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Mini Review

Cytomegalovirus and immune senescence: Culprit or innocent bystander?

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ABSTRACT

Immune senescence may be defined as the age-related reduction and dysregulation of immune function, and has been associated with increased incidence and severity of infectious diseases and with poor efficacy of prophylactic vaccines in the elderly. Several studies have demonstrated that persistent infections with Herpes viruses in general and Cytomegalovirus (CMV) in particular have a profound influence on subset distribution, phenotype and potentially also on the function of T cells in ageing individuals. The association of CMV-seropositivity and accumulation of CMV-specific $CD8^+$ T cells with decreased survival in longitudinal studies of very elderly has fostered the hypothesis that CMV-infection may be an important causative factor for the development of immune senescence. Here, we have critically summarized the current body of evidence supporting this hypothesis, highlight some controversial issues about its relevance and mechanisms and propose areas of future research to demonstrate unequivocally whether and how persistent infections might compromise the ageing immune system.

1. Introduction

In the elderly, morbidity and mortality of infectious diseases like influenza and pneumonia is significantly increased whereas the protective efficacy of most prophylactic vaccines is substantially reduced (Castle, 2000). Among the many factors that contribute to poor immunity in the elderly we will focus on immune senescence which is defined here as the alterations that occur in the immune system of an individual due to and during the process of ageing, as opposed to changes that are associated with co-morbidity and overt disease. This definition also includes changes to the immune system emerging during a life time of pathogen exposure since the nature and frequency of these encounters are inevitably involved in the moulding and ageing of the human immune system.

Although it is highly likely that immune senescence is fundamentally implicated in failing resistance against infections and in poor efficacy of vaccines in the elderly population, direct evidence in humans is still very limited. However, it is clear that all facets of immunity are affected by the process of ageing and some of the most profound alterations on the level of an individual host concern the T cell compartment (Linton and Dorshkind, 2004). Therefore, induction of protective immunity after infection with intracellular pathogens or after vaccinations, which both require adequate T cell responses, seem to be most strongly affected by immune senescence. While cellular alterations contributing to immune senescence have been thoroughly investigated in vitro (Linton and Dorshkind, 2004), solid in vivo data about underlying causes and propagating mechanisms is rather scarce, particularly in humans. This is partially due to a paucity of studies that relied on 'hard', predefined and functionally relevant endpoints like survival, incidence and outcome of infectious diseases or protective immunity after vaccination.

2. Cytomegalovirus-infection and survival of elderly individuals

As a notable exception a series of Swedish cohort studies of community-dwelling very elderly individuals investigated immunologic predictors of survival and death – arguably the most stringent endpoints possible – and subsequently defined a so called 'immune risk phenotype or profile' (IRP) (Olsson et al., 2000; Pawelec et al., 2001; Wikby et al., 2002). Individuals aged above 85 years, exhibiting the characteristics of the IRP, were much less likely to survive the next 4 years compared to non-IRP individuals. The following parameters were included to characterise the IRP: CD4/CD8 ratio <1, reduced absolute numbers of B cells, accumulation of $CD8^+$ T cells expressing CD57 and lacking CD28, poor T cell proliferation after polyclonal stimulation and seropositivity for Cytomegalovirus (CMV). Since persistent CMV-infection is associated with the accumulation of large populations of $CD8^+$ T cells exhibiting a late stage differentiated phenotype ($CD28^-/CD57^+$) and poor proliferative capacity (Appay and Rowland-Jones, 2004; Gratama et al., 1987; Olsson et al., 2000), four out of five IRP-parameters are potentially influenced by CMV-infection. This find-

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ing put CMV under increasing scrutiny concerning immune senescence. However, the best single predictor for IRP and survival was an inverted CD4/CD8 T cell ratio and this was used in combination with serum IL-6 levels as a marker of low grade inflammation to predict 57% of deaths and 97% of 2-year survival in a subsequent study (Wikby et al., 2006). Further, individuals reaching the age of >100 years did not display the characteristics of the IRP neither at baseline nor during follow-up despite 70% of centenarians being CMV-seropositive (Strindhall et al., 2007). This suggests an association of 'successful ageing' with avoidance of the IRP and preferential survival of non-IRP individuals. Interestingly, the rate of CMV-seropositivity dropped from 87% to 80% within 6 years of observation and was only 71% in centenarians. Although only a low number of individuals could be assessed at later time points, this could indicate a trend that CMV-infection may be associated with a survival disadvantage very late in life. However, these findings need to be corroborated in epidemiological studies and in large and more diverse cohorts of elderly individuals. These studies should include detailed information about causes of death and potential confounders like socio-economic situation, activities of daily living and co-morbidities.

Overall, CMV-seroprevalence shows an age-associated increase within a population with some variation due to three independent factors: (1) most individuals acquire CMV-infection in early childhood but a moderate risk of CMV-infection persists throughout life with a second peak after puberty; (2) reversion of CMV-seropositivity does usually not occur; (3) life-style changes have gradually reduced the risk of CMV-infection in economically privileged societies leading to decreasing rates of seroprevalence (Staras et al., 2006). If CMV-infection indeed has a significant influence on survival of elderly individuals, the maximum of CMV-seroprevalence should be reached at a certain age-threshold and then gradually decline due to a survival advantage of CMV-negative individuals, as suggested by the trend observed by Strindhall et al. (2007). To address this question, sufficiently large epidemiological studies should be initiated in populations with different genetic and socio-economic backgrounds.

