study in asymptomatic infection in utero. Marchant et al. have shown that a mature and functional CD8 T cell response to CMV occurs in fetal life (37). During acute infection, these cells show an early differentiation phenotype (CD27−, CD45RO) and express activation markers (CD38 and Ki67). Subsequently, these cells very quickly acquire a more differentiated (CD27−, CD45RA−) resting phenotype (CD38−, Ki67−), as observed in adults. This suggests that CMV is particularly efficient at stimulating the expansion and differentiation of CMV-specific T cells even early in life. EBV does appear to drive some differentiation to CD45RA−CCR7− very quickly in the postinfectious mononucleosis phase (23), but this is not as exaggerated as with CMV even after several years of infection. This is despite some responses being driven to immune exhaustion soon after primary infection (38).

We have also demonstrated functional immunity to herpesviruses in healthy elderly donors by IFN-γ staining poststimulation with viral peptides. Although optimal peptide concentrations required for CMV- and EBV-specific reactivities were not determined, it is likely that maximal responses were achieved at the high concentrations used. A high proportion of CMV-specific CD8 T cells (tetramer+) can produce IFN-γ within 6 h, whereas a lower proportion of EBV-specific CD8 T cells display this property.
through all age groups. This correlates with a difference in membrane phenotype between the two responses. Whereas CMV-specific CD8 T cells are predominantly CCR7+, both lytic and latent EBV-specific CD8 T cells maintain CCR7 expression to higher levels. The loss of CCR7 is associated with effector function, whereas expression of CCR7 represents a central memory subset of Ag-specific cells that migrate to lymph nodes and do not display effector function (22, 39). However, it appears that there are a large number of dysfunctional cells against both CMV and EBV in elderly donors, a phenomenon that has been reported by others (21). This challenges the model of T cell memory described above, as nearly all CMV-specific CD8 T cells appear to be CCR7− and should therefore be effector cells. Yet this is clearly not the case, and it is thus reasonable to conclude that even within the CCR7− subset there is functional heterogeneity. This is further emphasized by the present finding that function (as measured by IFN-γ release) can fall with age whereas phenotype remains unchanged.

We have previously shown that the frequency of pp65-specific CD8 T cells increases with age. This finding was reproduced using a new cohort of donors and was also demonstrated for both IE-1 and pp50-specific CD8 T cell responses. The highest CD8+ CTL responses were often directed toward IE-1- and pp50-derived peptides, up to 32% against single epitopes in both cases. When combined responses against the different CMV proteins were measured in individuals, the responses were also significantly higher with age, reaching up to 45% of the CD8 subset. The data in this study clearly demonstrate massive CD8 responses to CMV that accumulate with age. As the frequency of known responses can represent nearly half of all CD8 T cells in some donors, it is plausible that CMV is the most immunogenic pathogen known in healthy virus carriers. In fact, such numbers are comparable to transplant recipients where the viral load is much higher due to the imposed immunosuppression during treatment. One possible explanation for such high responses may be elevated virus load in old age, although we have not succeeded in detecting CMV in blood from these donors as is the case for the vast majority of healthy asymptomatic CMV carriers.

Studies on individuals aged over 80 and 90 years have shown that certain parameters are associated with increased mortality (16, 17). These include higher CD8 and decreased CD4 T cell counts and poor proliferative response to mitogens. These characteristics are significantly associated with CMV seropositivity. In a follow-up study, the authors then showed high responses against a single CMV epitope in some of these very old donors (21). Our study is more comprehensive due to the inclusion of 10 CMV epitopes and a number of EBV and influenza A epitopes and provides more compelling data on the magnitude of CMV-specific responses.

The findings in this study highlight the significant investment in immunity to combat persistent herpesvirus infections. Whether these are benign T cell expansions that pose no threat to the priming and/or maintenance of T cell responses to heterologous pathogens requires further study. Interestingly, a recent review has discussed the role of pathogens with immunosenescence (40). This has provoked debate on the potential application of CMV vaccination as a preemptive measure against the accumulation of CD28− CD8 T cells (which are predominantly CMV-specific) to counter the onset of immune senescence. Our study adds to the body of data showing the deleterious nature of CMV carriage.
Indeed, this may represent a public health issue that future work should seek to address.

Acknowledgments

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References


