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Review

Impact of stress on aged immune system compartments: Overview from fundamental to clinical data

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ABSTRACT

Life expectancy is continuously increasing due to major progress in preventing, delaying or curing various pathologies normally encountered in old age. However, both scientific and medical advances are still required to understand underlying cause of the disparate comorbidities occurrence with aging. In one hand, aging profoundly impairs the immune system; it is characterized by many changes in haematopoiesis, adaptive and innate systems, associated with pro-inflammatory environment. In another hand, stressful events (acute or chronic) can also impact the immune system through the secretion of hormones, which are also altered with aging. The field of psychoneuroimmunology is now providing evidences that in acute medical conditions, elderly people are not equal in their responses to stressors depending on many extrinsic and intrinsic factors. These parameters could interfere with elderly's ability to mount an effective immune response.

The objective of this review is to provide an overview of the literature (from fundamental to clinical observations) to draw a parallel between immune dysregulation caused by stress or by aging. Understanding this entanglement could enable us to target fundamental age-related pathways and thus open new avenues in improving both lifespan and health span.

1. Introduction

Around the world, elderly population is growing. The Department of economic and social affair estimated that the over-60s has tripled since 50 years and will be tripled again in 2050. In 2000, it has been estimated in the report titled “World population aging: 1950–2050” that 69.2 millions of people were aged of 80 years old and over. In 2050, they will be 379.2 millions. Moreover, in 2050, the number of centenarians will be eighteen times higher than in 2000 with 3.2 millions of people (Department of Economic and Social Affairs, 2001).

This population aging asks many questions in scientific, medical, societal or ethic areas. A better comprehension of fundamental mechanisms of aging is necessary to prevent and treat age-related diseases. The objective is to develop new therapeutics targeting aging, which involve a close collaboration between scientists and practitioners in the field of Geroscience (Kennedy et al., 2014).

Aging can be defined as a progressive decrease of reserve capacities that are specific of each individual. This process, called “frailty” by geriatricians, leads to a gradual loss of physical and cognitive capacities, with an alteration of functional autonomy and quality of life (Fried et al., 2004). Frailty is associated with higher mortality and medical complications as falls, swallowing disorder, hospitalizations or institutionalizations. Moreover, aging is the main factor risk for chronic diseases (Fried et al., 2004) and in acute medical conditions, elderly people are not equal to respond to unexpected threat in case of stress. The capacity to overcome an acute stress is depending on reserve capacities that are impacted by many factors such as the degree of physiological aging and chronic medical condition. These two factors are profoundly dependent on genetic background, epigenetic, immunological, biological and environmental factors (Lopez-Otin et al., 2013; El Assar et al., 2017). Elderly patients evolution depend on reserve capacities that are impacted by physiological aging, comorbidities and acute stress as suggested by Bouchon (Bouchon, 1984) and illustrated in the Fig. 1.

Knowledge in the area of human's immunosenescence improved these last decades, but mechanisms implicated in the impact of stress on immune system in the elderly are still poorly understood. Actors involved in resilience capacity need therefore to be better characterized to warrant not only an increased lifespan to the elderly population, but also and importantly to improve its health span.

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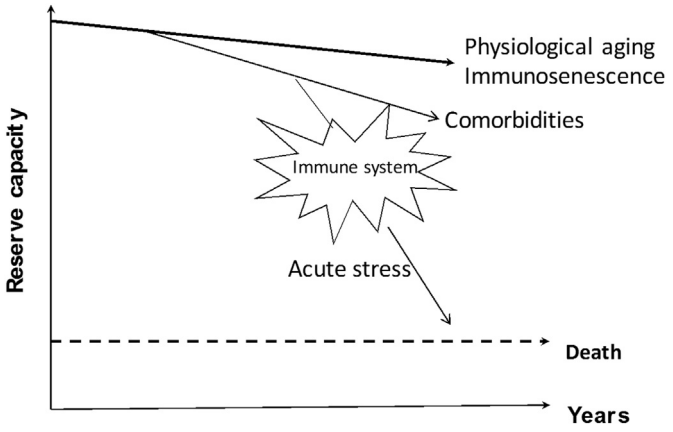

Fig. 1. Aging is a complex process with many inter-individual variations. Physiological modifications including immunosenescence and comorbidities contribute to the decrease of individual reserve capacities. Acute stress drives an important break in patient's evolution and can lead rapidly to death. The immune system is affected by this stress which participates to the bad evolution of elderly patients (Adapted from (Bouchon, 1984)).

The objective of this review is to provide an overview of the literature about immunosenescence and stress.

2. Immunological changes with aging

Aging is associated with a decline of the immune system competence termed immunosenescence. It's outlined by several characteristics that affect the adaptive and innate immune compartment (Goronzy & Weyand, 2013), as well as the hematopoietic compartment. It is also associated with of a high level of pro-inflammatory cytokines secretion at baseline, called “inflamm-aging”, resulting in a decreased ability to mount an effective immune response to antigens.