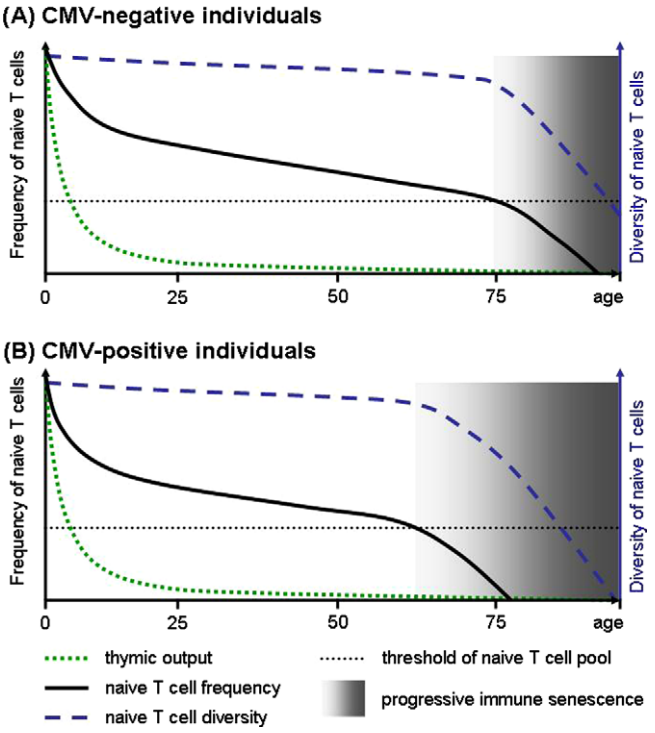

Fig. 1. Model of premature immune senescence by early dysregulation of T cell homeostasis in CMV-positive individuals. Green/dotted line: thymic output of naïve T cells; black line: frequency of naïve T cells; blue/dashed line: diversity of naïve T cells; fine dotted line: critical threshold of naïve T cell numbers; shaded area: dysregulation of T cell homeostasis and progressive immune senescence. (A) In CMV-negative individuals a critical threshold of low naïve T cell numbers is reached beyond the age of 75 years. Until this threshold is reached, T cell homeostasis is regulated and T cell diversity is maintained. Thereafter, decline of naïve T cell frequency and diversity is accelerated by dysregulated homeostatic proliferation. (B) In CMV-positive individuals the critical threshold of low naïve T cell numbers is reached earlier in life because of progressive accumulation of CMV-specific T cells. This leads to early breakdown of T cell homeostasis, accelerated loss of naïve T cell diversity and premature immune senescence.

3. Thymic involution, T cell homeostasis and naïve T cell diversity in the elderly

Maintenance of a diverse T cell pool into advanced age is paramount for the development of protective immune responses against new or evolving pathogens in elderly individuals (Nikolich-Zugich, 2008). Recent cross-sectional studies in humans and rhesus macaques have analysed the kinetics and the mechanisms responsible for age-associated repertoire shrinkage of naïve T cells (Cicin-Sain et al., 2007; Naylor et al., 2005). Using TCR excision circle (TREC) analysis, Naylor and co-workers confirmed that thymic output of naïve T cells in adults diminished by >95% between 25 and 60 years of age and was minimal thereafter (Fig. 1, green/dotted line) (Naylor et al., 2005). Nevertheless, naïve $CD4^+$ T cell diversity was maintained at an estimated 2×10^7 TCR β-chains until the age of 65–70 by a fairly constant rate of homeostatic proliferation. However, between the age of 70–80, T cell diversity crashed by two orders of magnitude to 2×10^5 TCR β-chains and this was accompanied by a doubling of homeostatic proliferation of naïve $CD45RO^-$ $CD4^+$ T cells (Naylor et al., 2005).

These findings were confirmed and extended in a recent study with aged rhesus macaques for both naïve $CD4^+$ and $CD8^+$ T cells: a strong negative correlation emerged between size and diversity of the naïve T cell pool and the rate of their homeostatic proliferation (Cicin-Sain et al., 2007). Since this association was not linear but logarithmic, a model emerged in which a minimal size of the naïve T cell pool exists, below which homeostatic proliferation becomes very prominent and potentially dysregulated, and this might be associated with a rapid decline in naïve T cell diversity (Fig. 1A). In these studies, naïve T cells were identified on the basis of phenotypic markers which may become more 'memory like' during phases of increased homeostatic proliferation which could lead to some underestimation of the compartment of truly naïve T cells (Goldrath et al., 2000; Pfister et al., 2006).

4. CMV-infection and T cell population dynamics

Obviously, studies focusing on thymic output and homeostatic proliferation mainly examine the production or input side of naïve T cells. To maintain equilibrium within the naïve T cell subset, the 'consumption' or output of naïve T cells needs to be sensed and regulated. Consumption of naïve T cells is increased for example by chronic antigenic challenge such as CMV-infection. Thus, the following question needs to be addressed: does CMV-infection and CMV-specific T cell responses consume sufficient immunologic resources to significantly decrease size and diversity of the naïve T cell pools, and to push the threshold of dysregulated homeostatic T cell proliferation and immune senescence to an earlier age (Fig. 1B)?

It has become clear in recent years that CMV-specific adaptive immunity is extremely prominent and occupies increasing T cell resources over time (Karrer et al., 2003; Khan et al., 2004; Snyder et al., 2008). We have introduced the term 'memory inflation' to