

Is immunosenescence infectious?

Graham Pawelec¹, Arne Akbar², Calogero Caruso³, Rita Effros⁴,
Beatrix Grubeck-Loebenstein⁵ and Anders Wikby⁶

¹University of Tübingen Medical School, Center for Medical Research, ZMF, Waldhörnlestr 22, D-72072 Tübingen, Germany

²Department of Immunology and Molecular Pathology, The Windeyer Institute For Medical Sciences, Royal Free and University College Medical School, 46 Cleveland Street, London W1T 4JF, UK

³Università di Palermo, Dipartimento di Biopatologia e Metodologie Biomediche, Gruppo di Studio sull'Immunosenescenza, Corso Tukory 211, 90134 Palermo, Italy

⁴David Geffen School of Medicine at UCLA, Department of Pathology and Laboratory Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1732, USA

⁵Austrian Academy of Sciences, Institute for Biomedical Ageing Research, Immunology Division, Rennweg 10, A-6020 Innsbruck, Austria

⁶School of Health Sciences, Jönköping University, Department of Natural Science and Biomedicine, P.O. Box 2038, Banarpsgatan 39, SE-551 11 Jönköping, Sweden

Herpes viruses are endemic. Once established, the virus is never eliminated but persists throughout life. The fraction of infected individuals gradually increases with age, such that the majority of elderly people are cytomegalovirus (CMV)⁺, Epstein–Barr virus (EBV)⁺ and Varicella⁺. Clinically relevant reactivation of Varicella causes painful shingles; CMV reactivation can cause fatal pneumonia. Overt reactivation, even in the very elderly, occurs only in immunocompromised individuals; however, the necessity for maintaining immunity to these viruses is costly. We argue that this cost is not only reflected in the requirement for continuous immunosurveillance against these viruses but, more importantly, results in a re-configuration of T-cell immunity due to the accumulation of dysfunctional virus-specific cells, which fail to be eliminated from the system. Thus, we hypothesize that it is the chronic antigenic stimulation by CMV (and possibly other persisting antigens) that leads to an increasing prevalence of senescent, dysfunctional T cells, and therefore contributes to more general alterations in the immune system, which are associated with earlier mortality.

Maintenance of protective immunity against cytomegalovirus (CMV) is clearly essential, which is graphically illustrated by earlier experiences in bone marrow transplantation (reviewed in Ref. [1]). Nonetheless, early reports of viral reactivation suggest that immunity is a continuous battle even in normal healthy persons [2]. At that time, the composition of the different T-cell subsets was just being identified, and, concurrently, reports were appearing that CMV infection could markedly alter components of those subsets [3]. One of the early studies showed an increased number of CD8⁺ cells in normal healthy donors and even identified expansions of CD8⁺CD57⁺ (HNK-1⁺) subsets in CMV seropositive individuals. It was over a decade later that differences between young and old donors were assessed in the context

of CMV status [4]. That study reported that CMV seropositivity was associated with an increased number of both CD4⁺ and CD8⁺ cells, which were CD28⁻. Importantly, the authors pointed out that this phenotype had previously been associated with age; however, they found that it was primarily associated with CMV status and only secondarily with age, given the increasing frequency of CMV-infection with age. However, both age and CMV status influenced the number of CD8⁺ cells and their expression of CD45RA and CD28.

Role of CMV in determining the 'immune risk phenotype'
Age-associated changes in the immune system have been extensively documented over the years, without reference to CMV status (Box 1). However, two different approaches have recently begun to shed more light on the unexpected way in which CMV infection shapes the ageing human immune system. The first is the development of tetramer technology, enabling direct identification of T cells carrying receptors for single peptide epitopes. The second is the

Box 1. Alterations in the T-cell compartment with age

- ↑ CD45RO⁺ cells (reviewed in Ref. [41])
- ↑ CD95⁺ cells (reviewed in Ref. [41])
- ↓ CD28 expression (reviewed in Ref. [41])
- ↑ CD152 expression (reviewed in Ref. [41])
- ↑ killer cell lectin-like receptor G1 (KLRG-1) expression [15]
- ↓ apoptosis of CD8 cells (reviewed in Ref. [41])
- ↑ apoptosis of CD4 cells (reviewed in Ref. [41])
- ↓ interferon-γ (IFN-γ) production; meta-analysis [42]^a
- ↓ ? interleukin-2 (IL 2) production; meta-analysis [42]^b
- ↓ telomere lengths (reviewed in Ref. [41])
- ↓ telomerase induction (reviewed in Ref. [41])
- ↑ DNA damage (reviewed in Ref. [41])
- ↓ DNA repair (reviewed in Ref. [41])
- ↓ stress resistance and heat-shock protein (HSP) expression (reviewed in Ref. [41])

^aData from meta-analysis: of 23 studies, 11 reported decreased IFN-γ production, 8 no change and 4 an increase.

