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Review

Naive T cells: The crux of cellular immune aging?

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ABSTRACT

When encountering foreign antigens, naïve T cells become activated and differentiate into effector and memory T cells. They represent therefore the primary source to mount an immune response against pathogens or tumors. Recent evidence of both quantitative and qualitative alterations of naïve T cells has accumulated in aged mice, indicating that the successful generation of primary T cell responses from the naïve T cell pool may be compromised with old age. However, the vast majority of the data supporting compromised naïve T cell priming efficacy with old age have been produced in animal models, and the situation is much less clear in humans. In the elderly, the involution of the thymus and the associated decline in thymic output result in a decreased number of naïve T cells, which is partially compensated by homeostatic proliferation. Emerging evidence suggest that alterations of the TCR repertoire diversity and intrinsic defects of old $CD4^+$ naïve T cells may impact on their responsiveness to antigenic stimulation. Increasing focus on the study of naïve T cells (in particular $CD8^+$) in old humans are needed to fill the gaps in our understanding of reduced cellular immunity with aging.

1. Introduction

Old age is associated with a significant decrease of the quality of life, in particular related to health deterioration. Elderly people suffer more often and more severely of infectious, autoimmune or malignant diseases than young individuals. Response to vaccination is also less effective in the elderly. For example, the effectiveness of influenza vaccine is estimated to be twice lower in people greater than 65 years of age; and the development of strong adjuvants is necessary to increase vaccine potency in this population (McElhaney, 2005). The decline of the immune system with age is thought to be the underlying factor behind these manifestations (Goronzy and Weyand, 2013). The study of the aging immune system, or immunogerontology, is therefore a public health priority with crucial implications to optimize care of elderly people, as well as to develop better vaccines for this population. However, this domain of investigation is still in its infancy. Although increasing evidence indicate that both innate and adaptive arms of immunity are affected with advanced age, our understanding of the causes and consequences in immune aging, and most importantly of the link between clinical and biological observations in old people remain limited and even confusing. Here, we will discuss mainly the age related alterations affecting cellular immunity, considered as the most studied and best understood changes in the elderly. T cells possess potent helper and effector functions, and are necessary to fight infectious pathogens and control tumor development.

2. Focus on the naïve T cell compartment

Historically, a primary hallmark of immunosenescence in humans has indeed been the increasing proportion of terminally differentiated memory $CD8^+$ T cells (CD28 negative), which exhibit limited proliferative capacity and are often considered as cells approaching senescence (Nikolich-Zugich, 2008). This is a reflection of the change in T cell subset distribution, with a shift towards more differentiated (with short telomeres) and more oligoclonal memory T cell populations, so that the lymphocyte repertoire becomes increasingly skewed towards previously encountered antigens. Persistent infection with cytomegalovirus (CMV), a prominent inducer of highly differentiated oligoclonal T cell populations, has been shown to enhance the development of such "immunosenescence phenotype" in humans (Koch et al., 2006). In one study, the sum of certain parameters such as a high frequency of highly differentiated T memory lymphocytes, a weak proliferative response of the T lymphocyte pool and CMV seropositivity has even been associated to all cause early mortality in the elderly (Wikby et al., 1998). Further studies are nonetheless necessary to confirm these observations. A number of studies have also focused on the functional attributes of virus specific memory T cells from old individuals. While decreased cytokine production capacity as well as lower T cell receptor (TCR) avidity has been reported (Griffiths et al., 2013; Ouyang et al., 2004), other

Abbreviations: CMV, cytomegaloviorus; DCs, dendritic cells; RTE, recent thymic emigrants; TCR, T cell receptor; TREC, T cell receptor excision circle; YATEC, young adults thymectomized during early childhood.

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studies have suggested that these cells remain fully functional even at old age (Lachmann et al., 2012; Lelic et al., 2012).

While of interest, many alterations of the memory T cell pool may represent merely an indicator of immune changes with advanced age, and do not provide a direct evidence or explanation for declining cellular immune function per se. One may even question the focus on studying the memory T cell compartment in the elderly since most recall responses to pathogens encountered during youth or adulthood are actually largely uncompromised. Instead a reduction of the elderly immune competence against cancer and pathogens may be more related to altered capacities to mount de novo cellular immune responses. This suggests that the naïve T cell compartment, which is characterized by the large diversity of its TCR repertoire, and from which originates effector and memory T cells, may hold the key to our understanding of cellular immune decline with old age. Although a number of studies described alterations of the naïve T cell pool in animal models, age-related naïve T cell defects are only partially understood in humans. Several factors need to be considered to grasp both the quantitative and qualitative changes of the naïve T cells with aging: their production by the thymus, their homeostatic proliferation, the diversity of their TCR repertoire, and cellular intrinsic alterations.

