Cytokine and Growth Factor Reviews 59 (2021) 9–21

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Hallmarks of aging and immunosenescence: Connecting the dots

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ARTICLE INFO

Keywords:
Aging
Senescence
Immunosenescence
Immune system
Inflammaging
Senotherapeutics

ABSTRACT

Aging is a natural physiological process that features various and variable challenges, associated with loss of homeostasis within the organism, often leading to negative consequences for health. Cellular senescence occurs when cells exhaust the capacity to renew themselves and their tissue environment as the cell cycle comes to a halt. This process is influenced by genetics, metabolism and extrinsic factors. Immunosenescence, the aging of the immune system, is a result of the aging process, but can also in turn act as a secondary inducer of senescence within other tissues. This review aims to summarize the current state of knowledge regarding hallmarks of aging in relation to immunosenescence, with a focus on aging-related imbalances in the medullary environment, as well as the components of the innate and adaptive immune responses. Aging within the immune system alters its functionality, and has consequences for the person's ability to fight infections, as well as for susceptibility to chronic diseases such as cancer and cardiovascular disease. The senescence-associated secretory phenotype is described, as well as the involvement of this phenomenon in the paracrine induction of senescence in otherwise healthy cells. Inflammaging is discussed in detail, along with the comorbidities associated with this process. A knowledge of these processes is required in order to consider possible targets for the application of senotherapeutic agents - interventions with the potential to modulate the senescence process, thus prolonging the healthy lifespan of the immune system and minimizing the secondary effects of immunosenescence.

1. Introduction

According to United Nations projections, the number of people over 60 years of age will increase from 962 million in 2017 to 1.4 billion in 2030 and 2.1 billion by 2050. This would reflect a projected increase from 12.8 % (2017) to 21.3 % of the world's population [1]. The rapid growth of the elderly population imposes major challenges to several sectors of society, including science and medicine. While governments struggle to implement programs and public policies with the objective of promoting health and well-being in old age, science faces the formidable challenge of explaining what aging is, what are its major drivers and how to tackle the negative aspects of aging.

Aging is a natural process, which is closely linked to the loss of homeostasis, a condition of stability necessary for the minimal functionality of different organismal systems. When the dynamic balance of a functional organism is disturbed, unfavorable impacts on health are soon observed [2–4]. In the context of aging, such disturbance in homeostasis seems to arise from multifactorial causes, which end up determining a limit on the duration of life [2].

As aging affects virtually all systems in the organism, the immune system would not be an exception. The alterations that the immune system usually presents during aging are termed immunosenescence and seem to stem from two complementary processes: the direct effect of senescence of the immune cells, and the indirect consequence of tissue cellular senescence, which weakens organismal barriers, and also fosters the release of several signaling molecules to which immune cells respond. Due to the paramount role of immunity in maintaining organismal homeostasis and eliminating damaged cells, it does not come as a surprise that immunosenescence constitutes both a consequence of aging, but also a further accelerator of organismal functional decay [5,

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https://doi.org/10.1016/j.cytogfr.2021.01.006
Received 15 January 2021; Accepted 24 January 2021
Available online 29 January 2021

6].

Aging is increasingly regarded as a single strategic and actionable target to prevent most age-related or age-aggravated illnesses at once. At the moment, different senotherapeutic strategies are under clinical investigation. The question of whether and how senotherapeutic strategies may benefit the aging immune system is very relevant and depends on a comprehensive analysis of how the cellular and molecular facets of aging influence the innate and adaptive immune systems. Therefore, the present review focuses on revisiting the literature and examining the connection between hallmarks of aging and immunosenescence, and presenting perspectives and interventions against this condition.

2. Immune system (and) aging

Why aging occurs is still a mostly unanswered question, but it is a fact that it is related to the passage of time, to the decay in organismal homeostasis, and to increased chances of death. Genetic factors, hormonal and metabolic status, as well as environmental stress trigger the decay of organismal function [7]. However complex, the aging process seems to always include some key events, which contribute in a greater or lesser fashion, according to individual genetic and environmental conditions. Those include genomic instability, degradation of telomeres, epigenetic changes, loss of proteostasis, dysregulation of the nutrient sensor pathways, mitochondrial dysfunction, stem cell exhaustion, altered intercellular communication, and cellular senescence [8,9]. Such events have been elected as aging hallmarks, and constitute active areas of investigation. Under experimental conditions, the modulation of at least some of these hallmarks can result in the delay of the aging process to some degree, highlighting their potential as actionable targets in the context of aging.

Cellular senescence can be characterized as a set of processes that cause the cell cycle to halt. Furthermore, it is accompanied by genetic changes, as well as metabolic and paracrine signaling alterations. In the context of homeostasis, cells that have suffered some type of damage or that can no longer undergo mitosis are induced to go through apoptosis or cellular senescence (which is a state resistant to apoptosis). In both cases, senescent cells attract and activate immune cells, ending up being eliminated and replaced by healthy tissues [10–12]. Nevertheless, during aging, while apoptosis-resistant cells increasingly become senescent, the elimination of such cells by the immune system does not occur efficiently [13].

Considering the current understanding of organismal aging, cellular senescence is considered a key and central element in the process. Cellular senescence is characterized by phenotypic and genotypic changes, such as: morphological alteration, chromatin remodeling, and, perhaps most importantly, a metabolic reprogramming, which results in the adoption of a senescence-associated secretory phenotype (SASP) [6,8]. The SASP includes several families of soluble and insoluble factors such as: interleukins, chemokines, inflammatory factors, growth factors, among others [14]. SASP is the most important reason why cellular senescence is considered both a result of aging, but also a driver of further cellular senescence. It has been shown that the SASP compromises immune system function, including the elimination of senescent cells [15]. Furthermore, the SASP promotes cellular senescence in a paracrine fashion, inducing senescence of neighboring cells that present

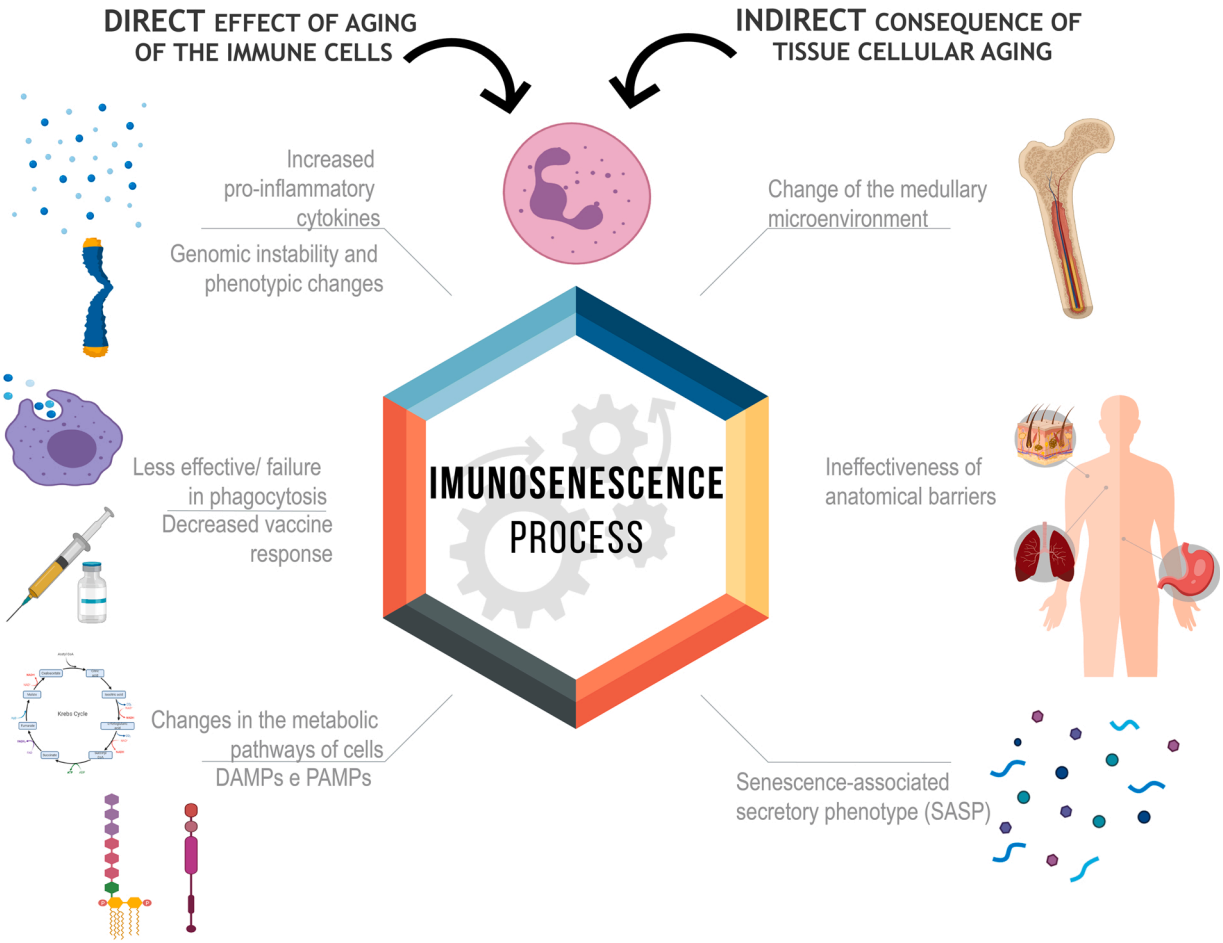

Fig. 1. Cytokines, phagocytosis, metabolic pathways, SASP, anatomical barriers and medullary microenvironment are associated with the immunosenescence process in immune cells and tissues.

none of the hallmarks of aging [16–18].

During aging, it is hypothesized that the aging hallmarks, and especially senescent cells, contribute to both innate and adaptive immunity alteration, which result in immunosenescence and inflammaging, further discussed below and illustrated in Fig. 1. Ultimately, these events result in compromised organismal barriers, excessive inflammatory signaling, and exhaustion of adaptive immunity, leading to a limited organismal ability to respond to novel antigens and vaccination, and contributing to high susceptibility to infectious and cardiovascular diseases, obesity and cancer, among other age-related diseases and conditions.

2.1. Immunosenescence and the medullary microenvironment

The bone marrow is a complex organ, whose architecture is still ill-defined at the cellular level. It is the main site of postnatal hematopoiesis, sustained by a small number of hematopoietic stem and progenitor cells (HPSC) [19]. The medullary stroma is shaped by a series of soluble and insoluble signals. Cytokines, chemokines, growth factors and hormones make bone marrow the ideal environment for the production of lymphoid and myeloid cells. It has been shown that HPSC function is characterized by a low oxidative phosphorylation metabolism and supported by a local niche, which favors a close interaction between HPSC, mesenchymal stem cells (MSC) and osteoprogenitor cells [19].

While HPSC originate all cells of the lymphoid and myeloid lineage, MSC have the ability to differentiate into various connective tissue cell types, especially from osteogenic and adipogenic lineages, that are crucial for bone hematopoiesis [20,21]. In general, cells which follow osteogenic differentiation are able to form “biochemical niches” favoring hematopoiesis. Osteoprogenitors secrete IL-7 and IGF-1, favoring the differentiation and maintenance of B lymphocytes, while immature osteoblasts participate in the expansion of hematopoietic stem cells, and mature osteoblasts express DLL4, inducing thymic mobilization of competent T lymphocytes. This indicates the important role of MSCs and their derivatives in supporting the hematopoietic system maintenance of immune cells [20,22]. In contrast, MSCs are also able to differentiate into adipocytes, which have a negative effect on hematopoietic recovery. It is known that, with the aging process, the original bone marrow tissue composed of fibroblasts, osteoclasts, megakaryocytes, chondrocytes (which offer conditions for differentiation), and stem cells, is gradually replaced by adipocytes [23]. Lipocalin 2, secreted by the adipocytes in the bone marrow, inhibits erythropoiesis and the presence of the adipocytes themselves reduces the hematopoietic activity, transforming the red marrow into yellow marrow [24]. Further factors, such as accumulation of DNA damage in bone marrow cells also promote HPSC senescence and reduced ability for self-renewal, with consequent myeloid skewing [25].

