Available online at www.sciencedirect.com
SCIENCE DIRECT
Mechanisms of Ageing and Development 127 (2006) 538–543
mechanisms of ageing and development
www.elsevier.com/locate/mechagedev

Human cytomegalovirus infection and T cell immunosenescence: A mini review

Sven Koch [a], Rafael Solana [b], Olga Dela Rosa [b], Graham Pawelec [a,*]

[a] Center for Medical Research (ZMF), University of Tübingen, Waldhörnlestr. 22, D-72072 Tübingen, Germany
[b] Department of Immunology, University of Córdoba, Hospital Reina Sofia, Ave. Menedez Pidal s/n, ES-14004 Córdoba, Spain

Available online 2 March 2006

Abstract

The mammalian immune system defends the organism against pathogens, and possibly cancer, but is known to become dysregulated with increasing age. This results in greater morbidity and mortality due to infectious disease in old people. The most important changes occur in T cell immunity, manifested sometimes dramatically as altered clonal expansions of cells of limited antigen specificity and a marked shrinkage of the T cell antigen receptor repertoire. At the same time, it was independently reported that CMV seropositivity was associated with many of the same T cell changes that were being identified as biomarkers of immune ageing. It has now become clear that CMV is commonly the driving force behind the oligoclonal expansions and altered phenotypes and functions of CD8 cells seen in most old people. These changes are much less obvious in centenarians and most extreme in people whom longitudinal studies have shown to possess an ''immune risk profile''. This is a cluster of immunological parameters of which CMV seropositivity is one component and which predicts incipient mortality in an elderly population. Taken together, these findings suggest the hypothesis that persistence of CMV as a chronic antigenic stressor is a major contributor to immunosenescence and associated mortality.

Keywords: T cell; CMV; CD8 cells; Immunosenescence

1. Introduction

The β-herpesvirus CMV is an activating virus persisting mostly in myeloid cells but also sometimes found in certain other cell types. Once infection is established, viral containment becomes a priority of the immune system, but complete elimination is never achieved. There are potentially interesting correlates between CMV and other persisting sources of antigen, the most notable being in immunogenic cancers, in terms of the detrimental effects of both predominantly on T cells. Clinically, CMV infection is assumed to be asymptomatic in normal hosts, with T cell memory rapidly established and maintained indefinitely. The vital importance of maintaining defence against an asymptomatic infection is dramatically demonstrated in immunosuppressed people, where viral escape is commonly fatal. However, it has recently been recognised that even immunocompetent people may quite commonly display symptoms of CMV infection, such as malaise, fever, sweats and abnormal liver function (Wreghitt et al., 2003). Moreover, instances, albeit rare, where CMV can have serious consequences even in immunocompetent hosts are beginning to emerge; these studies also implicate age as a risk factor (Galiatsatos et al., 2005). Nonetheless, even the very elderly generally maintain efficient CMV immunosurveillance and clinically-distressing symptoms do not occur (unlike the situation with the related virus Varicella Zoster, responsible for chickenpox and reactivating usually in later life as the very painful ''shingles'' syndrome, defence against which decreases with age). However, the price paid for this constant CMV vigilance may be high. Earlier reports had documented alterations in CD8+ T cell subset surface phenotypes very similar to those being found in ageing but caused by CMV infection (Looney et al., 1999). Thus, apparent age-associated changes may in fact be secondary to the age-associated increases in prevalence of CMV infection. This realisation, coupled with the identification of CMV infection (as diagnosed by CMV seropositivity) as the putative driving force behind the

* Corresponding author.
E-mail addresses: grahampawelec@aol.com, graham.pawelec@uni-tuebingen.de (G. Pawelec).

0047-6374/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mad.2006.01.011

age-associated CD8 clonal expansions that had been noticed many years previously in middle-aged to elderly humans (Posnett et al., 1994; Olsson et al., 2000) emphasised the unexpected impact of CMV on age-associated alterations to the T cell immune system. This is now being analysed in terms of the CD8 cell antigenic specificity (Khan et al., 2002, 2004), their surface phenotype (Wills et al., 2002) and function (Pittet et al., 2001). These phenomena are not limited to humans, although in mice they are not due to CMV. It is likely that they are caused by that other main source of chronic antigenic stress sadly often found also in humans, namely cancer antigens (Li et al., 2002; Posnett et al., 2003; Pawelec et al., 2005b).

2. CMV pp65 (495–503)-specific CD8 cells

It is well established that in the elderly very significant changes in CD8 lymphocyte subset distribution occur. In particular a dramatic decrease of naïve CD8 cells accompanied by the expansion of effector and effector-memory cells is observed in ageing. The possibility that this abnormal phenotype is due to the oligoclonal expansion of CMV-specific CD8 T cells has been previously proposed by ourselves and others (Pawelec and Solana, 2001), although it was unclear if the accumulation of CMV-specific CD8 T cells is a major factor contributing to the phenotypic changes found in CD8 cells in immunosenescence.