^bData from meta-analysis: of 28 studies, 14 reported decreased IL 2 production, 3 no change and 11 an increase.

Corresponding author: Graham Pawelec (graham.pawelec@uni-tuebingen.de).

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deployment of longitudinal studies of the naturally ageing population to begin to identify factors predicting mortality. In the Swedish longitudinal study, known as the OCTO study [5], age-related changes in several immune parameters are being investigated by monitoring a free-living population over time. Values for a cluster of parameters, including high CD8, low CD4 and poor proliferative response to concanavalin A (Con A), were found to predict higher two-year mortality in a relatively homogeneous population from this one city, selected only by virtue of having survived to the age of 80 [6]. This cluster was designated the 'immune risk phenotype' (IRP) [7] (Box 2). These results were confirmed in a second two-year follow-up, which also showed that additional individuals had moved into the IRP category during those two years [8]. Later, it became apparent that CMV seropositivity was significantly associated with the IRP [9]. The immune changes were confirmed in the subsequent Swedish NONA longitudinal study [10], which pinpointed the CD8⁺CD27⁻CD28⁻CD57⁺CD45RA⁺ phenotype as markedly expanded for individuals in the risk category. Importantly, this study also indicated that the risk phenotype was independent of the health status of the individual at that particular time [11]. Therefore, at least in the already elderly population, a cluster of immune parameters, including CMV status, can be identified, which accurately predicts mortality. What causes an individual to reside in the IRP category or to move into it as they age? Our hypothesis is that this state is strongly influenced by the ability of the individual to manage the consequences of CMV infection.

The OCTO and NONA samples have now also been examined using MHC-peptide tetramers capable of identifying CD8⁺ T cells from HLA-A*0201⁺ donors; these CD8⁺ T cells carry T-cell receptors for the immunodominant human CMV pp65-derived epitope Nlypmvatv. Although these studies were limited to only one HLA allele and one CMV epitope, interesting preliminary data have emerged [12]. It has been confirmed that, in this

population, marked expansions of CD8⁺CD28⁻ cells are frequently found in the elderly and that large numbers of these cells have receptors of exactly this CMV specificity [13]. These expansions presumably represent an adaptive physiological response, emphasizing the importance of controlling CMV [and other herpes viruses: Epstein-Barr virus (EBV)-specific T cells are also more frequent in the elderly than in the young, although their frequency is ten-fold lower than the CMV-specific cells [14]]. But why are they commonly present in much larger numbers than in the young? One clue came from the discovery that a very high proportion of such CMV-specific cells in these elderly also expressed high levels of the negative regulatory killer cell lectin-like receptor G1 (KLRG-1) [15]. This molecule is thought to be present on end-stage senescent cells, which, although they might retain cytotoxic function, are less able to secrete cytokines, such as the antiviral agent interferon- γ (IFN- γ). It is possible that the ability to secrete IFN- γ is more important for maintaining immunosurveillance than direct cytotoxicity, at least in the case of CMV. Moreover, there was a significant correlation between the degree of expansion of these CMV-specific cells and the assignment of the donor to the IRP category. Follow-up studies on these donors are being performed.

Other investigators have shown that expansions of CMV-specific cells in the elderly are indeed clonal, occasionally biclonal [16]. This study also used tetramers containing a second CMV epitope, this time restricted by an HLA-B allele. They made the important discovery that when an elderly donor carried both the HLA-A and -B alleles, T-cell expansions to only one of the two epitopes are seen (HLA-B-restricted responses being dominant over HLA-A-restricted). Thus, it is necessary to examine a larger number of epitopes on a bigger set of HLA alleles to get the full picture. Moreover, these studies addressed only CD8⁺ cells because the production of MHC class II tetramers has thus far proven difficult. Using whole CMV antigen and cytoplasmic cytokine staining, however, large numbers of CMV-reactive CD4⁺ cells have also been identified. The donors tested were middle-aged and the indicator cytokine used was IFN- γ [17]; thus, it will be interesting to examine age-associated changes within the CD4⁺ subpopulation as well.