Without a qualified stromal tissue, the bone marrow of the elderly, basically composed of adipose tissue, ceases to induce the production of HPSC, which imposes an important impact on the repertoire and competence of T and B lymphocytes to develop effective immune defense [7,26,27]. Therefore, the balance of differentiation into adipocytes or osteoblasts from MSC, as well as the cytochemical regulation of bone marrow depends on several factors, including aging [20,21].

If there is a compromise in the production and maintenance of cells that make up the population of the bone marrow environment, key cytokines important for immune modulation including IL-6, IL-7, IL-11, IL-15, and GM-CSF are no longer secreted, substantially affecting the overall immune response [23]. A summary of the major alterations in the cytokine levels of aging subjects is presented in Table 1; Fig. 2. Such a disturbance in cytokine production also affects hematopoietic and immune cells. For instance, T helper cells (TCD4+ cells) are maintained in niches organized by stromal cells that secrete IL-7, being the main survival factor for these cells. Furthermore, the maintenance of cytotoxic TCD8+ cells requires the presence of both IL-7 and IL-15 [28].

In the context of “inflammaging", the accumulated senescent cells

Table 1
Age-related cytokine alterations.

Proteins associated with SASP	Protein role	Profile after SASP activation	Action in Immunosenescence	SASP – stimulus [12, 13]
Interleukins				
IL-1	Pro-inflammatory activity	↑	Cognitive decline (acts by promoting the production of amyloid beta protein) [134].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
IL-6	Pleiotropic pro-inflammatory activity	↑	Increased production of C-reactive protein, contributing to an inflammatory profile, damage to DNA [135].[a,b]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
IL-7	Lymphocyte proliferation in peripheral tissue.	↑	Stimulates growth, maturation of B lymphocytes and activation of T lymphocytes [136].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
IL-11	Acts on hematopoiesis and cell proliferation of various tissues	–	Action on the immune response. Its reduced expression is related to osteopenia and adipogenesis [137].[b]	
IL-15	Regulation of T cells, regulation of tissue repair	↑	Interleukin required for lymphocyte maintenance, and cognitive performance. However, at high levels it has a pro-inflammatory profile [138].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
Chemokines				
IL-8	Chemotactic function	↑	Pro-inflammatory activity; senescent cells overexpress this cytokine [139].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
CXCL1 (GROα)	Neutrophil activating protein	↑	Tissue damage, tumorigenesis, angiogenesis [140].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
MCP2	Monocyte chemotactic protein	↑	Present in the senescent profile.[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS, IR and ATV.
TNFα	Apoptosis' activation	↑	Commitment immune response, maintenance of	Changes in the SASP due to the

(continued on next page)

Table 1 (*continued*)

Proteins associated with SASP	Protein role	Profile after SASP activation	Action in Immunosenescence	SASP – stimulus [12, 13]
			immunosenescence [141].[a]	loss of p53 and/or gain of oncogenic RAS
IGF-1	Activating several signaling pathways. Involved in proliferation, differentiation, survival, growth, apoptosis and regeneration.	–	Related to the maintenance of the microenvironment of the immune system's own cells, neurodegenerative conditions [142].[a]	Changes in the SASP due to the RAS, IR, and ATV.
VEGF	A signal protein produced by cells that stimulates the formation of blood vessels.	↑	Related to brain aging [14].[a]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS, IR and ATV.

[a] Studies executed in human models.
[b] Studies involving animal models. IR: X-irradiation; ATV: atazanavir treatment.

and the increasing SASP components contribute to changes in the medullary microenvironment and further favor immunosenescence [29]. In this context, IL-6 and IL-15, necessary for the maintenance of lymphocytes, can also act as pro-inflammatory cytokines and thus as part of the SASP profile. Accordingly, IL-6 and IL-15 show increasing levels with aging (Table 1, Fig. 2) [30–32].

High levels of IL-15 block the apoptotic process in TCD8+CD28- cells, preventing T-cell exhaustion and promoting host survival in experimental models of sepsis [33]. On the other hand, activated TCD8+ cells produce IFNγ and TNF-α, which in turn leads to an increase in IL-15, promoting further attraction of TCD8+CD28-, leading to a feed-forward inflammatory process, that results in immune response compromise in the elderly and the maintenance of immunosenescence [34,35]. Therefore, even though not completely detrimental [30,33], the levels of IL-15 and other cytokines should preferably be kept in balance during aging [36].

IL-6 is produced by several cells of the immune system such as monocytes, macrophages, and T and B lymphocytes. IL-6 promotes both anti-inflammatory and pro-inflammatory actions, in addition to different hematological, endocrine, and metabolic effects. The participation of IL-6 is essential for the maturation of T and B lymphocytes and also to the stimulation of the production of immunoglobulins [37]. In bone tissue, it acts by promoting the differentiation of monocytes and macrophages in osteoclasts, influencing bone resorption.

Studies also show IL-6 as a protagonist during chronic inflammatory activity, in which IL-6 acts as a mediator between the acute and chronic phases [38]. IL-6 elicits not only acute phase reactions but also the development of specific cellular and humoral immune responses, including end-stage B cell differentiation, immunoglobulin secretion and T cell activation. In addition, sIL-6Rα receptor signaling is capable of altering the nature of the neutrophilic leukocyte infiltrate (efficient in the acute phase of inflammation) to an infiltrate rich in lymphocytes (present in the chronic phase of the inflammatory process) [39,40]. Thus, circulating IL-6 levels are elevated in several inflammatory diseases, such as systemic juvenile idiopathic arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis and Crohn's disease. In an animal model, IL-6 has been shown to play a key role in the development of rheumatoid arthritis [41]. In elderly humans, the circulating levels of IL-6 were correlated with cognitive and physical performance, as well as risk of mortality in some studies [42–44], but not in others [45].

The inflammatory *milieu* in the bone marrow niche also disturbs the local redox homeostasis. *In vitro*, peripheral blood mononuclear cells stimulated with IFNγ had increased levels of reactive oxygen species (ROS) [46]. A proinflammatory niche and high levels of ROS were indeed found in the bone marrow of elderly people, which correlated with high levels of IFNγ [47,48]. As previously mentioned, ROS are drivers of genomic instability, mitochondrial dysfunction, and cellular senescence, and may reinforce the age-related alterations observed in the aging bone marrow.

As documented by Chang and colleagues, the senescent cell burden in the bone marrow is an important driver of hematopoietic system aging, and their elimination results in significant improvements in hematopoiesis [48]. In another study, the suppression of JAK-dependent cytokine synthesis, which includes IL-6, was effective to prevent age-associated bone loss. These authors also demonstrated that the selective elimination of senescent cells led to the same outcome [49]. Therefore, different hallmarks of aging, and especially senescent cells, bear relevant roles in the aging-associated alterations of the bone marrow niche, which compromises the immune system and favors immunosenescence.

2.2. Immunosenescence and innate immune response

Outside of the bone marrow, the immune system consists of a network of molecules, cells, tissues, and organs, that work to guarantee the homeostasis of the organism, with the responsibility of removing invading and abnormal agents. It is divided into two main branches: innate immunity, which comprises the immune system elements that immediately recognize conserved molecules and respond to such stimuli; and adaptive immunity, which recognizes a much wider range of antigens in a specific way, and also presents immunological memory.

The innate immune system is represented by physical (e.g. skin, gastrointestinal and respiratory epithelium) and chemical barriers (e.g. complement system and other plasma proteins), that prevent or delay the entry of invading agents. This branch of the immune system also features cells including neutrophils, monocytes/macrophages, dendritic cells, mast cells, natural killer cells, innate lymphoid cells, natural killer cells, and lymphocytes with limited diversity. Adaptive immunity, on the other hand, is mainly represented by lymphocytes [50]. The implications of aging over different cells in the immune system are depicted in Fig. 3 and explored in Table 2.

The innate immunity components rely on pattern recognition receptors (PRR) to identify and respond to microbes and damaged cells. These mainly recognize pathogen-associated molecular patterns (PAMPs), such as the bacterial componentes lipopolysaccharide and lipoteichoic acids, and viral double stranded RNA. PRRs also detect damage-associated molecular patterns (DAMPs), including high mobility group box-1, heat-shock and S100 proteins. During the aging process, both PAMPs and DAMPs become more abundant [51].

2.2.1. Anatomical barriers and aging

The gastrointestinal (GI) tract presents the most extensive interface between the human organism and the environment, heavily influencing organismal homeostasis and the immune system. While the GI tract restricts the entry of pathogens, it works in balance with dietary and microbial components in a highly dynamic fashion. Associated with the GI epithelium is the gut-associated lymphoid tissue (GALT), which is home to about 30 % of all lymphocytes present in the body, as well as immunoglobulins that are responsible for binding to and inactivating antigens, therefore influencing organismal homeostasis.

Even though the process of intestinal aging has not been completely

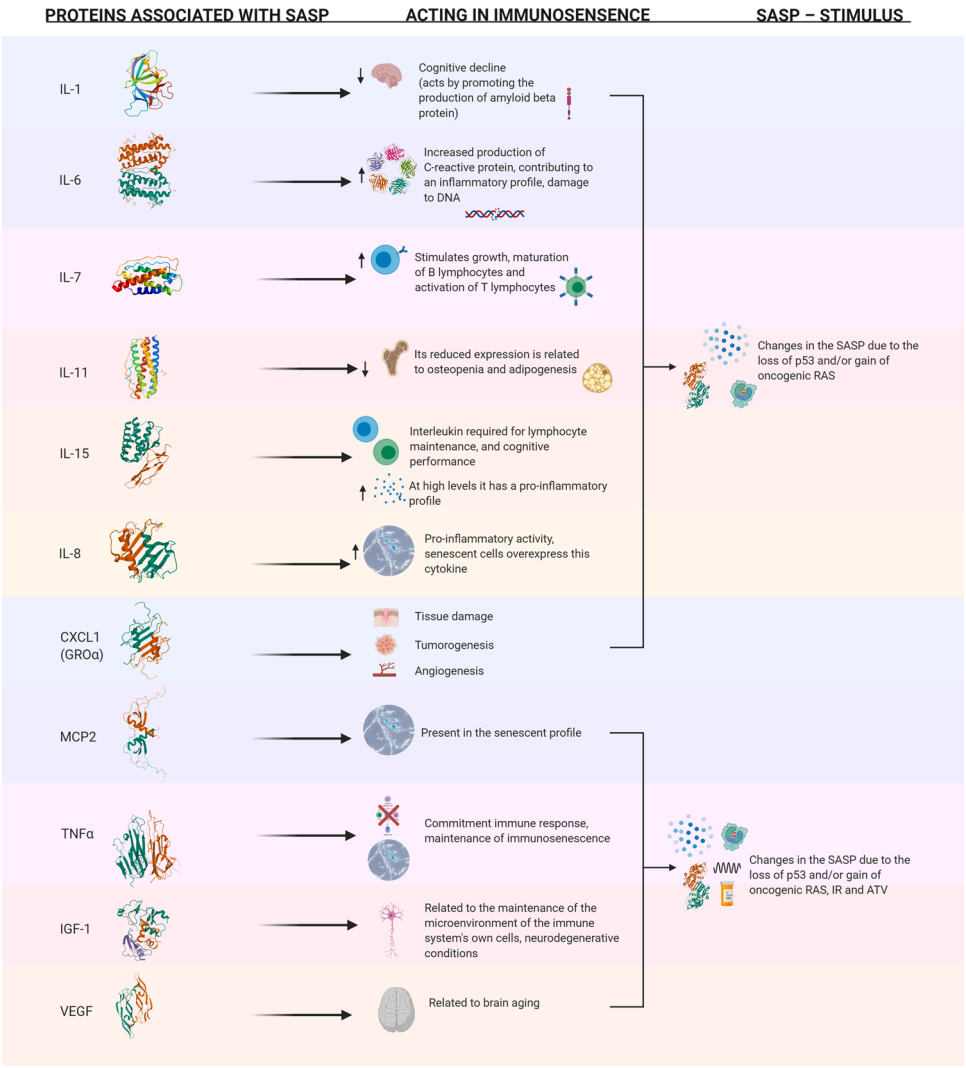

Fig. 2. Cytokine and soluble factor changes associated with immunosenescence and their implications in organismal function.

