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**BIOMEDICAL SCIENCES**

**Immune System Dysfunction in the Elderly**

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**ABSTRACT**

Human aging is characterized by both physical and physiological frailty that profoundly affects the immune system. In this context aging is associated with declines in adaptive and innate immunity established as immunosenescence. Immunosenescence is a new concept that reflects the age-associated restructuring changes of innate and adaptive immune functions. Thus elderly individuals usually present chronic low-level inflammation, higher infection rates and chronic diseases. A study of alterations in the immune system during aging could provide a potentially useful biomarker for the evaluation of immune senescence treatment. The immune system is the result of the interplay between innate and adaptive immunity, yet the impact of aging on this function is unclear. In this article the function of the immune system during aging is explored.

**Key words:**aging; immunosenescence; adaptive immunity; innate immunity; inflammation.

**INTRODUCTION**

Human aging is characterized by both physical and physiological frailty. With progressive age, the immune system and the propensity for abnormal immunity change fundamentally ([Weyand et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B167)). Aging is associated with declines in adaptive and innate immunity ([Lutz and Quinn 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B98), [Golomb et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B64), [Wong and Goldstein 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B168)). Infections, cancer and autoimmune diseases occur more frequently in the elderly, and although many factors contribute to this, the age-related remodeling of the immune system, termed immunosenescence, plays a major role ([Bueno et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B17), [Mocchegiani et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B105), [Sharma et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B136)).

Immunosenescence involves age-associated restructuring changes of innate and adaptive immune functions ([Baeza et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B8), [Dace and Apte 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B39)). Immunosenescence describing alterations including the decline of immune responses with age is comprised of inappropriate elevations, decreases, and dysregulated immune responses, leading to more severe consequences of bacterial and viral infections and reduced responses to vaccination ([Montgomery and Shaw 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B107)). Elderly individuals usually present chronic low level inflammation, likely as the consequence of continued exposure to antigens combined with poor immune function, increases in the production of pro-inflammatory cytokines by effector memory and senescent T cells and macrophages ([Campos et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B27)). In addition, there may be disease impairment through a compromised adaptive immune response due to accelerated aging of the immune system in patients with an advanced clinical status ([Moro-Garcia et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B111)).

The immune system is the result of interplay between innate and adaptive immunity, yet the impact of aging on this function is unclear. In this article the function of the immune system during aging is explored.

**IMMUNOSENESCENCE**

Aging is associated with a decline in multiple areas of immune function ([Burns and Goodwin 1997](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B23)). ***Aging is associated with a sort of paradox: a state of increased autoimmunity and inflammation coexistent with a state of immunodeficiency*** ([Sardi et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B132)). Immunosenescence is a new concept that reflects the immunological changes associated with age. ([Boraschi and Italiani 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B12), [Fulop et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B60), [Poland et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B123)). There are three theories that explain the phenomenon of immunosenescence:

**AUTOIMMUNITY THEORY**

The autoimmune theory of aging was first introduced by [Walford (1969](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B163)). According to this theory, the immune system tends to lose efficiency and experiences widespread dysfunction, evidenced by autoimmunity (immune reactions against one's own body proteins) ([Diggs 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B44)). Two age- related processes cause autoimmune diseases: (i) different rates of senescent cell accumulation in the immune system and target tissue/organ and ([Pietilä et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B122)) heterogeneous accumulation of senescent cells in tissues/organs. Separately or combined, these two processes are at the base of autoimmune diseases ([Manestar-Blazic and Volf 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B100)). The production of autoantibodies has been hypothesized to be secondary to thymus involution with a decline of naïve T cells and the accumulation of clonal T cells with activation due to "neoantigens" during the aging process ([Prelog 2006](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B125)). Indeed, increased CD5+ B lymphocytes in the elderly population play a key role as producers of autoantibodies that lead to an imbalance of the mechanism controlling the immune response against self antigens ([Bulati et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B20), [Weksler 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B166)).