We have studied one subset of CMV-specific T cells by investigating CD8 cells binding HLA-A2/pp65 (495–503) tetramers and assessing their functional status using specific antigenic compared to mitogenic stimulation. The phenotypic analysis of these pp65 (495–503)-specific CD8 cells has demonstrated that the proportion of cells coexpressing CD27 and CD28 is strongly decreased in the elderly when compared with young individuals (Fig. 1A). Furthermore, studying differentiation stages as defined by Sallusto et al. (2004) by the combined use of CCR7 and CD45RA also showed that while in young individuals a significant proportion of CMV-specific CD8 cells are included in the naïve subpopulation (CCR7+CD45RA+), in elderly donors CMV-specific CD8 T cells exhibit a phenotype associated with effector-memory (CCR7null CD45RA low) or effector (CCR7null CD45RA+) T cells (Fig. 1B). These results strongly suggest that CMV-specific CD8 cells show a different phenotype in young and old individuals indicating that they represent distinct differentiation stages, with a particular age-associated expansion of effector-memory 2 CD8 cells that do not express CD27, CD28, CCR7 or CD45RA and terminally differentiated effector cells with a CD27null, CD28null, CCR7null CD45RA+ phenotype (Fig. 1C) (Tomiyama et al., 2002; Wills et al., 2002; Rufer et al., 2003). The expansion of these highly differentiated CD8 T cells in the elderly seems to be restricted to CMV-specific T cells as it has been reported that EBV-specific CD8 T cells maintain expression of CD28 and have a lower expression of CD45RA than observed in CMV-specific CD8 T cells (Vescovini et al., 2004).

Several clear findings have emerged concerning the functional integrity of these CMV-specific cells, which can be profitably summarised here, because some seem to have created confusion in the past. The first finding is that on average the number of functional CMV-specific CD8 cells is quite similar in young and old individuals—if anything, the number is somewhat increased in many of the elderly, possibly reflecting increased viral load, but certainly not decreased (Ouyang et al., 2003a). In stark contrast, the number of dysfunctional CD8 cells carrying receptors for this CMV antigen is markedly increased in the elderly compared to the young (Ouyang et al., 2003b, 2004a,b). Second, although these cells do respond to mitogenic stimulation with IFN-γ release, they do not respond to antigenic stimulation, and are in this respect anergic (Ouyang et al., 2003a,b, 2004a,b). Third, many CMV-specific cells in the young express CD28 but very few in the elderly; and whereas essentially all cells in the elderly are killer cell lectin-like receptor G-1 (KLRG-1)-positive, significantly fewer are in the young (Ouyang et al., 2003a). KLRG-1 expressed by memory cells (CD28-negative) is a marker of end-stage differentiation and apoptosis resistance. It is interesting to note that our recent data suggest that in ''successfully aged'' populations of centenarians, it is exactly these parameters that more closely resemble the status of the young rather than the old (Table 1).

The main difference, therefore, between CD8+ CMV-specific cells in the young and old may be the relative proportions of KLRG-1- and CD28-bearing cells. In the elderly, there is an accumulation of KLRG-1-positive, CD28-negative cells; these have short telomeres and no proliferative capacity, but are resistant to spontaneous or induced apoptosis and so persist (Koch et al., unpublished results). In contrast, while cells of this phenotype already exist in the young, most CMV-specific cells are still CD28-positive and far fewer co-express KLRG-1. According to a recent report (Ibegbu et al., 2005) despite KLRG-1-positivity, these CD28+ cells are still capable of proliferation, whereas the CD28-negative, CD57-positives are not. This finding is consistent with the accumulation of CD28-negative, CD57-positive cells present preferentially in CMV-seropositive elderly donors belonging to the immune risk profile (IRP)-positive at-risk group in the Swedish OCTO/NONA longitudinal studies (Wikby et al., 2002). A striking finding in these longitudinal studies was that the number of

Table 1
Comparison of young, old and centenarians

	Young (<40)	Old (>65)	Centenarian (100)
Number of functional CMV-specific CD8 cells	+	+	+
Clonal expansion of CMV-specific CD8 cells	–	+	–
Fraction of CMV-specific cells KLRG-1-positive	Low	High	Low
Antigen responsiveness (IFN-γ secretion)	+	–	Nt
Mitogen responsiveness (IFN-γ secretion)	+	+	Nt
Apoptosis resistance	Low	High	Nt

Nt, not tested.