elucidated at this point, it has been shown that aging leads to compromised stem cell function in the intestinal mucosa, as well as altered architecture of mucosal villi [52]. Accompanying that phenotype, at least some components of the GI tract mucosa are altered, including lower mucus layer thickness [53], and increased intestinal permeability [54], the latter of which was associated with frailty in tested subjects. Furthermore, a reduction of microbial community diversity has been observed in elderly subjects [55,56], being correlated to chronic inflammation [57] and neurodegeneration [58]. The role of the local microbiota in the intestinal mucosa aging is not clear at this point, but it has been possible to closely correlate some microbiota components to chronological age, in a study yet in preprint status [59]. Defects in the barrier function of the GI tract are related to local and systemic diseases, such as irritable bowel syndrome [60], and obesity [55]. In the context of dysfunctional GI tract epithelium, microbial components from the intestine, such as lipopolysaccharides (LPS), present in the cell wall of gram-negative bacteria, are able to induce an inflammatory response and damage this intestinal barrier. Inflammation then increases the permeation of molecules in the intestinal wall, provoking further tissue alterations.

Recently, similar observations were made for the skin, which is the major organ in the human body, composing 15 % of body weight [61]. The barrier function of the skin is also compromised with aging, due to cellular senescence [62], and stem cell dysfunction associated with inflammatory signaling [62], both events rooted in intrinsic and extrinsic factors [63]. Skin that accumulates senescent cells and shows stem cell dysfunction frequently takes longer to renew itself, and shows a thinner epidermis with scarce stratum corneum, which is the upper most layer of the skin composed of cornified cells and protects the inner layers of the skin [64]. Recently, the age-related dysfunction of the skin barrier was significantly associated with high circulating levels of IL-1β, IL-6 and TNFα in both mice [65] and humans [66]. It was found that a 30-day emollient application was able to restore the normal levels of circulating IL-1b and IL-6, according to a small trial in humans [66].

Thus, aging hallmarks can be associated with dysfunctional anatomical barriers and increased exposure and circulation of PAMPs and DAMPs [67], which may promote the constant innate immunity activation and inflammation - as hypothesized by different authors [68], and ultimately disturb the organismal immune system homeostasis.

2.2.2. *Aging and DAMP-induced inflammation*

Inflammaging is one of the consequences of immunosenescence, being characterized by an inflammatory state frequently connected with sterile inflammation, underscoring the importance of DAMP-induced activation of the innate immunity in this scenario. Hallmarks of aging appear here once again, since a few of them (e.g. genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, and mitochondrial dysfunction) may directly result in the release of DAMPs [51], or concatenate to promote cellular senescence, the SASP being shown to include several DAMPs [14]. Corroborating such a perspective,

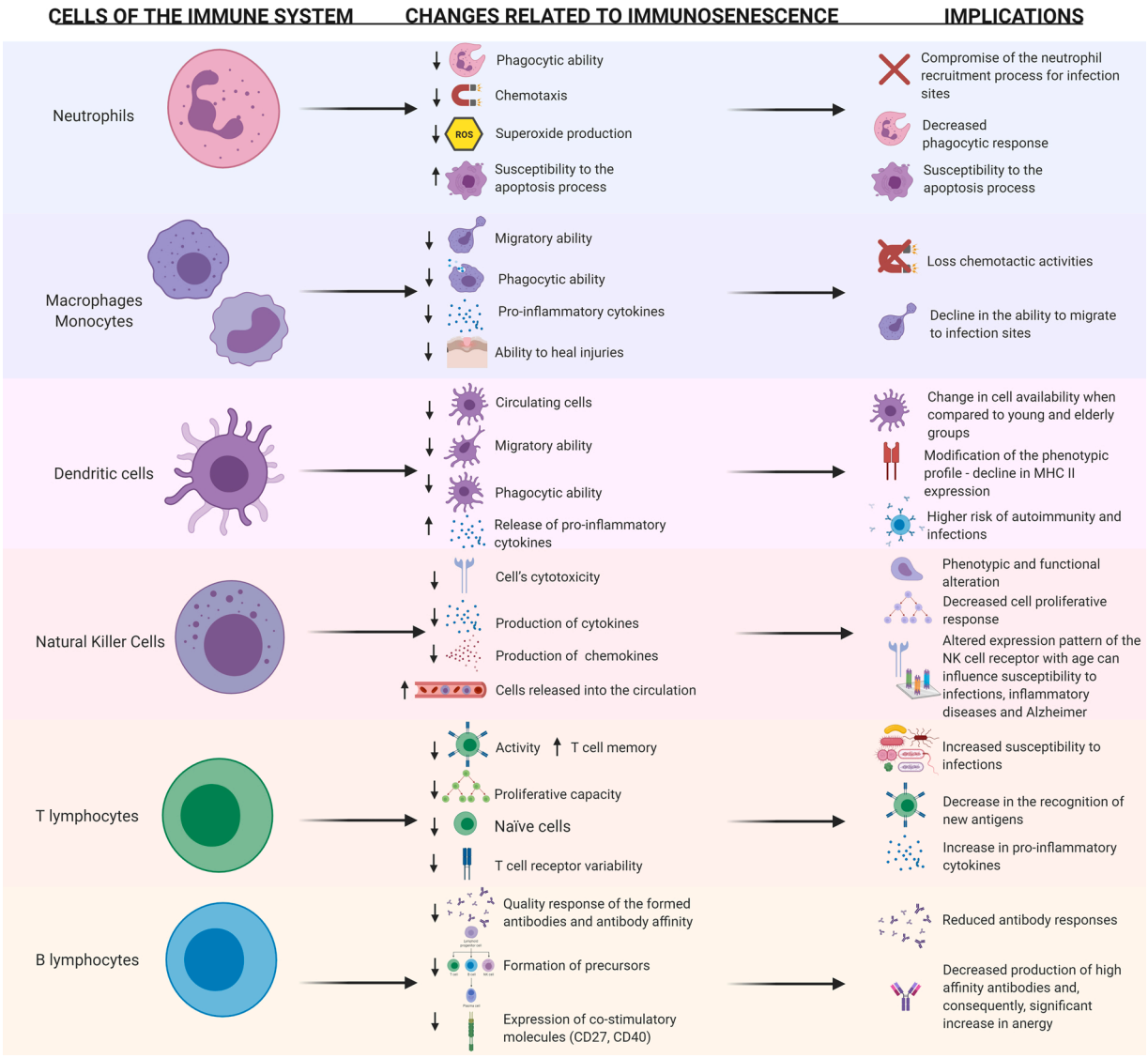

Fig. 3. Cellular changes associated with immunosenescence and their implications in the behaviour of neutrophils; macrophages and monocytes; dendritic cells; natural killer cells; and T and B lymphocytes.

DAMPs generated from mitochondria have also been shown to be pro-inflammatory [69] and associated with age-related diseases, such as neurodegeneration [70,71]. Furthermore, as experimentally shown by De Cecco et al., LINE-1 activation increases exponentially with replicative senescence, activating a type I interferon response and inflammation [72]. PAMP stimulation has also been shown to induce DAMP secretion by immune cells [51]. Thus, aging may promote inflammation in two fashions: directly by compromising cellular metabolism and activating internal inflammatory pathways; and indirectly by provoking senescent cell accumulation and the release of inflammatory cytokines and DAMPs through SASP.

Taken together, the altered anatomical barriers and the accumulation of damaged and senescent cells synergise to alter the function of innate immunity components, which influence adaptive immunity cells and contribute to the subclinical inflammatory and exhausted state observed in aging.

2.2.3. *Innate immune cells and aging*

As described in the bone marrow, aging alters the milieu of most, if not all, tissues in the body. Associated with increased PAMPs and DAMPs, as well as SASP, the aging process results in altered numbers and functions of innate immune cells, as summarized in Table 2, and depicted in Fig. 3.

Neutrophils are one the most abundant leukocytes in the blood, and constitute a paramount component of the innate immune system. They are the first cells to reach sites of infection, where they recognize and phagocytose pathogens. Even though there seem to be no significant differences in the numbers of circulating neutrophils of healthy older people compared to younger subjects [73], their function may be compromised in the elderly population (Table 2). Indeed, it has been documented that activated neutrophils obtained from older individuals are more prone to apoptosis [74] and less effective in phagocytosis and chemotaxis [75]. In aged mice, neutrophil migration is compromised [76], as is their capacity for phagocytosis and elimination of dead cells [77,78]. In this sense, it has been shown that the persistence of inflammatory neutrophils in lesioned sites may contribute to a failure in the mechanisms that promote the resolution of inflammation, ultimately leading to tissue lesion and even mortality [79,80].

Macrophages constitute important innate immunity components, comprising a heterogeneous cell population that may differ in phenotype and behavior according to the site at which they are found [81]. As cells which are sensitive to the local milieu and also subject to senescence [82], macrophages also present functional alterations with aging. As revised by van Beek et al. [83], aged macrophages derived from

Table 2
Age-related alterations in innate and adaptive immune system cell types.

