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The role of oxidative and inflammatory stress and persistent viral infections in immunosenescence

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ABSTRACT

Immunosenescence involves age-related remodeling changes in the organization of lymphoid organs and functionality of immune cells, which have been associated with increased morbidity and mortality The pace of immunosenescence is modulated, however, by both intrinsic and extrinsic factors. Here, we review the mechanisms by which some factors, like the oxidative stress and certain chronic viral infections, may modulate the ageing immune system. Mounting evidence indicates that human cytomegalovirus (CMV) drives the expansion of late-differentiated T cells with an inflammatory profile. This would add to the "inflammaging" phenomenon, characterized by a low-grade inflammatory state, importantly involved in the etiology of several age-related diseases. We discuss that age-related oxidative stress is associated with chronic inflammation, and the oxidation-inflammation theory of ageing is summarized. According to this theory, the ageing process is a chronic oxidative and inflammatory stress, leading to damage of cell components, including proteins, lipids and DNA, and contributing to the age-related decline of physiological functions. Moreover oxi-inflamm-aging is associated with immunosenescence, which could be involved in the rate of ageing of individuals.

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1. Introduction

Elderly populations are fast growing in both developed and developing countries. The current estimates indicate that by 2025 the populations over age 65 will be increasing 3.5 times as rapidly as total population (Oeppen and Vaupel, 2002). The proportion of older adults, which accounted for 10% of world population in 2000, will dramatically increase to 22% by 2050. This is even more alarming for some developing countries, like Brazil which is increasing its elderly population by 3× as faster as global average (WHO, 2011). As consequence, increasing hospitalization and mortality rates because of age-related diseases are demanding urgent governmental initiatives. In order to develop adequate preventative and therapeutic strategies, it is essential that we understand the underlying mechanisms that contribute to age-related diseases.

Ageing of the immune system (immunosenescence) involves remodeling changes in its organization and functionality that negatively impact the health of older adults. Immunosenes-

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cence has been associated with the etiology and clinical course of most (if not all) age-related diseases, including cardiovascular diseases, osteoporosis, Alzheimer's disease, diabetes, cancer, autoimmune disorders, infectious diseases and poorer vaccine responses (Licastro et al., 2005; Aspinall et al., 2007; Pera et al., 2015). However, the increasing age-related morbidity is not evenly distributed and seems to be influenced by other immune-modulating factors. The components of the immune system are not ageing at the same speed or the same direction (Fulop et al., 2013). The speed of individual's biological clock depends on the important interaction between genetic inheritance and environment. Key environmental modulators (e.g., early-life stress, negative lifestyles, diet/obesity, repeated infections, etc.) are well known to shape the DNA and modulate gene expression via epigenetic mechanisms during lifetime (epigenetic drift). In addition, the methylation profile observed in CpG DNA sites across different tissues can accurately predict the chronological age (epigenetic clock) (Horvath, 2013) and premature senescence (as observed in HIV infection) involves the acceleration of age-related methylation patterns (Rickabaugh et al., 2015). Genetic polymorphisms of immune-related genes (e.g., HLA), genes in the inflammatory network and regulatory genes have all been implicated with either pathological or successful ageing (Ruan et al., 2014). Also, several extrinsic/intrinsic factors are known to influence the pace of immunosenescence, including stress hormones (glucocorticoids), chronic inflammatory conditions, and persistent viral infections. Here, we review the mechanisms by which some intervening factors, such as oxidative and inflammatory stress, two related processes, and certain chronic viral infections, may modulate the ageing immune system.

Leukocytes also increase the amount of intracellular oxidative products during ageing. Under normal physiological conditions, there is a balance between the generation of oxygen free radicals and antioxidant defenses. The immune cells produce oxidants and inflammatory compounds to carry out their defensive functions. However, the excess of reactive oxygen species (ROS) can cause damage to immune cells, even more considering the membrane characteristics of these cells make them very vulnerable to oxidative damage (De la Fuente and Miquel, 2009). Here we review that age-related oxidative stress is associated with certain persistent viral infections and chronic inflammation during ageing.