**IMMUNODEFICIENCY THEORY**

With advancing age the body is unable to defend itself from pathogens and results in a detrimental harm ([van Deursen 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B155), [Childs et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B30)).

Clinical evidence indicates that with advancing age, immune responses against recall antigens may still be conserved, but the ability to mount primary immune responses against novel antigens declines significantly. The impaired ability to mount immune responses to new antigens may result in a high susceptibility to infectious diseases ([Fagnoni et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B50), [Ahmed and Gray 1996](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B4)). The immune responses to novel antigens rely on the availability of naive T cells ([Fagnoni et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B50)). Together with the age-related thymic involution, and the consequent age-related decrease of thymic output of naive CD8+ T-cell reservoir, this situation leaves the body practically devoid of virgin T cells, and thus likely more prone to a variety of infectious and non infectious diseases ([Franceschi et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B54), [Fagnoni et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B50)).

**DEREGULATION THEORY**

Ageing is associated with various changes in immune parameters, therefore many authors have postulated that these age-related diseases could be explained, at least in part, by an overall deregulation in the immune system response ([McElhaney and Effros 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B104), [Franceschi et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B55)). This is supported by an age-associated disruption to the balance of alternatively expressed isoforms for selected genes, suggesting that a modification of the mRNA processing may be a feature of human aging ([Harries et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B68)). The observed down regulation of toll-like receptors (TLRs) and nod-like receptors (NLRs) during the aging process may contribute to the lack of effective recognition of invading pathogens or the commensal flora. This effect results in aberrant secondary immune cell activation and could significantly contribute to morbidity and mortality at an advanced age ([Rosenstiel et al. 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B130), [Montoya-Ortiz 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B108)).

**EFFECTS OF AGING ON THE IMMUNE SYSTEM**

Response mechanisms associated with the immune system are divided into innate and adaptive immunity ([Dunkelberger and Song 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B45), [Iwasaki and Medzhitov 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B75)). The first relates to anatomical and biochemical barriers, unspecific cellular responses that are mediated by monocytes, natural killer (NK) and dendritic cells ([Vesely et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B159)). The second relates to the fact that the response to specific antigens is mediated by B and T lymphocytes ([Denson 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B41)). Both are involved in immune senescence, where the adaptive response is affected the most in this process ([Franceschi et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B54)).

**INNATE IMMUNITY**

The innate immune system is the first line of host defense against pathogens. We will describe the effect of aging on the function of innate immunity ([Figure 1](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#f1)).



**Figure 1**Schematic representation of the main cells and their alterations involved in immunosenescence of ageing. INF: interferon, IL: interleukin, TLR: toll like receptor, MHC: major histocompatibility complex, TNF: tumor necrosis factor.

**SKIN AND MUCOUS**

These are the first line of defense of our body against pathogens, with age the replacement of skin cells decreases, sweat production is reduced, changes at the structural level of epithelial cells are produced, depletion of Langerhans and melanocyte cells occurs and subcutaneous tissue atrophy ([Kottner et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B88), [Campisi and d'Adda di Fagagna 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B26), [Chilosi et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B31)).

In skin, aging is associated with overall epidermal thinning, decreased barrier function, pro-inflammatory state and gradual deterioration of the epidermal immune response ([Kinn et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B84)). The mucus membranes of hair cells, which play an important role in removing pathogens, are reduced in quantity and movement, as well as presenting ultra structural changes ([Kim et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B82)). Immunoglobulin (Ig) A, the main constituent in secretions, levels increase up to 60 years old and thereafter a significant reduction in levels begins ([Jafarzadeh et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B76), [Smith et al. 1987](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B142), [Ebersole and Steffen 1989](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B47)). Therefore, structural and physiologic changes occur as a consequence of intrinsic aging combined with the environment can produce a marked susceptibility to dermatologic disorders in the elderly. For example, immunologic senescence in the elderly also sets the stage for potential reactivation of the Varicella zoster virus, in which initial dermatologic involvement expands into the major sensory ganglia ([Farage et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B51), [Kim et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B84)).