Cell type	Role in the immune system	Imunosenescence-related alterations	Implications
Neutrophils	Recognition, phagocytosis and destruction of pathogens	↓ phagocytic ability, chemotaxis, superoxide production (ROS) ↑ susceptibility to the apoptosis process	Susceptibility to the apoptosis process. Compromise of the efficiency of the neutrophil recruitment process for infection sites. Decreased phagocytic response [143,144].[a]
Macrophages Monocytes	Activation of the immune response, act as "pathogenic sensors". Act as tissue sentinels	↓ migratory ability, phagocytic ability, phagosomal ability, decreased pro-inflammatory cytokines, ability to heal injuries	Decline in the ability to migrate to infection sites. Loss of chemotactic activities [145].[b]
Dendritic cells	Specialized in the capture and presentation of antigens. Important interaction with adaptive immunity.	↓ circulating cells, migratory ability, phagocytic ability ↑ release of pro-inflammatory cytokines	Change in cell availability when compared to young and elderly groups Modification of the phenotypic profile, with decline in MHC II expression [146].[a]Higher risk of autoimmunity and infections [147].
Natural Killer Cells	Higher risk of autoimmunity and infections. Important nonspecific line of defense, recognizing and lysing cells infectedby viruses, bacteria and protozoa, as well as tumor cells. They recruit neutrophils and macrophages, activate DCs and T and B lymphocytes	↓ cell cytotoxicity, production of cytokines and chemokines ↑ cells released into the circulation	Phenotypic and functional alteration. Decreased cell proliferative response. The altered expression pattern of the NK cell receptor with age can influence susceptibility to infections, inflammatory diseases and Alzheimer [148].
T lymphocytes	Induction of an adequate response to pathogens and neoplasms. Protection after vaccination.	↓ activity, proliferative capacity, naïve cells, T cell receptor variability ↑ memory T cells	Increased susceptibility to infectious processes. Lower capacity of new antigen recognition. Increased proinflammatory cytokine secretion [149,150].
B lymphocytes	Antibody production	↓ effective antibodies, precursor formation, expression of costimulatory molecules (CD27, CD40), antibody affinity.	Reduced response to antibodies. Reduced production of high affinity antibodies. Increased anergy [145].[a]

[a] Studies executed in human models.
[b] Studies involving animal models.

different sites (e.g. circulating monocytes, peritoneum, skin, brain) present unchanged or compromised phagocytosis activity, and altered response to lipopolysaccharide (either higher or lower response, compared to young counterparts) (Table 2). The macrophage behavior is frequently associated with their state of polarization, which is dichotomized as pro-inflammatory M1 or anti-inflammatory and fibrotic M2, despite being two extremes of a continuum [84]. The M1/M2 polarization has been shown to be an intricate product of macrophage stimulation, metabolic status and cellular stress [83]. Nevertheless, during aging, endoplasmic reticulum stress, altered nutrient sensing, and inflamed surroundings promote the accumulation of non-conventional, alternatively activated proinflammatory M2 cells [83]. Since macrophages represent an important link between innate and adaptive immunity, their altered phenotype promotes adaptive immunity exacerbation and exhaustion, as discussed in the following section.

Dendritic cells can be classified as conventional or plasmacytoid dendritic cells [85]. These cells are essential links between innate and adaptive immune systems because they are the major antigen presenting cells for naive T-cells, and heavily influence the polarization of TCD4+ cells into Th1, Th2 and other cell patterns. Due to the difficulty in obtaining human samples for isolation of these cell types, information regarding their numbers and functionality during aging in humans is relatively scarce (Table 2). However, a few studies reveal that the numbers of circulating plasmacytoid dendritic cells are reduced in healthy elderly, compared to healthy young subjects, and even more in frail elderly. Reduction of conventional dendritic cells (cDC) has also been demonstrated in frail elderly [86]. Still, in a large study involving different tissue samples of patients ranging from 0 to 93 years old, dendritic cell distribution in different tissues seemed unchanged during aging [87]. These results show that there are still divergences between studies and changes in the number of dendritic cells during aging is not completely clear.

Upon stimulation, plasmacytoid dendritic cells isolated from elderly donors presented lower IFN I and II producing capacity, which was associated with lower TLR expression, and compromised antiviral response [86]. Considering conventional dendritic cells, Zacca et al. [88] found that conventional dendritic cells from old mice have a weak ability to stimulate a T CD8 + cell-mediated cytotoxic response, suggesting that immunosenescence affects cDC function, which in turn compromises the activation of naive CD8 + T cells and the generation of effector cytotoxic T cells. Agrawal et al. [89] demonstrated that there is an increase in the production of IL-6 and TNF-a in aged dendritic cells, suggesting a pro-inflammatory bias nonetheless. Monocyte-derived dendritic cells can be considered a third subpopulation of dendritic cells [85]. Agrawal et al. noticed reduced functional capacity of monocyte-derived dendritic cells (CD14- / HLA-DR+ / CD11+) derived from older subjects [90].

Among the current explanations for dendritic cell alteration during aging, there is the excessive NF-κB stimulation [91,92] engendered by different processes, such as cellular senescence, DAMP and PAMP stimulation, and changes in local and circulating cytokine levels, as previously discussed. Therefore, despite the limited data available, dendritic cells also seem compromised during aging, and this could help explain several phenotypes of immunosenescence, including the increased susceptibility to infection, loss of tolerance and compromised response to vaccination [93].

Natural killer (NK) cells are a subpopulation of lymphocytes involved in innate immunity. They are characterized as important modulators of antitumor activity and also act against intracellular organisms. These cells have the important ability to produce cytokines and chemokines after cell recognition, so they are important parts of innate immunity during aging, and also to promote cytotoxicity. Studies have shown that there are different changes in NK cell subsets with age, generally accompanied with altered functional activity [94]. Age-related NK cell population remodeling seems to result in a predominant NK cell profile characterized by a lower capacity to respond to cytokines, leading to

dysregulation of DC activation and low interaction with macrophages. This behavior can contribute to the increased risk of infections with increased morbidity and mortality in the elderly [95].

The studies cited above provide hints about how aging leads to multiple alterations of key innate immune components. The compromised barriers in the organism and the accumulation of processes identified as aging hallmarks lead to an environment characterized by abundant DAMPs and PAMPs, as well as inflammatory cytokines, which promote cellular phenotype and functional alterations, from progenitor to mature cell types.

2.3. Immunosenescence and adaptive immune response

The adaptive immune system is intrinsically associated with and tuned by the innate immune system. Therefore, it follows that, as the innate system is altered by aging, the adaptive immunity is also impaired.

The adaptive immune system is formed by B lymphocytes, T lymphocytes and by the complement of antibodies present in the body. After the recognition of antigens by surface receptors, lymphocytes multiply in large quantities (clonal expansion), differentiating into effector and memory cells. However, several cross-sectional studies document that elderly people have a characteristic immunological profile. They have low numbers of naive T lymphocytes and a high number of memory T lymphocytes, especially CD8+ cells (cytotoxic) in an advanced stage of differentiation [21]. Corroborating this notion, the Leiden Longevity Study (LLS) - which evaluated a cohort of long-lived individuals representing 0.5 % of the general population and enjoying a reduced (30 %) mortality rate compared to the general population - has shown that, in these individuals, there is no accumulation of highly differentiated T cells, nor is there a significant reduction in naive T cells [96]. Such an observation allows one to suppose that the greater susceptibility to viral and chronic infections in the elderly may be related to the limited availability of naive cells for the recognition of new antigens, which is influenced by genetic factors, but also the individual's history of exposure to antigens.

For lymphocytes to act efficiently in the defense of the organism, the maturation / selection process of these cells is essential. B-lymphocytes, which originate plasmocytes (responsible for the production of antibodies and memory cells), may also give rise to regulatory B-cells, which produce IL-10, essential for the regulation of immune responses, and the prevention of unnecessary stimuli from activating the immune system.

With age, the altered bone marrow niche is associated with a skew towards the generation of myeloid cell types [25] in detriment to the production of lymphocytes (Table 2). In the case of B-cells, the bone marrow niche has been related to this phenomenon, since experiments in mice have shown that the transfer of old bone marrow progenitors to a young bone marrow niche resulted in normal numbers of circulating pre-B-cells, while the transfer of young bone marrow progenitors to an old recipient led to the low number of pre-B-cells found in aged mice [97]. Furthermore, intrinsic factors also seem to compromise B-cell generation in the aged bone marrow, since Rag2 and recombinase function are compromised with aging [97], and Pax5 expression (relevant for the maintenance of the B-cell phenotype - [98]) is not optimal [99]. Corroborating such observations, Kosuke Hashimoto [100] et al. carried out single-cell transcriptomic evaluation of PBMCs in elderly people over the age of 110 years and observed a significant decrease in the overall number of circulating B-cells in this group in comparison to people between their 50s and 80s, as well as in the naive B-cell subset.

The aged bone marrow is also less effective in selecting autoreactive B-cells for elimination [101,102]. These processes lead to the accumulation of long-lived age-associated B-cells (ABCs), first identified in mice [103], but also identified in humans, at least in some pathological contexts [104–106]. In mice, it has recently been suggested that the ABCs are memory B-cells [107], with specific characteristics of autoreactivity, as well as secretion of TNF-α. The latter acts in the bone marrow niche, leading to a decreased survival of B-cell precursors, and also to a proinflammatory environment characterized by reduced synthesis of IL-10 and IL-4. ABCs also mediate antigen presentation to CD4 + T-cells in the T-cell zone of lymph nodes, further contributing to the immune system dysregulation [108].

In recognition of such effects of peripheral cells over the bone marrow niche [109], the elimination of circulating B-cells in aged mice resulted in the rejuvenation of the hematopoietic system, with the reestablishment of the B-lymphopoiesis [110]. Such an intervention has not led to restored immunocompetence in mice, however [111].

Unlike B-cells, which are produced and matured in the medullary microenvironment, T-cells are produced in the medulla and matured in the thymus. The thymus is considered a primary lymphoid organ, located at the back of the sternum. It is divided into lobes, each lobule having a cortical and stroma region, these zones being closely involved in specific processes of maturation and differentiation of T lymphocytes, providing a specialized environment for this task. The production of reactive T-cells occurs more robustly during childhood, but the maintenance of production occurs throughout life. However, as people age, the thymus involutes, considerably reducing the production of T-cells [7,112].

In 1985, Steinman and collaborators demonstrated that the process of involution of thymus begins from the first year of life. With thymus involution, there is a lag in the thymic microenvironment with a consequent decrease in IL-7 production (Table 1), highly compromising the activation of T lymphocytes [112].

B- and T-cells have important functions in the immune system. With the progression of age and evolution of the immunosenescence process, there is a consequent alteration in these cell classes. Studies show that the levels of composition and expression of the population of peripheral lymphocytes change dynamically over time. The number of naive T lymphocytes falls and there is an increase in memory T lymphocytes, with a significant decrease in B lymphocytes (Table 2; Fig. 3), contributing to a greater risk of occurrence of infectious diseases, cancer and autoimmune diseases observed with aging [112,113].

In centenarians, T cell numbers were shown to be similar to controls, aged between their 50s and 80s, but their profiles were altered. In addition to the decrease in naive T-cells, CD4+ T cells presented an altered phenotype. CD4+ T cells, which primarily have an auxiliary function, mainly coordinating immune response and activating humoral mechanisms through the connection with B lymphocytes, presented cytotoxic characteristics in the studied centenarians. According to the authors of the study [100], the conversion of CD4+ helper T cells into a cytotoxic phenotype can be seen as a favorable adaptation, which might be protective against aging.

Underlying these and other modifications observed in the immune cells lie different processes, telomere shortening being one of the most well established immunosenescence markers. Peripheral lymphocyte telomere length is actually a marker of biological aging and health [114], and is paramount for T-reg function [115]. T-cell differentiation leads to lower telomerase expression, and is associated with a lower T-cell proliferation [116]. Mitochondrial stress is related to oxidative stress in different cell types, and seems to accelerate telomere shortening. In T cells, such a correlation was experimentally confirmed by Sanderson and Simon [117]. In this line, the authors also showed that antioxidant treatment prevented telomere shortening.

As revised by McHugh and Gil [118], telomere erosion, mitochondrial dysfunction and the associated oxidative stress lead to cellular senescence. Though not a consensus, it seems that T cells may evolve to a senescent-like state and accumulate with aging. Even though they seem to lack some of the classic markers of cellular senescence, senescent-like T cells acquire a specific phenotype related to such a cellular state, characterized by loss of CD27 and CD28, as well as the expression of CD57, CD45RA, and/or KLRG-1 [119]. Despite a lack of consensus, the senescence of T cells may compromise their senescent-cell elimination response, as suggested by Pereira et al. [13]. According to their

observations, senescent cells increase expression of HLA-E, while mature T cells are characterized by high expression of NKG2A. The interaction between both surface proteins compromises the elimination of senescent cells, while the blockade fostered the cytotoxic effect of T cells over senescent dermal fibroblasts.