2. Immunosenescence—an overview

We present here a brief review on immunosenescence and more in-depth information can be obtained elsewhere (Muller et al., 2013; Shaw et al., 2013; Nikolich-Zugich, 2014). Immunosenescence is characterized by remodelling changes of the immune system during ageing (Fig. 1). In the past, there was a general assumption that all immune functions were blunted during ageing, but current knowledge clearly indicates that compensatory increases also occur over time. For example, regarding the innate immunity, most studies report increasing peripheral counts of natural killer (NK) cells in contrast to impaired cytotoxic function during ageing (Faria et al., 2008; Camous et al., 2012). Although some work reported increased macrophage-related immunity to pathogens in mice (Ortega et al., 2000), other studies observed a decrease in functions such as chemotaxis, phagocytosis and intracellular superoxide anion production in old mice (Arranz et al., 2010a; De la Fuente et al., 2011). Moreover, decreased neutrophil and monocyte functions including impaired chemotaxis, intracellular bacterial killing, phagocytosis and neutrophil extracellular traps (NETs) formation have been observed in both ageing mice and humans (Shaw et al., 2013). Antigen-presenting cells generally show impaired functions with ageing (Shaw et al., 2013). Interestingly, the increase in some innate functions reported in mice can be mediated by stress mediators including glucocorticoids, noradrenaline, and eHSP72 (De la Fuente et al., 2011; Ortega et al., 2012; Martinez de Toda and De la Fuente, 2015).

Ageing is characterized by a low-grade inflammatory status, known as "inflammaging". This has been associated with increasing plasma levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-1), acute phase reactants (C-reactive protein, CRP), and soluble cytokine receptors (Franceschi et al., 2000; Licastro et al., 2005). Of note, "inflammaging" has repeatedly been associated with increased morbidity and mortality during ageing (Franceschi and Campisi, 2014). In addition, higher levels of circulating pro-inflammatory markers (e.g., IL-6 and CRP) are strong predictors of all-cause mortality risk in several longitudinal studies of elderly cohorts (Harris et al., 1999; Giovannini et al., 2011). However, centenarians have high levels of proinflammatory markers and have postponed disease onset, making it difficult to understand whether "inflammaging" is beneficial or detrimental (Franceschi and Campisi, 2014). To date, it is unknown whether this imbalance in the regulation of inflammatory responses is a cause or rather an effect of the ageing process per se. Although it is not clear what drives inflammaging, chronic antigenic exposure may be an important contributing factor. Indeed, subclinical infections with virus of the herpesviridae family, particularly cytomegalovirus (CMV), are very common during ageing and have been associated with accelerated features of immunosenescence, increased morbidity and mortality (to be discussed in the next section).

With respect to the age-related changes in the levels of pro-inflammatory cytokines, the results depend on the kind of sample, which is measured. Thus, in peritoneal leukocyte cultures, in basal conditions the levels were higher, whereas in response to mitogens such as ConA and LPS, they were lower in old animals in comparison to adults (Arranz et al., 2010b). Similar results were obtained in cultures of human peripheral blood mononuclear cells. However, when in humans the total blood cells were used, and consequently neutrophils were present, the levels of these cytokines were higher in elderly men and women (work in progress). Moreover, plasma pro-inflammatory cytokines can be produced by cells other than leukocytes, which are more active, in this aspect, in old subjects. Leukocytes can also contribute to these plasma cytokines but not necessarily as a defence against infections. These facts could explain the presence of what is termed a "sterile inflammation" in aged subjects (Rubartelli et al., 2013). Thus, even in the absence of infections innate mechanisms could be activated, which lead to a sterile inflammatory response, which if not appropriately resolved could produce chronic inflammation (Feldman et al., 2015), as will be commented further on.

In addition to those changes described for innate immunity, the innate lymphoid subsets, which link innate and adaptive immune systems, should be considered since they are involved in inflammation (Russell and Walsh, 2012), but their age-related changes have not yet been studied. With respect to the adaptive immune system (i.e., B and T cells) this is particularly targeted and remodeled during ageing (Fig. 1). The peripheral T cells develop key phenotypic and functional changes during ageing (Fig. 2), albeit the total size of the T-cell pool remains the same as we age. Mammal ageing is associated with progressive thymic involution (3% per year following adolescence) and consequently reduced export of naïve T cells (CD27 + CD28 + CD45RA +) (Hirokawa and Makinodan, 1975; Schwab et al., 1997). About 50% of young adult T cells are naïve compared to ~35% in 70-year-olds (Fagnoni et al., 2000; Saule et al., 2006). Furthermore, this naïve loss is more pronounced in CD8+ T cells than CD4+ T cells: by the age 70, the proportion of naïve CD8+ T cells is around 10% and naïve CD4+ T cells consist of 40% of total CD4+ T cells (Fagnoni et al., 2000). Reciprocal changes in absolute

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