**DENDRITIC CELLS**

Dendritic cells (DC) ([Rainham et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B127)) are responsible for the first recognition of pathogens, antigen processing and regulation of T and B lymphocytes and NK. Thus DC are a bridge between innate and adaptive immunity and with age a group of them can decrease such as the Langerhans cells in skin and plasmocytes ([Agrawal and Gupta 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B3)). Aged DC exhibited profound signs of mitochondrial dysfunction, illustrated by lower Δψm, reduced ATP turnover and coupling efficiency, decreased baseline oxidative phosphorylation, and greater proton leak and reactive oxygen species (ROS) production ([Chougnet et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B35)). Therefore, DC in aging appears to be functionally impaired with regard to the response to uptake of antigens, phagocytosis of apoptotic cells and migration (Gupta 2014).

Other altered DC elements during aging are associated with the function of TLR (Inappropriate persistence of TLR activation in specific systems), in addition to the antigen processing and cell migration, which is associated with an alteration of phosphoinositide 3 kinase pathway ([Panda et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B118), [Agrawal et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B2), [Shaw et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B137)). Also, a decrease in interleukin (IL)-15 interferon alpha (INF-α) levels and tumor necrosis factor-alpha (TNF-α) has been seen ([Moretto et al. 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B109), [Stout-Delgado et al. 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B147)).

The DC from older mice have a poor ability to stimulate a CD8+ T cell-mediated cytotoxic response ([Zacca et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B169)). Impaired influenza-specific CD8+ T cell response in older adults is associated with a reduced TNF-α production and lower DC maturation. Therefore the production of TNF-α is a determining factor in the DC-mediated CD8+ T cell response against influenza ([Liu et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B96)). In addition, a comparison of the antigen-presenting capacity of aged plasmacytoid dendritic cell (PDC) with young PDC revealed that PDC from aged subjects displays reduced capacity to induce proliferation and IFN-γ secretion in CD4+ and CD8+ T cells as compared with PDC from young subjects ([Sridharan et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B145), [Prakash et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B124)).

**NATURAL KILLERS**

The NK cells are a key component of innate immunity involved not only in the elimination of virus-infected or tumor cells but also in the regulation of the immune response by producing cytokines and chemokines that can activate other cellular components of innate and adaptive immunity ([Gayoso et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B62), [Camous et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B25), [Vivier et al. 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B162)).

Aged nonhematopoietic environment is an important contributor to the impaired maturation and function of NK cells in aging ([Shehata et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B138)). Changes in NK cell biology that accompany human ageing are: (i) the increased reactivation rates of latent Mycobacterium tuberculosis, ([Pietilä et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B122)) a slower resolution of inflammatory responses and (ii) the increased incidence of bacterial and fungal infection are attributable in part to an age-associated decline in NK cell function ([Hazeldine and Lord 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B71), [Mariani et al. 2002](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B101), [Rajagopalan and Long 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B128), [Borrego et al. 1999](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B14)).

Human NK cells can be subdivided into two populations based on the density of cell surface CD56 antigen. The great majority (approximately 90%) of NK cells express CD56 at low levels (the CD56dim phenotype), whereas a small NK cell subset (approximately 10%) exhibits approximately fivefold greater density of surface CD56 (CD56bright). Under normal conditions, exposure to exogenous IL-2 induces tenfold greater proliferation of CD56bright cells compared to CD56dim lymphocytes ([Baume et al. 1992](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B9)). However, during aging there is a redistribution of NK cell subsets as shown by a decrease of CD56bright cells and an increase of CD56-CD16+ NK cells ([Solana et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B143), [Krishnaraj 1997](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B89)). In this way, the amount of IFN-γ secreted by NK cells from the elderly was only 25 percent of that released by the cells from younger samples ([Krishnaraj 1997](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B89)). Even, a decrease in the expression of activating receptors (NKp30 and NKp46) was observed in NK cells in elderly individuals ([Almeida-Oliveira et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B105)) ([Hayhoe et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B69), [Hazeldine and Lord 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B71)). Conversely, aging-related functional NK cell deficiency was completely reversed by injecting soluble IL-15/IL-15Rα complexes ([Chiu et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B33), [Elpek et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B49)).