The age-related phenotypes of B and T cells also compromise their interaction, as shown by Eaton et al. [120] and others. Finally, non-proliferative T lymphocytes secrete pro-inflammatory cytokines, such as IL-6 and TNF-α [119,121]. Such a SASP may be interpreted as an attempt to defend the organism from the development of cancer, leading cells to programmed aging.

3. Inflammaging, aging and comorbidities: cause or consequence?

Understanding the intra- and intercellular events that occur in the immune system components during aging contributes to the comprehension of how immunosenescence, inflammaging and the aging hallmarks interconnect.

As summarized by Fulop et al. [122], immunosenescence is the state of the immune system after accumulating the changes that occur with aging. Inflammaging, the condition characterized by dysregulation and increased release of inflammatory mediators, is therefore a consequence of immunosenescence. Nevertheless, inflammaging may engender a feedforward process further promoting immunosenescence. Organismal aging also seems to play a dual role in the context of inflammaging and immunosenescence. As an event associated with functional decay of the organism, aging of anatomical barriers, cardiovascular components, neural components, among others, contribute to accumulated DAMPs and PAMPs in the organism. Such an accumulation also contributes to chronic immune system activation, which intrinsically relates to immunosenescence and inflammaging. In this sense, inflammaging can be seen as the consequence of immunosenescence-related immune dysfunction, age-related organismal function decay, cellular senescence and environmental factors, such as infections and obesity.

To some authors, immunosenescence underlies major age-related illnesses, such as cardiovascular disease, autoimmune disorders, cancer and neurodegeneration [123]. Indeed, inflammatory markers, such as NF-kB, are associated with signs of accelerated aging, alopecia, kyphosis, osteoporosis, central nervous system changes and even increased cellular senescence, reduced regenerative capacity and shorter lifespan in aged mice [124].

4. Perspectives and interventions against immunosenescence

Aging must be understood as a multifaceted process influenced by intrinsic and extrinsic factors. Even though biological aging is beginning to be unraveled in a more mechanistic way, several aspects remain poorly elucidated at this point. The influence of psychosocial factors over the immune system, mediated via neuroendocrine-immune interactions, for instance, must be better investigated, both during youth and aging. Understanding of the influence of microbiota is also in its infancy at this point. In the future, ever more holistic approaches may be incorporated into the investigation of immunity and immunosenescence, the whole exposome possibly becoming investigated in this sense.

Given the acquired knowledge at this point, there are a few interventions which may be considered with a view to delaying immunosenescence. The practice of regular physical exercise, in conjunction with a balanced diet and body fat control, for instance, has shown, through cross-sectional studies, to be associated with a reduction in inflammatory levels, with a concomitant reduction of SASP-related cytokines. Nahrendorf and colleagues [125] showed that physical exercise decreases the cardiovascular inflammatory profile and also decreases atherosclerotic plaque formation. This happens due to the potential that physical activity has in regulating the hematopoietic microenvironment, reducing the systemic supply of inflammatory leukocytes. Nevertheless, it is possible that physical exercise exerts more direct effects over cellular senescence than just modulating inflammation.

An important point in relation to maintaining a healthy diet is the key role that body mass plays in immunomodulation. A diet low in nutrients and amino acids favors the appearance of opportunistic diseases [126], while diets rich in cysteine, glutamine and arginine have been shown to be effective in strengthening the immune system [127–129]. Unbalanced diets may also cause dysfunction in energy sensing signaling pathways, in an opposite fashion compared to fasting. Diets may also influence aging by altering local intestinal microbiota. For instance, it is known that high-fiber diets act in the positive modulation of intestinal immune function. Butyrate, a short-chain fatty acid, for example, is produced by bacteria located in the colon through the fermentation of fibers, and inhibits the interaction between macrophages and adipocytes, attenuating inflammatory responses [130,131]. Butyrate has also been shown to control the differentiation and maturation of dendritic cells [132], in addition to their capacity to induce T-reg generation [133]. The anti-inflammatory and antioxidant potential of some ingredients may also mitigate pro-inflammatory responses. Corroborating such a notion, fruit and vegetable-rich diets were shown to reduce neurodegenerative processes and contribute to memory and cognition.

Since aging is an increasingly fast-pace field, it is important to recapitulate the most important aspects of aging and to connect the underlying molecular events to the functional and phenotypic mechanisms of immunosenescence. So far, our little understanding regarding the connection between hallmarks of aging and immunosenescence has already provided exciting paths towards the biological rejuvenation of the immune system and the organism. As knowledge in this theme accumulates, geroprotector and senotherapeutic strategies are set to expand.

Declaration of Competing Interest

JLC is co-founder of OneSkin. All authors declare no conflict of interest.

Acknowledgments

This study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Distrito Federal (FAPDF).

References

[1] Pessoas idosas, ONU, Brasil, 2014 (Accessed March 31, 2020), https://nacoesunidas.org/acao/pessoas-idosas/.
[2] A.J. Parry, M. Narita, Old cells, new tricks: chromatin structure in senescence, Mamm. Genome 27 (2016) 320–331.
[3] A. Calcinotto, J. Kohli, E. Zagato, L. Pellegrini, M. Demaria, A. Alimonti, Cellular senescence: aging, cancer, and injury, Physiol. Rev. 99 (2019) 1047–1078.
[4] J. Campisi, Cellular senescence, aging, and cancer, Innov. Aging 2 (2018) 798, https://doi.org/10.1093/geroni/igy023.2963.
[5] J.-P. Coppé, P.-Y. Desprez, A. Krtolica, J. Campisi, The senescence-associated secretory phenotype: the dark side of tumor suppression, Annu. Rev. Pathol. 5 (2010) 99–118.
[6] J.-P. Coppé, C.K. Patil, F. Rodier, Y. Sun, D.P. Muñoz, J. Goldstein, P.S. Nelson, P.-Y. Desprez, J. Campisi, Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor, PLoS Biol. 6 (2008) 2853–2868.
[7] G. Pawelec, Hallmarks of human “immunosenescence”: adaptation or dysregulation? Immun. Ageing 9 (2012) https://doi.org/10.1186/1742-4933-9-15.
[8] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging, Cell 153 (2013) 1194–1217.
[9] V. Gorgoulis, P.D. Adams, A. Alimonti, D.C. Bennett, O. Bischof, C. Bishop, J. Campisi, M. Collado, K. Evangelou, G. Ferbeyre, J. Gil, E. Hara, V. Krizhanovsky, D. Jurk, A.B. Maier, M. Narita, L. Niedernhofer, J.F. Passos, P. D. Robbins, C.A. Schmitt, J. Sedivy, K. Vougas, T. von Zglinicki, D. Zhou, M. Serrano, M. Demaria, Cellular Senescence, Defining a path forward, Cell 179 (2019) 813–827.