2.1. Aging of adaptive immune system

2.1.1. T-cells

Age-related changes in T cell compartment are characterized by 3 main hallmarks: (i) decrease of naïve T cells numbers related to thymic involution (Sauce et al., 2009; Zlamy et al., 2016). The thymus is the primary lymphoid organ where lymphoid precursors mature into naïve T cells. With aging, the thymus changes in structuration with a progressive decreased mass of functional tissues, progressively replaced by fat accumulation. (ii) Shrinking of the TCR repertoire that determines antigenic diversity broadness and thus preconditions the successful elimination of pathogens from the system (Naylor et al., 2005; Britanova et al., 2014). (iii) Increased proportion of terminally differentiated oligoclonal effector memory T-cell populations, particularly encountered with the control of persistent viral infections such as cytomegalovirus (Sansoni et al., 2008). Additionally, T cells switch to a pro-inflammatory cytokine profile with an increase production of IL-6, TNF-α and IFN-γ implicated in the ‘inflamm-aging” process. Furthermore, frequency of $FOXP3^+$ $CD4^+$ regulatory T cells increases with age (Raynor et al., 2012), and their capacity in regulating IL-10 production from target $CD4^+$ T cells increases in humans (Hwang et al., 2009).

Global gene-expression profiles have been analysed in T cell subpopulations during aging. Based on their known functions, altered genes expression is observed with increased lifespan: (i) the cell-surface receptor expression, exemplified by the loss of CD28 expression on aged memory $CD8^+$ T cell who switch to the accumulation of effector/senescent CD57+ T cells (Tarazona et al., 2000) with low level of proliferative capacity (Nikolich-Zugich, 2008) and higher level of NK cell markers (CD16); (ii) high level expression of chemokine and cytokine receptors in both $CD4^+$ and $CD8^+$ aged T cells (CX3CR1, CCRL1 (Fann et al., 2005)), (iii) altered expression of effector molecules (reduced expression of IL-7R and IL-12R on memory $CD8^+$ T cells and reduced expression of IL-13, CCL4 and Granzyme B) (iv) altered transcription factors in memory T cells (elevated expression of T-bet related to TH1 lineage development and of EOMES which induces production of IFNγ, perforin and Granzyme B). Reduced expression of MYC, an important regulator of cell proliferation, differentiation and apoptosis, is also found in memory T cells from elderly.

2.1.2. B-cells

It has been reported that age-associated changes in the distribution of the peripheral B cells reflect both decreased B cell generation from the bone marrow and increased B cell longevity. Effectively, the number of B cells in the periphery decreases in old humans. As a consequence of decreased generation of early progenitor B cells, the output of new naïve B cells is reduced (Allman & Miller, 2005; Frasca et al., 2017), and consequently antigen-experienced memory B cells are expanded (Frasca et al., 2017). This causes an altered antigen-recognition repertoire of B cells and optimal pro-inflammatory cytokines production in old humans (Johnson & Cambier, 2004). Moreover, class switch recombination is impaired in memory B cells with aging (Frasca et al., 2008; Frasca et al., 2012); this may also participate in the decline of the quality of humoral response (Shi et al., 2005). It has been reported that both, the enzyme for class switching, activation-induced cytidine deaminase (AID) and E47 proteins, the transcription factor that controls it expression, are down regulated in B cell from elderly individuals (Frasca et al., 2007; Muramatsu et al., 2007). This leads to impaired production of higher affinity protective antibody (Khurana et al., 2012). In addition, the incidence of B cell malignancy in older adults with oligoclonally expanded B cells is increased (Henry et al., 2015).

The fact that higher level of autoantibodies and increased frequency of autoimmune diseases are observed in older individuals suggests a failure in B-cell tolerance mechanisms during the aging process. It is probably during transitional B-cell development in elderly, where the reduced production of early B cell progenitor impacts on the peripheral B cells distribution that leads to the emergence of a unique auto-inflammatory B cell subset. This age-associated B cells (ABC) are defined in human by high expression of the transcription factor T-bet and surface marker CD11c (Hao et al., 2011; Naradikian et al., 2016).

2.2. Aging of innate immune system

The innate immune system of older individuals appears also to be affected with aging. Despite a constant number of polynuclear neutrophils (PNN) (Fortin et al., 2008), their functions are altered (Angelis et al., 1997; Corberand et al., 1981) with a decrease capacity of LPS activation, phagocytosis (Butcher et al., 2001), chemotactism (Fulop et al., 2004), oxidative burst (Braga et al., 1998) and antioxidant shield. Changes in the elderlies' functions of PNNs are reflected in decreased signalling transduction cascades and pathways (Fortin et al., 2008; Fortin et al., 2007; Tortorella et al., 2004), altered Toll-like receptors (TLRs) signal transduction, skewed granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced signal transduction, alterations in the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and p38 mitogen-activated protein kinase (p38 MAPK) signalling pathways.

In the elderly population, number of monocytes and macrophages is comparable to young population. Nevertheless, aging is associated with a redistribution of the different substes in favor of pro-inflammatory subsets. There is an increase of pro-inflammatory ($CD14^{++(high)}$/$CD16^+$) and non-classical ($CD14^{+(low)}$/$CD16^+$) monocytes and a decrease of conventional ($CD14^+$/$CD16^-$) monocytes in human elderly (Fehlings & Nguyen, 2010). Moreover, compared to young population, elderly human monocytes express more CD11b (integrin involved in migration) and less L-selectin (involved in rolling and adhesion to endothelial cells) that could affect monocytes functions in elderly (Hearps et al., 2012; De Martinis et al., 2004). Finally, age is associated with an