Box 2. The immune risk phenotype (IRP)

Longitudinal studies are beginning to show that an 'immune risk phenotype' can be determined in the very old. Importantly, this seems independent of current clinical health status.

Parameters included in the IRP

- * CD4:CD8 ratio of <1
- * Poor T-cell proliferative responses to mitogens
- * Increased CD8⁺, CD28⁻, CD57⁺ cells
- * Low B cells
- * Cytomegalovirus (CMV)-seropositivity

As hypothesized here:

- * Clonal expansions of CD8 cells carrying receptors for CMV or Epstein-Barr virus (EBV) antigens
- * A high proportion of dysfunctional cells among the CMV-specific CD8 cells, which are CD28⁻ but positive for a natural-killer (NK)⁻ receptor, killer cell lectin-like receptor G1 (KLRG-1), cannot proliferate, secrete little interferon- γ (IFN- γ) but retain interleukin-10 (IL-10) secretion capacity.

Note that the IRP consists of a cluster of these parameters, not each parameter individually. Which are the most important and which additional factors are involved remains to be determined.

Impact of immune system obsession with CMV on other immune responses

Intuitively, one might feel that the presence of large expansions of CD8 cells specific for a single CMV epitope, together with lesser expansions of those specific for other herpes viruses, such as EBV, must have some impact on general immunity, especially when these expansions might represent >25% of all peripheral CD8 cells in some individuals. But is there any evidence for this? As mentioned earlier, the number of CMV-specific cells constitutes part of the IRP defined in longitudinal studies; this is strong evidence for the clinical relevance of such cells.

The clonal expansions of CMV-reactive CD8 T cells (at least that majority that are CD45RO⁺), which accumulate progressively with age, resemble CD8 T cells that are driven to the end-stage of replicative senescence in cell

culture in response to repeated rounds of antigen-driven proliferation. Like the CD45RO⁺ differentiated T cells reactive to CMV and EBV isolated *ex vivo*, senescent CD8 T-cell cultures do not express CD28 and have shortened telomeres [18–20]. In fact, the oligoclonally expanded cells within the CD8⁺CD28⁻ T-cell population generally have even shorter telomeres than the CD28⁻ subset as a whole [21], suggesting extensive proliferation, presumably in response to chronic antigenic exposure. The minority of CMV-specific CD45RA⁺ cells found in the elderly studied in the OCTO context, however, might constitute a different population: one that remains capable of proliferation and IFN secretion (albeit at low levels, see Ref. [15]), as shown in young donors [22]. The same applies to EBV-specific CD8⁺CD45RA⁺ cells [23]. Nonetheless, in the OCTO study, the majority of both CD45RA⁺ and CD45RO⁺CD8 cells are CD28⁻, indicating a lack of co-stimulation for T-cell activation, which could result in the blockade of either activation-induced cell death or further clonal expansion.

What causes this accumulation of dysfunctional CMV-specific cells in the elderly? At this stage, one can only speculate. What seems clear, and is also seen in *in vitro* models of chronic antigenic stress, is that CD8 cells acquire apoptosis resistance at senescence. The reason for the difference between individuals with large apoptosis-resistant expansion, compared with those of the same age with expansions similar to those seen in middle-aged donors, is also unclear. Obviously, a genetic influence cannot be discounted. There is a significant role for inheritance in host immune responses to infections. Both HLA-linked genes and other genes, in particular cytokine genes, are increasingly being identified as influencing the susceptibility to, or the course of, a particular infectious disease [24]. For example, possession of HLA-DR7 in AIDS patients or kidney transplant recipients is a risk factor for CMV infection and/or its complications (reviewed in Ref. [25]). However, in adult blood donors, the presence of both the tumour necrosis factor 2 (TNF2) (-308A) and the interleukin-1 receptor antagonist (IL-1RA) allele 2 (IL1RN*2) is significantly more frequent in CMV-seronegative subjects. These last data suggest that alleles within the MHC (e.g. TNF genes), some of which are known to be associated with a strong inflammatory reaction, might have a protective role against CMV infection [26]. Thus, an immune system polymorphism modulating the type and intensity of the immune response might determine the outcome of CMV infection, and hence the accumulation of dysfunctional cells in old age.