[10] A. Lujambio, To clear, or not to clear (senescent cells)? That is the question, Bioessays 38 (Suppl 1) (2016) S56–64.
[11] L. Hoenicke, L. Zender, Immune surveillance of senescent cells–biological significance in cancer- and non-cancer pathologies, Carcinogenesis 33 (2012) 1123–1126.
[12] T.-W. Kang, T. Yevsa, N. Woller, L. Hoenicke, T. Wuestefeld, D. Dauch, A. Hohmeyer, M. Gereke, R. Rudalska, A. Potapova, M. Iken, M. Vucur, S. Weiss, M. Heikenwalder, S. Khan, J. Gil, D. Bruder, M. Manns, P. Schirmacher, F. Tacke, M. Ott, T. Luedde, T. Longerich, S. Kubicka, L. Zender, Senescence surveillance of pre-malignant hepatocytes limits liver cancer development, Nature 479 (2011) 547–551.
[13] B.I. Pereira, O.P. Devine, M. Vukmanovic-Stejic, E.S. Chambers, P. Subramanian, N. Patel, A. Virasami, N.J. Sebire, V. Kinsler, A. Valdovinos, C.J. LeSaux, J. F. Passos, A. Antoniou, M.H.A. Rustin, J. Campisi, A.N. Akbar, Senescent cells evade immune clearance via HLA-E-mediated NK and CD8 T cell inhibition, Nat. Commun. 10 (2019) 2387.
[14] N. Basisty, A. Kale, O.H. Jeon, C. Kuehnemann, T. Payne, C. Rao, A. Holtz, S. Shah, V. Sharma, L. Ferrucci, J. Campisi, B. Schilling, A proteomic atlas of senescence-associated secretomes for aging biomarker development, PLoS Biol. 18 (2020), e3000599.
[15] Y. Ovadya, T. Landsberger, H. Leins, E. Vadai, H. Gal, A. Biran, R. Yosef, A. Sagiv, A. Agrawal, A. Shapira, J. Windheim, M. Tsoory, R. Schirmbeck, I. Amit, H. Geiger, V. Krizhanovsky, Impaired immune surveillance accelerates accumulation of senescent cells and aging, Nat. Commun. 9 (2018) 5435.
[16] S. Hubackova, K. Krejcikova, J. Bartek, Z. Hodny, IL1- and TGFβ-Nox4 signaling, oxidative stress and DNA damage response are shared features of replicative, oncogene-induced, and drug-induced paracrine "bystander senescence", Aging 4 (2012) 932–951.
[17] M. Hoare, M. Narita, Transmitting senescence to the cell neighbourhood, Nat. Cell Biol. 15 (2013) 887–889.
[18] J.C. Acosta, A. Banito, T. Wuestefeld, A. Georgilis, P. Janich, J.P. Morton, D. Athineos, T.-W. Kang, F. Lasitschka, M. Andrulis, G. Pascual, K.J. Morris, S. Khan, H. Jin, G. Dharmalingam, A.P. Snijders, T. Carroll, D. Capper, C. Pritchard, G.J. Inman, T. Longerich, O.J. Sansom, S.A. Benitah, L. Zender, J. Gil, A complex secretory program orchestrated by the inflammasome controls paracrine senescence, Nat. Cell Biol. 15 (2013) 978–990.
[19] C. Nombela-Arrieta, G. Pivarnik, B. Winkel, K.J. Canty, B. Harley, J.E. Mahoney, S.-Y. Park, J. Lu, A. Protopopov, L.E. Silberstein, Quantitative imaging of haematopoietic stem and progenitor cell localization and hypoxic status in the bone marrow microenvironment, Nat. Cell Biol. 15 (2013) 533–543.
[20] J.L. Spees, R.H. Lee, C.A. Gregory, Mechanisms of mesenchymal stem/stromal cell function, Stem Cell Res. Ther. 7 (2016), https://doi.org/10.1186/s13287-016-0363-7.
[21] D. Aw, A.B. Silva, D.B. Palmer, Immunosenescence: emerging challenges for an ageing population, Immunology 120 (2007) 435–446.
[22] A.H. Undale, J.J. Westendorf, M.J. Yaszemski, S. Khosla, Mesenchymal stem cells for bone repair and metabolic bone diseases, Mayo Clin. Proc. 84 (2009) 893–902, https://doi.org/10.4065/84.10.893.
[23] P. Bianco, M. Riminucci, S. Gronthos, P.G. Robey, Bone marrow stromal stem cells: nature, biology, and potential applications, Stem Cells 19 (2001) 180–192.
[24] K. Miharada, T. Hiroyama, K. Sudo, I. Danjo, T. Nagasawa, Y. Nakamura, Lipocalin 2-mediated growth suppression is evident in human erythroid and monocyte/macrophage lineage cells, J. Cell. Physiol. 215 (2008) 526–537.
[25] L.A. Warren, D.J. Rossi, Stem cells and aging in the hematopoietic system, Mech. Ageing Dev. 130 (2009) 46–53.
[26] K. Yoshida, J.B. Cologne, K. Cordova, M. Misumi, M. Yamaoka, S. Kyoizumi, T. Hayashi, H. Robins, Y. Kusunoki, Aging-related changes in human T-cell repertoire over 20years delineated by deep sequencing of peripheral T-cell receptors, Exp. Gerontol. 96 (2017) 29–37.
[27] V. Martin, Y.-C. (bryan) Wu, D. Kipling, D. Dunn-Walters, Ageing of the B-cell repertoire, Philos. Trans. Biol. Sci. 370 (2015), 20140237, https://doi.org/10.1098/rstb.2014.0237.
[28] J. Wu, W. Zhang, Q. Ran, Y. Xiang, J.F. Zhong, S.C. Li, Z. Li, The differentiation balance of bone marrow mesenchymal stem cells is crucial to hematopoiesis, Stem Cells Int. 2018 (2018), 1540148.
[29] C. Franceschi, M. Bonafè, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, G. De Benedictis, Inflamm-aging. An evolutionary perspective on immunosenescence, Ann. N. Y. Acad. Sci. 908 (2000) 244–254.
[30] S. Gangemi, G. Basile, D. Monti, R.A. Merendino, G. Di Pasquale, U. Bisignano, V. Nicita-Mauro, C. Franceschi, Age-related modifications in circulating IL-15 levels in humans, Mediators Inflamm. 2005 (2005) 245–247.
[31] B.A. Barajas-Gómez, O. Rosas-Carrasco, S.L. Morales-Rosales, G. Pedraza Vázquez, V.Y. González-Puertos, T. Juárez-Cedillo, J.A. García-Álvarez, N. E. López-Diazguerrero, P. Damián-Matsumura, M. Königsberg, A. Luna-López, Relationship of inflammatory profile of elderly patients serum and senescence-associated secretory phenotype with human breast cancer cells proliferation: role of IL6/IL8 ratio, Cytokine 91 (2017) 13–29.
[32] P. Ortiz-Montero, A. Londoño-Vallejo, J.-P. Vernot, Senescence-associated IL-6 and IL-8 cytokines induce a self- and cross-reinforced senescence/inflammatory milieu strengthening tumorigenic capabilities in the MCF-7 breast cancer cell line, Cell Commun. Signal 15 (2017) 17.
[33] M. Saito, S. Inoue, K. Yamashita, Y. Kakeji, T. Fukumoto, J. Kotani, IL-15 improves aging-induced persistent t cell exhaustion in mouse models of repeated Sepsis, Shock 53 (2020) 228–235.
[34] P.L. Minciullo, A. Catalano, G. Mandraffino, M. Casciaro, A. Crucitti, G. Maltese, N. Morabito, A. Lasco, S. Gangemi, G. Basile, Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity, Arch. Immunol. Ther. Exp. 64 (2016) 111–126.
[35] T. Fulop, C. Franceschi, K. Hirokawa, G. Pawelec, Handbook of Immunosenescence: Basic Understanding and Clinical Implications, Springer, 2019.
[36] C. Franceschi, P. Garagnani, G. Vitale, M. Capri, S. Salvioli, Inflammaging and "Garb-aging,", Trends Endocrinol. Metab. 28 (2017) 199–212, https://doi.org/10.1016/j.tem.2016.09.005.
[37] A.K. Abbas, A.H. Lichtman, Cell-mediated immune responses, Basic Immunol. (2011) 89–111, https://doi.org/10.1016/b978-1-4160-5569-3.50008-1.
[38] C.D. Buckley, D. Pilling, J.M. Lord, A.N. Akbar, D. Scheel-Toellner, M. Salmon, Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation, Trends Immunol. 22 (2001) 199–204, https://doi.org/10.1016/s1471-4906(01)01863-4.
[39] C. Gabay, I. Kushner, Acute-phase proteins and other systemic responses to inflammation, N. Engl. J. Med. 340 (1999) 448–454, https://doi.org/10.1056/nejm199902113400607.
[40] C. Gabay, Interleukin-6 and chronic inflammation, Arthritis Res. Ther. 8 (Suppl 2) (2006) S3.
[41] N. Takagi, M. Mihara, Y. Moriya, N. Nishimoto, K. Yoshizaki, T. Kishimoto, Y. Takeda, Y. Ohsugi, Blockage of interleukin-6 receptor ameliorates joint disease in murine collagen-induced arthritis, Arthritis Rheum. 41 (1998) 2117–2121.
[42] M. Puzianowska-Kuźnicka, M. Owczarz, K. Wieczorowska-Tobis, P. Nadrowski, J. Chudek, P. Slusarczyk, A. Skalska, M. Jonas, E. Franek, M. Mossakowska, Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study, Immun. Ageing 13 (2016) 21.
[43] H.J. Cohen, T. Harris, C.F. Pieper, Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly, Am. J. Med. 114 (2003) 180–187.
[44] L. Ferrucci, T.B. Harris, J.M. Guralnik, R.P. Tracy, M.C. Corti, H.J. Cohen, B. Penninx, M. Pahor, R. Wallace, R.J. Havlik, Serum IL-6 level and the development of disability in older persons, J. Am. Geriatr. Soc. 47 (1999) 639–646.
[45] A.A. Beharka, M. Meydani, D. Wu, L.S. Leka, A. Meydani, S.N. Meydani, Interleukin-6 production does not increase with age, J. Gerontol. A Biol. Sci. Med. Sci. 56 (2001) B81–B88, https://doi.org/10.1093/gerona/56.2.b81.
[46] T. Tataranni, C. Mazzoccoli, F. Agriesti, L. De Luca, I. Laurenzana, V. Simeon, V. Ruggieri, C. Pacelli, G. Della Sala, P. Musto, N. Capitanio, C. Piccoli, Deferasirox drives ROS-mediated differentiation and induces interferon-stimulated gene expression in human healthy haematopoietic stem/progenitor cells and in leukemia cells, Stem Cell Res. Ther. 10 (2019) 171.
[47] L. Pangrazzi, A. Meryk, E. Naismith, R. Koziel, J. Lair, M. Krismer, K. Trieb, B. Grubeck-Loebenstein, "Inflamm-aging" influences immune cell survival factors in human bone marrow, Eur. J. Immunol. 47 (2017) 481–492.
[48] J. Chang, Y. Wang, L. Shao, R.-M. Laberge, M. Demaria, J. Campisi, K. Janakiraman, N.E. Sharpless, S. Ding, W. Feng, Y. Luo, X. Wang, N. Aykin-Burns, K. Krager, U. Ponnappan, M. Hauer-Jensen, A. Meng, D. Zhou, Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice, Nat. Med. 22 (2016) 78–83.
[49] J.N. Farr, M. Xu, M.M. Weivoda, D.G. Monroe, D.G. Fraser, J.L. Onken, B. A. Negley, J.G. Sfeir, M.B. Ogrodnik, C.M. Hachfeld, N.K. LeBrasseur, M.T. Drake, R.J. Pignolo, T. Pirtskhalava, T. Tchkonia, M.J. Oursler, J.L. Kirkland, S. Khosla, Targeting cellular senescence prevents age-related bone loss in mice, Nat. Med. 23 (2017) 1072–1079.
[50] A.K. Abbas, A.H. Lichtman, Basic Immunology: Functions and Disorders of the Immune System, W B Saunders Company, 2010.
[51] J. Huang, Y. Xie, X. Sun, H.J. Zeh 3rd, R. Kang, M.T. Lotze, D. Tang, DAMPs, ageing, and cancer: the "DAMP Hypothesis", Ageing Res. Rev. 24 (2015) 3–16.
[52] K. Nalapareddy, K.J. Nattamai, R.S. Kumar, R. Karns, K.A. Wikenheiser-Brokamp, L.L. Sampson, M.M. Mahe, N. Sundaram, M.-B. Yacyshyn, B. Yacyshyn, M. A. Helmrath, Y. Zheng, H. Geiger, Canonical Wnt signaling ameliorates aging of intestinal stem cells, Cell Rep. 18 (2017) 2608–2621.
[53] B. Sovran, F. Hugenholtz, M. Elderman, A.A. Van Beek, K. Graversen, M. Huijskes, M.V. Boekschoten, H.F.J. Savelkoul, P. De Vos, J. Dekker, J.M. Wells, Age-associated impairment of the mucus barrier function is associated with profound changes in microbiota and immunity, Sci. Rep. 9 (2019), https://doi.org/10.1038/s41598-018-35228-3.
[54] Y. Qi, R. Goel, S. Kim, E.M. Richards, C.S. Carter, C.J. Pepine, M.K. Raizada, T. W. Buford, Intestinal permeability biomarker Zonulin is elevated in healthy aging, J. Am. Med. Dir. Assoc. 18 (2017) 810.e1–810.e4.
[55] J. Wilbrink, N. Bernards, Z. Mujagic, M. van Avesaat, K. Pijls, T. Klaassen, H. van Eijk, S. Nienhuijs, A. Stronkhorst, E. Wilms, F. Troost, A. Masclee, Intestinal barrier function in morbid obesity: results of a prospective study on the effect of sleeve gastrectomy, Int. J. Obes. 44 (2020) 368–376.
[56] F. Deng, Y. Li, J. Zhao, The gut microbiome of healthy long-living people, Aging 11 (2019) 289–290.
[57] T. Rehman, Role of the gut microbiota in age-related chronic inflammation, Endocr. Metab. Immune Disord. Drug Targets 12 (2012) 361–367.
[58] K. Kowalski, A. Mulak, Brain-gut-Microbiota Axis in Alzheimer's disease, J. Neurogastroenterol. Motil. 25 (2019) 48–60.
[59] F. Galkin, A. Aliper, E. Putin, I. Kuznetsov, V.N. Gladyshev, A. Zhavoronkov, Human Microbiome Aging Clocks Based on Deep Learning and Tandem of Permutation Feature Importance and Accumulated Local Effects, 2021, https://doi.org/10.1101/507780 (n.d.).
[60] E. Wilms, F.J. Troost, M. Elizalde, B. Winkens, P. de Vos, Z. Mujagic, D.M.A. E. Jonkers, A.A.M. Masclee, Intestinal barrier function is maintained with aging -