**NEUTROPHILS**

Neutrophils are recruited to the infection site by cytokine and chemokine mainly by IL-1 and IL-8 ([Sica et al. 1990](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B140), [Kunkel et al. 1991](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B90)). When involved in phagocytosis, the generation of ROS, degranulation releasing enzymes and antimicrobial peptides and neutrophil extracellular traps (NETs), in order to eliminate the pathogen from our organism ([Zawrotniak and Rapala-Kozik 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B170), [Borregaard 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B13)). In addition, they facilitate the maturation and migration of DC that will initiate the adaptive immune response ([Solana et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B144)).

Neutrophil has a short half-life, presenting a spontaneous apoptosis, which is augmented by pro-inflammatory cytokines such as INF-1 and stimulating factor granulocyte-monocyte colony of (G-CSF), this effect is diminished as we age since there is an alteration in the activation of the Jak-STAT ([Fortin et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B53), [Kojima et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B86)). In addition, the marked decline in TCRL(n) repertoire diversity in old age identifies a novel mechanism of immunosenescence in neutrophils ([Fuchs et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B57)).

Neutrophil migration into the lungs is impaired in aged mice 24h after intratracheal infection despite elevated chemokine levels, suggesting that immunosenescence is impairing neutrophil migration ([Chen et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B29)). Inaccurate migration was causally associated with increased constitutive phosphoinositide 3-kinase (PI3K) signaling; untreated neutrophils from old donors demonstrated significant PI3K activation compared with cells from young donors. PI3K-blocking strategies, specifically inhibition of PI3Kγ or PI3Kδ, restored neutrophil migratory accuracy, whereas SHIP1 inhibition worsened migratory flaws ([Sapey et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B131)). In addition, phagocytosis also altered, for example a reduction in receptor expression is observed CD16 ([Fulop et al. 1985](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B59), [Butcher et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B24)).

Recently an alteration in pathogen destruction mechanism mediated by neutrophil extracellular traps (NETs) was demonstrated, which it is one of the results of increased infections in older individuals ([Brinkmann and Zychlinsky 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B16)). Besides these neutrophils have lower activation against TNF-α, interleukin (IL)-8 and lipopolysaccharide (LPS), with a consequent reduction in production of ROS ([Hazeldine et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B70), [Summers et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B150)).

**MACROPHAGES**

Macrophages main function is involved in phagocytosis synthesize pro-inflammatory cytokines TNF-α, IL-1, IL-6 and IL-8, in addition to processing and presenting antigens to T cells and participating in adaptive immunity ([Weiskopf et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B165), [Shi and Pamer 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B139)). Activated macrophages are now broadly classified into two subsets; pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. Classical activation is induced by IFN-γ and LPS and produces cells with a M1 phenotype, and alternative activation is induced by IL-4 and IL-13 and produces M2 cells. M1 and M2 cells differentially express a range of chemokines and also have distinct metabolic programmes ([Fuentes et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B58)). In this context, expression of both M1 and M2 markers was reduced in adherent splenocytes from old mice, indicating that ageing did not cause a skew towards M1 or M2 phenotype ([Mahbub et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B99)). The reduced expression of M2 markers may be, in part, due to lower numbers of splenic F4/80+IL-4R+ cells in aged mice compared with young ([Mahbub et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B99)).

Telomeres shorten with age in macrophages leading to a decreased GM-CSF but not M-CSF-dependent proliferation of these cells as a result of decreased phosphorylation of STAT5. Macrophages from aged mice showed increased susceptibility to oxidants and an accumulation of intracellular reactive oxygen species ([Sebastian et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B135), [Guayerbas et al. 2002](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B66)). Also, macrophages from older animals lost the capacity to respond to pharmacological (10(-3) M) concentrations of norepinephrine (NE). The lower capacity of response to NE by macrophages from older animals possibly contributes to immunosenescence ([Ortega et al. 2000](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B116)). The changes observed in the macrophages (stronger generation of nitric oxide (NO) and ROS) isolated from the elderly indicate that these cells could contribute to the development of metabolic disorders like atherosclerosis and diabetes ([Suchy et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B149)).