Whereas senescent CD8⁺ cells *in vivo* and *in vitro* show apoptosis resistance [27,28], CD4⁺ cells seem to become increasingly susceptible to apoptosis with age, at least *in vitro* [29]. Increased resistance of CD8⁺ cells and increased susceptibility of CD4⁺ cells to apoptosis could explain the inverted CD4:CD8 ratio in the elderly, which is also part of the IRP. In addition, telomerase activity, which compensates for the telomere attrition associated with the massive clonal expansion of virus-specific CD8⁺ T cells in the blood [23] and also the lymphoid tissue [30] during the acute infection with herpes viruses, is progressively diminished in CD8 T cells during repeated rounds of antigen-driven proliferation [31].

Further evidence for a clinical impact of chronic CMV infection can be derived from studies investigating whether there is a correlation between clinically relevant vaccination procedures and CMV status. For influenza vaccination, CMV seropositivity and high proportions of the associated CD8⁺CD28⁻ T cells correlate with markedly diminished antibody responses [32–34]. Here, the concept of filling the ‘immunological space’ might be applicable – the presence of so many CMV-specific cells dilutes out cells with other specificities. Alternatively, and perhaps more probable, CD8⁺CD28⁻ T cells might actually exert suppressive influences on immune function. Indeed, cells with this phenotype have been associated with a variety of suppressor cell functions *in vivo*, in such diverse situations as organ transplantation and autoimmune diseases [35]. In this context, it is of interest that the number of IL-2- and IL-4-producing memory T cells of an early differentiation stage is extremely low in elderly persons who fail to raise a humoral immune response following vaccination [36]. Recent evidence suggests that these persons suffer from latent CMV infections accompanied by high numbers of CD8⁺CD28⁻ effector cells (S. Schwaiger *et al.*, unpublished). This indicates that latent CMV infections are associated with a change in the composition of the CD8⁺ T-cell pool in old age, namely a loss of early memory cells, but an increase in the number of highly differentiated cells.

The majority of these CD8⁺ CMV-specific cells are dysfunctional (in terms of IFN- γ production, at least). Interestingly, a similar loss of antigen-specific IFN- γ production has been observed in HIV-specific CD8 T cells that are driven to senescence in cell culture [37] and is also seen *ex vivo* in influenza-vaccinated elderly persons [38]. The small fraction of functionally intact cells in the IRP elderly is still similar in overall number to those present in the young and CMV reactivation is not known to occur. Nonetheless, a shorter remaining life expectancy awaits them. This is presumably not due to greater difficulty in containing CMV infection, but must be caused by some consequence of the accumulation of so many cells. It will be important to establish causes of death in this study.

Remediation?

Given that large clonal expansions of CMV-specific cells contribute to the IRP and therefore mortality, but knowing that this is not due to lack of immune control of the virus, it is legitimate to ask whether deleting these unnecessary cells would improve matters for the individual. Possibilities for remediation in the IRP category might include attempting to reverse the putative apoptosis resistance of the CMV-specific cells, for example, using bcl-2 iRNA. Re-introduction of CD28 might also cause the cells to recover function and allow homeostatic processes to eliminate excess cells. The feasibility of the latter approach has been demonstrated *in vitro* using CD8⁺CD28⁻ CMV-specific cells into which the re-introduction of CD28 by retroviral vector reconstituted IL 2 production capacity [39]. Alternatively, enforced expression of the catalytic component of telomerase (hTERT), which enhances proliferative potential and antiviral function in HIV-specific CD8 T cells [37], might be a useful strategy. Finally, physical removal of the

CD28⁻ T cells might enable expansion of more functional CD8 T cells and expansion of the repertoire. The most promising, simple, cost-effective and safest approach would, however, be to prevent the accumulation of CD28⁻ effector T cells right from the beginning. Because CMV seems to be the main driving factor for their expansion, early vaccination against CMV should be considered. Application of antiviral agents might also become an option because these are already in use in other contexts. Promising immunization strategies against CMV are being discussed [40], but so far have been viewed as hardly worth further development in view of the small number of potential beneficiaries presently considered. This view would be drastically changed by the acceptance of the fact that protection from CMV infection could delay or prevent the onset of immune senescence.

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