a comprehensive study in healthy subjects and irritable bowel syndrome patients, Sci. Rep. 10 (2020) 475.
[61] J. Fenner, R.A.F. Clark, Anatomy, physiology, histology, and immunohistochemistry of human skin, Skin Tissue Eng. Regener. Med. (2016) 1–17, https://doi.org/10.1016/b978-0-12-801654-1.00001-2.
[62] M. Toutfaire, E. Bauwens, F. Debacq-Chainiaux, The impact of cellular senescence in skin ageing: a notion of mosaic and therapeutic strategies, Biochem. Pharmacol. 142 (2017) 1–12.
[63] M. Ramos-e-Silva, L.R. Celem, S. Ramos-e-Silva, A.P. Fucci-da-Costa, Anti-aging cosmetics: facts and controversies, Clin. Dermatol. 31 (2013) 750–758.
[64] I.L. Kruglikov, P.E. Scherer, Skin aging as a mechanical phenomenon: the main weak links, Nutr. Healthy Aging 4 (2018) 291–307.
[65] L. Hu, T.M. Mauro, E. Dang, G. Man, J. Zhang, D. Lee, G. Wang, K.R. Feingold, P. M. Elias, M.-Q. Man, Epidermal dysfunction leads to an age-associated increase in levels of serum inflammatory cytokines, J. Invest. Dermatol. 137 (2017) 1277–1285, https://doi.org/10.1016/j.jid.2017.01.007.
[66] L. Ye, T.M. Mauro, E. Dang, G. Wang, L.Z. Hu, C. Yu, S. Jeong, K. Feingold, P. M. Elias, C.Z. Lv, M.Q. Man, Topical applications of an emollient reduce circulating pro-inflammatory cytokine levels in chronically aged humans: a pilot clinical study, J. Eur. Acad. Dermatol. Venereol. 33 (2019) 2197–2201.
[67] A.L. Man, E. Bertelli, S. Rentini, M. Regoli, G. Briars, M. Marini, A.J.M. Watson, C. Nicoletti, Age-associated modifications of intestinal permeability and innate immunity in human small intestine, Clin. Sci. 129 (2015) 515–527.
[68] Y. Oishi, I. Manabe, Macrophages in age-related chronic inflammatory diseases, NPJ Aging Mech. Dis. 2 (2016) 16018.
[69] Q. Zhang, M. Raoof, Y. Chen, Y. Sumi, T. Sursal, W. Junger, K. Brohi, K. Itagaki, C. J. Hauser, Circulating mitochondrial DAMPs cause inflammatory responses to injury, Nature 464 (2010) 104–107.
[70] G. Petrosillo, M. Matera, G. Casanova, F.M. Ruggiero, G. Paradies, Mitochondrial dysfunction in rat brain with aging Involvement of complex I, reactive oxygen species and cardiolipin, Neurochem. Int. 53 (2008) 126–131.
[71] E. Bajwa, C.B. Pointer, A. Klegeris, The role of mitochondrial damage-associated molecular patterns in chronic neuroinflammation, Mediators Inflamm. 2019 (2019), 4050796.
[72] M. De Cecco, T. Ito, A.P. Petrashen, A.E. Elias, N.J. Skvir, S.W. Criscione, A. Caligiana, G. Brocculi, E.M. Adney, J.D. Boeke, O. Le, C. Beauséjour, J. Ambati, K. Ambati, M. Simon, A. Seluanov, V. Gorbunova, P.E. Slagboom, S.L. Helfand, N. Neretti, J.M. Sedivy, L1 drives IFN in senescent cells and promotes age-associated inflammation, Nature 566 (2019) 73–78.
[73] G.S. Chatta, R.G. Andrews, E. Rodger, M. Schrag, W.P. Hammond, D.C. Dale, Hematopoietic progenitors and aging: alterations in granulocytic precursors and responsiveness to recombinant human G-CSF, GM-CSF, and IL-3, J. Gerontol. 48 (1993) M207–12.
[74] T.P. Plackett, E.D. Boehmer, D.E. Faunce, E.J. Kovacs, Aging and innate immune cells, J. Leukoc. Biol. 76 (2004) 291–299, https://doi.org/10.1189/jlb.1103592.
[75] C. Wenisch, S. Patruta, F. Daxböck, R. Krause, W. Hörl, Effect of age on human neutrophil function, J. Leukoc. Biol. 67 (2000) 40–45.
[76] C.W. Tseng, P.A. Kyme, A. Arruda, V. Krishnan Ramanujan, W. Tawackoli, G. Y. Liu, Innate immune dysfunctions in aged mice facilitate the systemic dissemination of methicillin-resistant S. aureus, PLoS One 7 (2012) e41454, https://doi.org/10.1371/journal.pone.0041454.
[77] I. Wessels, J. Jansen, L. Rink, P. Uciechowski, Immunosenescence of polymorphonuclear neutrophils, Scientif. World J. 10 (2010) 145–160.
[78] T. Aprahamian, Y. Takemura, D. Goukassian, K. Walsh, Ageing is associated with diminished apoptotic cell clearance in vivo, Clin. Exp. Immunol. 152 (2008) 448–455.
[79] H.W. Stout-Delgado, W. Du, A.C. Shirali, C.J. Booth, D.R. Goldstein, Aging promotes neutrophil-induced mortality by augmenting IL-17 production during viral infection, Cell Host Microbe 6 (2009) 446–456.
[80] W. Sendama, The effect of ageing on the resolution of inflammation, Ageing Res. Rev. 57 (2020), 101000.
[81] M.L. Kohut, D.S. Senchina, K.S. Madden, A.E. Martin, D.L. Felten, J.A. Moynihan, Age effects on macrophage function vary by tissue site, nature of stimulant, and exercise behavior, Exp. Gerontol. 39 (2004) 1347–1360, https://doi.org/10.1016/j.exger.2004.07.001.
[82] B.M. Hall, V. Balan, A.S. Gleiberman, E. Strom, P. Krasnov, L.P. Virtuoso, E. Rydkina, S. Vujcic, K. Balan, I. Gitlin, K. Leonova, A. Polinsky, O.B. Chernova, A.V. Gudkov, Aging of mice is associated with p16(Ink4a)- and β-galactosidase-positive macrophage accumulation that can be induced in young mice by senescent cells, Aging 8 (2016) 1294–1315, https://doi.org/10.18632/aging.100991.
[83] A.A. van Beek, J. Van den Bossche, P.G. Mastroberardino, M.P.J. de Winther, P.J. M. Leenen, Metabolic Alterations in Aging Macrophages: Ingredients for Inflammaging? Trends Immunol. 40 (2019) 113–127.
[84] F. Ginhoux, J.L. Schultze, P.J. Murray, J. Ochando, S.K. Biswas, New insights into the multidimensional concept of macrophage ontogeny, activation and function, Nat. Immunol. 17 (2016) 34–40.
[85] M. Guilliams, F. Ginhoux, C. Jakubzick, S.H. Naik, N. Onai, B.U. Schraml, E. Segura, R. Tussiwand, S. Yona, Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny, Nat. Rev. Immunol. 14 (2014) 571–578.
[86] Y. Jing, E. Shaheen, R.R. Drake, N. Chen, S. Gravenstein, Y. Deng, Aging is associated with a numerical and functional decline in plasmacytoid dendritic cells, whereas myeloid dendritic cells are relatively unaltered in human peripheral blood, Hum. Immunol. 70 (2009) 777–784.
[87] T. Granot, T. Senda, D.J. Carpenter, N. Matsuoka, J. Weiner, C.L. Gordon, M. Miron, B.V. Kumar, A. Griesemer, S.-H. Ho, H. Lerner, J.J.C. Thome, T. Connors, B. Reizis, D.L. Farber, Dendritic cells display subset and tissue-specific maturation dynamics over human life, Immunity 46 (2017) 504–515.
[88] E.R. Zacca, M.I. Crespo, R.P. Acland, E. Roselli, N.G. Núñez, M. Maccioni, B. A. Maletto, M.C. Pistoresi-Palencia, G. Morón, Aging impairs the ability of conventional dendritic cells to cross-prime CD8+ t cells upon stimulation with a TLR7 ligand, PLoS One 10 (2015), e0140672.
[89] A. Agrawal, S. Gupta, Impact of aging on dendritic cell functions in humans, Ageing Res. Rev. 10 (2011) 336–345.
[90] A. Agrawal, S. Agrawal, J.-N. Cao, H. Su, K. Osann, S. Gupta, Altered innate immune functioning of dendritic cells in elderly humans: a role of phosphoinositide 3-kinase-signaling pathway, J. Immunol. 178 (2007) 6912–6922.
[91] A. Agrawal, J. Tay, S. Ton, S. Agrawal, S. Gupta, Increased reactivity of dendritic cells from aged subjects to self-antigen, the human DNA, J. Immunol. 182 (2009) 1138–1145.
[92] A. Panda, F. Qian, S. Mohanty, D. van Duin, F.K. Newman, L. Zhang, S. Chen, V. Towle, R.B. Belshe, E. Fikrig, H.G. Allore, R.R. Montgomery, A.C. Shaw, Age-associated decrease in TLR function in primary human dendritic cells predicts influenza vaccine response, J. Immunol. 184 (2010) 2518–2527.
[93] A. Agrawal, S. Agrawal, S. Gupta, Role of dendritic cells in inflammation and loss of tolerance in the elderly, Front. Immunol. 8 (2017) 896.
[94] I. Gayoso, B. Sanchez-Correa, C. Campos, C. Alonso, A. Pera, J.G. Casado, S. Morgado, R. Tarazona, R. Solana, Immunosenescence of human natural killer cells, J. Innate Immun. 3 (2011) 337–343.
[95] R. Solana, C. Campos, A. Pera, R. Tarazona, Shaping of NK cell subsets by aging, Curr. Opin. Immunol. 29 (2014) 56–61, https://doi.org/10.1016/j.coi.2014.04.002.
[96] E. Derhovanessian, A.B. Maier, R. Beck, G. Jahn, K. Hähnel, P.E. Slagboom, A.J. M. de Craen, R.G.J. Westendorp, G. Pawelec, Hallmark features of immunosenescence are absent in familial longevity, J. Immunol. 185 (2010) 4618–4624.
[97] J.E. Labrie, A.P. Sah, D.M. Allman, M.P. Cancro, R.M. Gerstein, Bone marrow microenvironmental changes underlie reduced RAG-mediated recombination and B cell generation in aged mice, J. Exp. Med. 200 (2004) 411–423, https://doi.org/10.1084/jem.20040845.
[98] I. Mikkola, B. Heavey, M. Horcher, M. Busslinger, Reversion of B cell commitment upon loss of Pax5 expression, Science 297 (2002) 110–113.
[99] E. Van der Put, D. Frasca, A.M. King, B.B. Blomberg, R.L. Riley, Decreased E47 in senescent B cell precursors is stage specific and regulated posttranslationally by protein turnover, J. Immunol. 173 (2004) 818–827.
[100] K. Hashimoto, T. Kouno, T. Ikawa, N. Hayatsu, Y. Miyajima, H. Yabukami, T. Terooatea, T. Sasaki, T. Suzuki, M. Valentine, G. Pascarella, Y. Okazaki, H. Suzuki, J.W. Shin, A. Minoda, I. Taniuchi, H. Okano, Y. Arai, N. Hirose, P. Carninci, Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 24242–24251.
[101] R.L. Riley, Impaired B lymphopoiesis in old age: a role for inflammatory B cells? Immunol. Res. 57 (2013) 361–369.
[102] D.K. Dunn-Walters, The ageing human B cell repertoire: a failure of selection? Clin. Exp. Immunol. 183 (2016) 50–56, https://doi.org/10.1111/cei.12700.
[103] Y. Hao, P. O'Neill, M.S. Naradikian, J.L. Scholz, M.P. Cancro, A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice, Blood 118 (2011) 1294–1304.
[104] A.V. Rubtsov, K. Rubtsova, A. Fischer, R.T. Meehan, J.Z. Gillis, J.W. Kappler, P. Marrack, Toll-like receptor 7 (TLR7)-driven accumulation of a novel CD11c^{+} B-cell population is important for the development of autoimmunity, Blood 118 (2011) 1305–1315.
[105] S. Wang, J. Wang, V. Kumar, J.L. Karnell, B. Naiman, P.S. Gross, S. Rahman, K. Zerrouki, R. Hanna, C. Morehouse, N. Holoweckyj, H. Liu, Autoimmunity Molecular Medicine Team, Z. Manna, R. Goldbach-Mansky, S. Hasni, R. Siegel, M. Sanjuan, K. Streicher, M.P. Cancro, R. Kolbeck, R. Ettinger, IL-21 drives expansion and plasma cell differentiation of autoreactive CD11cT-bet B cells in SLE, Nat. Commun. 9 (2018) 1758.
[106] S.A. Jenks, K.S. Cashman, E. Zumaquero, U.M. Marigorta, A.V. Patel, X. Wang, D. Tomar, M.C. Woodruff, Z. Simon, R. Bugrovsky, E.L. Blalock, C.D. Scharer, C. M. Tipton, C. Wei, S. Sam Lim, M. Petri, T.B. Niewold, J.H. Anolik, G. Gibson, F. Eun-Hyung Lee, J.M. Boss, F.E. Lund, I. Sanz, Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus, Immunity 49 (2018) 725–739, https://doi.org/10.1016/j.immuni.2018.08.015, e6.
[107] S.W. Du, T. Arkatkar, F. Al Qureshah, H.M. Jacobs, C.D. Thouvenel, K. Chiang, A. D. Largent, Q.-Z. Li, B. Hou, D.J. Rawlings, S.W. Jackson, Functional characterization of CD11c age-associated B cells as memory B cells, J. Immunol. 203 (2019) 2817–2826, https://doi.org/10.4049/jimmunol.1900404.
[108] S. Ma, C. Wang, X. Mao, Y. Hao, B cell dysfunction associated with aging and autoimmune diseases, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.00318.
[109] P.D. Pioli, D. Casero, E. Montecino-Rodriguez, S.L. Morrison, K. Dorshkind, Plasma cells are obligate effectors of enhanced myelopoiesis in aging bone marrow, Immunity 51 (2019) 351–366, e6.
[110] Z. Keren, S. Naor, S. Nussbaum, K. Golan, T. Itkin, Y. Sasaki, M. Schmidt-Supprian, T. Lapidot, D. Melamed, B-cell depletion reactivates B lymphopoiesis in the BM and rejuvenates the B lineage in aging, Blood 117 (2011) 3104–3112, https://doi.org/10.1182/blood-2010-09-307983.