During aging macrophages considerably reduce the production of cytokines such as TNF-α and IL-6 (van Duin et al. 2007b, [Davalos et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B40)), and decrease in B7 receptor expression, which allows the activation of T cell ([van Duin et al. 2007a](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B157)). This also shows a reduction in the expression of major histocompatibility complex (MHC) class II gene IA complex product and the levels of intracellular IAbeta protein and mRNA ([Villanueva et al. 1990](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B160), [Herrero et al. 2002](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B74), [2001](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B73)). Meanwhile, activated macrophages which function as antigen presenting cells were decreased in aged rats ([Kizaki et al. 2002](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B85)).

Significant up regulation of miR-101b and miR-26b effectively prevented LPS-induced excessive expression of cyclooxygenase ([Odden et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B114))-2 in young mice. Meanwhile, histone deacetylase suppressed the expression of miR-101b and miR-26b in the LPS-treated macrophages of aged mice and contributed to the aging process ([Liu et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B95)).

The miR-146a, which negatively regulated the expression of IL-1β and IL-6, was highly expressed in aged mice. The dysregulated expression of miR-146a results in the age-associated dysfunction of macrophages, and miR-146a may be a good target for the treatment of age-related inflammatory diseases ([Jiang et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B77)). In addition, autophagy modulation may prevent excess inflammation and preserve macrophage function during aging, improving immune responses and reducing the morbidity and mortality associated with inflamm-aging ([Stranks et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B148)).

**MICROGLIAL CELLS**

Microglia reside in the central nervous system (CNS), comprising of approximately 12% of the brain, and serve as the brain's immune defense. Microglia cells are unique from neurons, oligodendrocytes, and astrocytes in that they are not derived from the neuroectoderm ([Dheen et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B43)). Microglia cells play an important role in CNS homeostasis during development, adulthood and ageing. Microglia function is tightly regulated by the CNS microenvironment, and increasing evidence suggests that disturbances, such as neurodegeneration and ageing, can have profound consequences for microglial phenotype and function ([Perry and Teeling 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B121)). Accumulating evidence points to activated microglia as a chronic source of multiple neurotoxic factors, including TNF-α, NO, IL1-β, and ROS, driving progressive neuron damage, particularly in the case of Parkinson's Disease ([Lull and Block 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B97), [Graeber et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B65)).

Under physiological conditions, the number and function of microglia is tightly controlled by the local microenvironment. In response to neurodegeneration and the accumulation of abnormally folded proteins, however, microglia multiply and adopt an activated state - a process referred to as priming. Priming makes the microglia susceptible to a secondary inflammatory stimulus, which can then trigger an exaggerated inflammatory response. The secondary stimulus can arise within the CNS, but in elderly individuals, the secondary stimulus most commonly arises from a systemic disease with an inflammatory component ([Perry and Holmes 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B120)). The cause of this amplified microglial activation may be related to impairments in several key regulatory systems with age that make it more difficult to resolve microglial activation ([Norden and Godbout 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B113)). Thus, microglias of the aged brain are termed primed with a higher expression of MHC II and pro-inflammatory cytokines including IL-1β. In addition, there are clear age associated deficits in memory and learning and neuronal plasticity ([Henry et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B72)).

**ADAPTIVE IMMUNITY**

The adaptive immune system depends on the generation of a diverse repertoire of antigen receptors on T and B lymphocytes and subsequent activation and clonal expansion. The induction of adaptive immunity, not only depends on the recognition of the particular antigen receptor, but is also based on essential signals that are delivered by the innate immune system ([Schenten and Medzhitov 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B133)). A well-described age-related alteration of the immune system is the decrease of de novo generation of T and B cells ([Stervbo et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B146)). We will describe the effect of aging on the function of B and T lymphocytes ([Figure 1](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#f1)).