3. Thymic involution

The thymus is the primary lymphoid organ where lymphoid precursors mature into naïve T cells. Changes in the architecture of the thymus and decreased mass of functional tissues result in the progressive shrinking of the thymus with age, referred to as thymic involution. Historically, it has been accepted that the young thymus sets the T-lymphocyte repertoire during the childhood, whereupon atrophy begins until the elderly thymus is a non-functional residual trace. Evidence points towards a declining but still functioning thymus during adulthood until old age (i.e. >70 years), especially using T cell receptor excision circle (TREC) assays, which allows an accurate measurement of thymic output in humans (Douek et al., 1998; Ferrando-Martinez et al., 2010). Nonetheless, this deterioration of the thymic output has been proposed as a triggering event of the reduction in immunosurveillance in the elderly (Linton and Dorshkind, 2004). In young adults thymectomized during early childhood (YATEC), the number of naïve T cells was lower compared to age-matched controls (Sauce et al., 2009). Old age coincides with severe perturbations of the naive T cell number, and impaired immunity in mice (Ahmed et al., 2009; Naylor et al., 2005; Yager et al., 2008). In the elderly, higher thymic function has been associated with a younger immune system, while thymic function failure is associated with all-cause mortality: in one study, multivariate analysis revealed that thymic function and inflammatory markers (C-reactive protein level) were independently associated with time to death of healthy elderly humans (Ferrando-Martinez et al., 2013). Overall, in both mice and humans, thymus output declines with age, which is associated with the gradual reduction in naïve $CD4^+$ and $CD8^+$ T cell numbers, although naïve T cell numbers appear to decline less dramatically than thymocyte numbers (Fagnoni et al., 2000; Sempowski et al., 2002).

4. Homeostatic proliferation

Despite a dramatic decline in thymic output from puberty to old-age, humans have a remarkable ability to maintain relatively constant lymphocyte numbers across many decades, despite the immune system being challenged by multiple pathogens across lifespan. This phenomenon, called homeostasis, is achieved by matching the production, self renewal, death, and phenotype transition rates across a network of varied lymphocyte subpopulations. A correlation between the age related contraction of naïve T cells and the rise of the naïve T cell proliferation has been reported in primates (Cicin-Sain et al., 2007). In humans, similarly, increased naïve T cell proliferation has been reported in people over 70 years old as well as in thymectomized individuals (Ferrando-Martinez et al., 2011; Naylor et al., 2005; Prelog et al., 2009). In these settings, partial lymphopenia associated with the loss of thymic function results in increasing naïve T cell proliferation rates (Kohler and Thiel, 2009; Nikolich-Zugich, 2008; Sauce et al., 2012). Moreover, percentage of $CD4^+CD31^+$ recent thymic emigrants (RTE) diminishes with age, while the percentage $CD4^+CD31^-$ T cells (i.e. non-RTE) remains constant, suggesting that peripheral mechanisms could be influencing naïve T cell dynamics (Kilpatrick et al., 2008). This mechanism is likely linked to IL-7 availability, whose serum levels are increased in the old person. T-cell responsiveness to IL-7 depends largely on the surface expression of CD127 (or IL-7R), which is a hallmark of naïve T cells, as well as IL-7 intracellular signal transduction pathway (via STAT-5). Both CD127 expression and STAT-5 phosphorylation levels in naïve T cells are comparable between elderly and younger individuals, indicating that old naïve T cells are fully sensitive to IL-7 stimulation (Sauce et al., 2012). It remains though to be determined if increased homeostatic proliferation may eventually affect naïve T cell functionality in the elderly.

Recently, Den Barber et al. have directly quantified the contribution of de novo T cell production by the thymus and peripheral naïve T cell division comparing mice and men, using a combination of approaches including TREC content measurement in mouse and human naïve T cells, labeling with deuterated water ($2H_2O$) in mice and mathematical modeling (den Braber et al., 2012). The authors reported different life spans between naïve T cells in humans and mice and that around 90% of the naïve $CD4^+$ T cell pool is generated through peripheral T cell proliferation in healthy human adults. Based on these data, the authors suggest that the mechanisms maintaining phenotypically naïve T cells might be fundamentally different in mice and humans: thymic output maintains naïve T cell populations in mice, while, in contrast, human naïve T cells may divide in the periphery without losing their naïve phenotype. However, it should be noted that while increased homeostatic proliferation can compensate reduced thymic output, this does not appear to be sufficient to maintain a constant number of peripheral naïve T cells in elderly adults as well as YATEC (Sauce et al., 2012). Overall, the preservation of the pool of peripheral naïve T cells in humans is likely to be more complex than in mice, requiring both thymic output and homeostatic proliferation.

5. TCR repertoire of the naïve T cell pool

Nonetheless, the quantitative changes of naïve T cells observed with old age do not necessarily mean that qualitative changes and poor responsiveness upon challenge occur as well. A central facet of the naïve T cell pool resides in the large diversity of its TCR repertoire, which permits the response to an infinite array of antigens, and is key for effective immunity. A progressive loss of naïve TCR repertoire diversity, with small clonal expansions among naïve T cell compartment, has been reported in aging murine models. It has even been shown in mice that some naïve precursors are preferentially maintained at the expense of others (Rudd et al., 2011). Mouse infection models showed that contraction of the naïve T cell repertoire can result in impaired T cell response to immunodominant epitopes (Yager et al., 2008). This is in line with studies suggesting that the frequencies of naïve T cell precursors affect the magnitude and immunodominance patterns of the primary T cell response (Obar et al., 2008) and the differentiation kinetics into memory T cells (Marzo et al., 2005). A lower precursor frequency is thus likely to affect negatively the properties and efficacy of T cell responses. The extent of naïve TCR repertoire diversity loss and its influence on subsequent T cell responses remain nonetheless to be determined in elderly humans, as there is currently very little data available. One study suggested that the diversity of the naïve $CD4^+$ T cell TCR repertoire is maintained until older age, but experienced a sudden and profound decline around