**B LYMPHOCYTES**

The primary function of B lymphocytes is the production of antibodies in response to infection from a pathogen ([Tedder et al. 1997](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B151), [Gitlin and Nussenzweig 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B63)). The B cell arm of adaptive immunity undergoes significant modifications with age. Elderly people are characterized by impaired B cell responses and defective antibody production reflected in a reduced ability to effectively respond against viruses and bacteria ([Buffa et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B19), [Ademokun et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B1), [Visentini et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B161)). Thus, the formation of antibodies in response to vaccination against hepatitis B virus infection was significantly reduced for donors with a mean age of 61 years compared with a group with a mean age of 33 years ([Rosenberg et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B129)).

Immunosenescence is characterized by the impairment of humoral immunity with changes in the memory/naive B cell compartment ([Martorana et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B103)). The increase of memory B cells (IgG(+)IgD(-)CD27(-), double negative, DN) population in the elderly, in which there is also a typical inflammatory micro-environment. In the elderly, naïve/memory B cell populations present a different expression of the studied receptors that could be discussed in terms of "inflamm-aging". In particular IgG(+)IgD(-)CD27(-) DN B cells show a tissue trafficking phenotype and they can be stimulated to produce granzyme B ([Bulati et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B21)). Double negative (IgG+IgD-CD27-) B cells are increased in a cohort of moderate-severe Alzheimer's disease patients and show a pro-inflammatory trafficking receptor phenotype ([Bulati et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B22)).

Immunosenescence in the B-lineage is not irreversible and depletion of the long-lived B cells in old mice rejuvenates the B-lineage and enhances immune competence ([Keren et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B80)). Naïve B cells from young donors need a sufficiently strong stimulus to be activated "*in vitro*", while naïve B cells from old subjects are able to produce IL-10 and TNF-α when stimulated "physiologically" (α-CD40/IL-4), suggesting that these cells might play a role in the control of the immuno-inflammatory environment in the elderly ([Buffa et al. 2011](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B18)).

Plasma cells are terminally differentiated elements derived from B lymphocytes. Plasma cell numbers decrease in the bone marrow of old patients ([Pritz et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B126)). This reduction of clonal expansion of plasma cells results in a low affinity of antibodies to antigens (Dunn-Walters et al. 2003, [Effros et al. 2005](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B48), [Johnson and Cambier 2004](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B79)).

**T LYMPHOCYTES**

These can be divided into CD4 and CD8 recognizing antigens in the context of MHC ([Lenardo et al. 1999](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B92), [Arsenio et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B7), [King et al. 2008](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B83)). Aging is associated with an increased susceptibility to infection and disease. It is also associated with reduced functionality and altered distribution of the immune cells, especially T cells ([Vasudev et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B158), [Tesar et al. 2006](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B152)).

Age-related regression of the thymus is associated with a decline in naïve T cell output ([Moro-Garcia et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B110), [Chou and Effros 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B34), Alonso-Arias et al. 2011). This is thought to contribute to the reduction in T cell diversity seen in older individuals and linked with increased susceptibility to infection, autoimmune disease and cancer ([Palmer 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B117)). Oxidative stress and chronic antigenic load increases with age reduced lymphocyte susceptibility to damage-induced cell death and enhances proinflammatory status leading to increased activation induced cell death ([Sikora 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B141)).

Altered lymphocyte potassium channel inhibitory patterns, regulators of calcium influx kinetics, might contribute to the development of age-related changes of T cell function ([Kollar et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B87)). It also presents a reduction of membrane receptors such as CD28 (important in lymphocyte activation) and CD27 (limited proliferative capacity by T lymphocytes) ([Vallejo 2005](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B154), [Parish et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B119), [Warrington et al. 2003](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B164), Ferrando-Martinez et al. 2011, [Cao et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B28)). In addition to a decrease in intracellular calcium levels and alterations in the signal transduction pathways NF kB and MAPK have been observed ([Deruy et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B42), [Garcia and Miller 2002](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B61), [Jing and Lee 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B78)). Recently decreased miR-181a has been associated with age, this controls lymphocyte activation via their T cell receptor this decline results in poor cell activation and also recognizing autoantigens ([Li et al. 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B94), [2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B93)).

Endogenous p53 isoforms Δ133p53 and p53β are physiological regulators of proliferation and senescence in human T lymphocytes *in vivo*. Conversely, Δ133p53 knockdown or p53β overexpression in CD8+CD28+ cells inhibited cell proliferation and induced senescence ([Mondal et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B106)). CD4 T cell lymphopenia is an important T cell defect associated to ageing ([Martinet et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B102)). Meanwhile, menin binding at Bach2 locus and Bach2 expression are decreased in the senescent CD4 T cells. T cell-specific Menin deficiency results in the premature senescence of CD4 T cells, which is accompanied by the senescence-associated secretory phenotype after antigenic stimulation and dysregulated cytokine production ([Kuwahara et al. 2014](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B91)). In aging individuals, reduced CD8+ T-cell priming capacity *in vitro* was further associated with poor primary immune responsiveness *in vivo*. This immune deficit likely arises as a consequence of intrinsic cellular defects and a reduction in the size of the naïve CD8+ T-cell pool ([Briceno et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B15)). Immunosenescence appeared to be pronounced in patients with breast cancer, with senescent CD8+ T-cells playing a role ([Onyema et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B115)).

Changes in the TH17/Treg ratios (TH17 cells were significantly increased in older individuals whereas Tregs were reduced) in combination with altered cytokine expression during aging may contribute to an imbalance between the pro-inflammatory and the anti-inflammatory immune response. This indicates a higher susceptibility to develop inflammatory diseases with increasing age ([Schmitt et al. 2013](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B134)).

**BIOMARKERS OF SENESCENCE**

Senescence biomarkers should be applicable for use *in vivo* due to the role of increased senescence in age-related diseases ([Bernardes de Jesus and Blasco 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B10)). The CD8+CD28−CD27+ cell and antithymocyte globulin (ATG)-induced CD4(+) T cell lymphopenia are used as a biological marker of accelerated immunosenescence ([Ng et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B112), [Crepin et al. 2015](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B38)).

It is believed that senescence is activated in an intermediate state where the tumor started but did not reach full malignancy, which usually coincides with the normal function of the major barriers p53 and p16. ([Collado et al. 2005](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B36)). Moreover, aged heart patients presented an increase in senescent cells (positive for p16, p21, p53, and presenting short telomeres), which, together with the aforementioned characteristics, resulted in the development of cardiac failure ([Chimenti et al. 2003](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B32), [Torella et al. 2004](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B153)).

A number of senescence markers have been used to identify senescent cells. For example, growth arrest, although a necessary condition for senescence, is not sufficient to define the state - many cells *in vivo* are terminally differentiated or quiescent. p16INK4a is highly correlated with senescence and age, and lamin B1 declines in mouse tissues with persistent senescent cells and therefore may be useful in both research and clinical applications, and senescence-associated beta-galactosidase (SA-βgal), the most widely used senescence marker ([Campisi and d'Adda di Fagagna 2007](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B26), [Freund et al. 2012](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B56)). Moreover, senescent cells secrete interleukins, inflammatory cytokines, and growth factors that can affect surrounding cells. Thus plasminogen activator inhibitor-1 (PAI)-1, IL-1, IL-6, IL-8 and colony-stimulating factors (CSFs, including GM-CSF and G-CSF) are candidate biomarkers of senescence because they are soluble factors overexpressed by senescent cells ([Coppe et al. 2010](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B37), [Binet et al. 2009](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0001-37652017000100285#B11)).

**CONCLUSIONS**

During aging, immune senescence is a process that affects the entire immune system. It corresponds to multiple alterations of the immune system, which results in a higher rate of infections and increase of diseases. In addition, alterations of the immune system during aging could provide a potentially useful biomarker for the evaluation of immune senescence treatment.

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