[111] I. Avivi, S. Zisman-Rozen, S. Naor, I. Dai, D. Benhamou, G. Shahaf, H. Tabibian-Keissar, N. Rosenthal, A. Rakovsky, A. Hanna, A. Shechter, E. Peled, N. Benyamini, E. Dmitrukha, I. Barshack, R. Mehr, D. Melamed, Depletion of B cells rejuvenates the peripheral B-cell compartment but is insufficient to restore immune competence in aging, Aging Cell 18 (2019), e12959.
[112] G. Pawelec, Age and immunity: what is "immunosenescence"? Exp. Gerontol. 105 (2018) 4–9.
[113] A. Mizoguchi, A.K. Bhan, A case for regulatory B cells, J. Immunol. 176 (2006) 705–710.
[114] E. Tedone, E. Huang, R. O'Hara, K. Batten, A.T. Ludlow, T.-P. Lai, B. Arosio, D. Mari, W.E. Wright, J.W. Shay, Telomere length and telomerase activity in T cells are biomarkers of high-performing centenarians, Aging Cell 18 (2019) e12859, https://doi.org/10.1111/acel.12859.
[115] G.D. Richardson, A. Sage, K. Bennaceur, N. Al Zhrany, J. Coelho-Lima, E. Dookun, L. Draganova, G. Saretzki, D.T. Breault, Z. Mallat, I. Spyridopoulos, Telomerase mediates lymphocyte proliferation but not the atherosclerosis-suppressive potential of regulatory T-Cells, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 1283–1296, https://doi.org/10.1161/atvbaha.117.309940.
[116] M.S. Patrick, N.-L. Cheng, J. Kim, J. An, F. Dong, Q. Yang, I. Zou, N.-P. Weng, Human t cell differentiation negatively regulates telomerase expression resulting in reduced activation-induced proliferation and survival, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.01993.
[117] S.L. Sanderson, A.K. Simon, In aged primary T cells, mitochondrial stress contributes to telomere attrition measured by a novel imaging flow cytometry assay, Aging Cell 16 (2017) 1234–1243.
[118] D. McHugh, J. Gil, Senescence and aging: causes, consequences, and therapeutic avenues, J. Cell Biol. 217 (2018) 65–77.
[119] L. Pangrazzi, B. Weinberger, T cells, aging and senescence, Exp. Gerontol. 134 (2020), 110887.
[120] S.M. Eaton, E.M. Burns, K. Kusser, T.D. Randall, L. Haynes, Age-related defects in CD4 T cell cognate helper function lead to reductions in humoral responses, J. Exp. Med. 200 (2004) 1613–1622.
[121] L.A. Callender, E.C. Carroll, R.W.J. Beal, E.S. Chambers, S. Nourshargh, A. N. Akbar, S.M. Henson, Human CD8 EMRA T cells display a senescence-associated secretory phenotype regulated by p38 MAPK, Aging Cell 17 (2018), https://doi.org/10.1111/acel.12675.
[122] T. Fulop, A. Larbi, G. Dupuis, A. Le Page, E.H. Frost, A.A. Cohen, J.M. Witkowski, C. Franceschi, Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front. Immunol. 8 (2018) https://doi.org/10.3389/fimmu.2017.01960.
[123] T. Fülöp, G. Dupuis, J.M. Witkowski, A. Larbi, The role of immunosenescence in the development of age-related diseases, Rev. Invest. Clin. 68 (2016) 84–91.
[124] F.G. Osorio, C. Bárcena, C. Soria-Valles, A.J. Ramsay, F. de Carlos, J. Cobo, A. Fueyo, J.M.P. Freije, C. López-Otín, Nuclear lamina defects cause ATM-dependent NF-κB activation and link accelerated aging to a systemic inflammatory response, Genes Dev. 26 (2012) 2311–2324.
[125] M. Nahrendorf, F.K. Swirski, Lifestyle effects on hematopoiesis and atherosclerosis, Circ. Res. 116 (2015) 884–894.
[126] D. Statovci, M. Aguilera, J. MacSharry, S. Melgar, The impact of western diet and nutrients on the microbiota and immune response at mucosal interfaces, Front. Immunol. 8 (2017) 838.
[127] V. Cruzat, M. Macedo Rogero, K. Noel Keane, R. Curi, P. Newsholme, Glutamine: metabolism and immune function, supplementation and clinical translation, Nutrients 10 (2018), https://doi.org/10.3390/nu10111564.
[128] A.K. Sikalidis, Amino acids and immune response: a role for cysteine, glutamine, phenylalanine, tryptophan and arginine in T-cell function and cancer? Pathol. Oncol. Res. 21 (2015) 9–17.
[129] N. Clemente Plaza, M. Reig García-Galbis, R.M. Martínez-Espinosa, Effects of the usage of l-Cysteine (l-Cys) on human health, Molecules 23 (2018), https://doi.org/10.3390/molecules23030575.
[130] H. Ohira, Y. Fujioka, C. Katagiri, R. Mamoto, M. Aoyama-Ishikawa, K. Amako, Y. Izumi, S. Nishiumi, M. Yoshida, M. Usami, M. Ikeda, Butyrate attenuates inflammation and lipolysis generated by the interaction of adipocytes and macrophages, J. Atheroscler. Thromb. 20 (2013) 425–442.
[131] H. Ohira, W. Tsutsui, R. Mamoto, S. Yamaguchi, M. Nishida, M. Ito, Y. Fujioka, Butyrate attenuates lipolysis in adipocytes co-cultured with macrophages through non-prostaglandin E2–mediated and prostaglandin E2–mediated pathways, Lipids Health Dis. 15 (2016), https://doi.org/10.1186/s12944-016-0387-0.
[132] A.L. Millard, P.M. Mertes, D. Ittelet, F. Villard, P. Jeannesson, J. Bernard, Butyrate affects differentiation, maturation and function of human monocyte-derived dendritic cells and macrophages, Clin. Exp. Immunol. 130 (2002) 245–255.
[133] M.M.M. Kaisar, L.R. Pelgrom, A.J. van der Ham, M. Yazdanbakhsh, B. Everts, Butyrate conditions human dendritic cells to prime type 1 regulatory t cells both histone deacetylase inhibition and g protein-coupled receptor 109A signaling, Front. Immunol. 8 (2017) 1429.
[134] D. Goldgaber, H.W. Harris, T. Hla, T. Maciag, R.J. Donnelly, J.S. Jacobsen, M. P. Vitek, D.C. Gajdusek, Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells, Proc. Natl. Acad. Sci. U. S. A. 86 (1989) 7606–7610.
[135] T. Kuilman, C. Michaloglou, L.C.W. Vredeveld, S. Douma, R. van Doorn, C. J. Desmet, L.A. Aarden, W.J. Mooi, D.S. Peeper, Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network, Cell 133 (2008) 1019–1031.
[136] M. Moutschen, H. Martens, V. Geenen, Immunosenescence and Infectious Diseases, Oxford Textbook of Geriatric Medicine, 2017, pp. 607–612, https://doi.org/10.1093/med/9780198701590.003.0079.
[137] Y. Kodama, Y. Takeuchi, M. Suzawa, S. Fukumoto, H. Murayama, H. Yamato, T. Fujita, T. Kurokawa, T. Matsumoto, Reduced expression of interleukin-11 in bone marrow stromal cells of senescence-accelerated mice (SAMP6): relationship to osteopenia with enhanced adipogenesis, J. Bone Miner. Res. 13 (1998) 1370–1377.
[138] R.J. Bishnoi, R.F. Palmer, D.R. Royall, Serum interleukin (IL)-15 as a biomarker of Alzheimer's disease, PLoS One 10 (2015), e0117282.
[139] D. Sarkar, I.V. Lebedeva, L. Emdad, D.-C. Kang, A.S. Baldwin Jr, P.B. Fisher, Human polynucleotide phosphorylase (hPNPaseold-35): a potential link between aging and inflammation, Cancer Res. 64 (2004) 7473–7478.
[140] S. Fimmel, L. Devermann, A. Herrmann, C. Zouboulis, GRO-alpha: a potential marker for cancer and aging silenced by RNA interference, Ann. N. Y. Acad. Sci. 1119 (2007) 176–189.
[141] C.A. Magalhães, C.N. Ferreira, C.M.G. Loures, V.G. Fraga, A.C. Chaves, A.C. R. Oliveira, L.C. de Souza, E. de P.F. Resende, K.C. Carmona, H.C. Guimarães, M. T.G. Cintra, I.N. Lanna, D.A.G. Zauli, M.A. Bicalho, M.G. Carvalho, L.P. Sousa, P. Caramelli, K.B. Gomes, Leptin, hsCRP, TNF-α and IL-6 levels from normal aging to dementia: relationship with cognitive and functional status, J. Clin. Neurosci. 56 (2018) 150–155.
[142] T.J. Hohman, S.P. Bell, A.L. Jefferson, Alzheimer's Disease neuroimaging Initiative, the role of vascular endothelial growth factor in neurodegeneration and cognitive decline: exploring interactions with biomarkers of Alzheimer disease, JAMA Neurol. 72 (2015) 520–529.
[143] S.K. Dewan, S.-B. Zheng, S.-J. Xia, K. Bill, Senescent remodeling of the immune system and its contribution to the predisposition of the elderly to infections, Chin. Med. J. 125 (2012) 3325–3331.
[144] A.B. Lopes, L.B. Lopes, R.N. da Silveira Antunes, J.T. Fukasawa, D. de A Cavaretto, Z. Calamita, Effects of immunosenescence on the lower expression of surface molecules in neutrophils and lymphocytes, Curr. Aging Sci. 11 (2018) 118–125.
[145] N.I. El-Naseery, H.S.E. Mousa, A.E. Noreldin, A.H. El-Far, Y.H.A. Elewa, Aging-associated immunosenescence via alterations in splenic immune cell populations in rat, Life Sci. 241 (2020), 117168.
[146] M. van Splunter, O. Perdijk, H. Fick-Brinkhof, E.G. Floris-Vollenbroek, B. Meijer, S. Brugman, H.F.J. Savelkoul, E. van Hoffen, R.J. Joost van Neerven, Plasmacytoid dendritic cell and myeloid dendritic cell function in ageing: A comparison between elderly and young adult women, PLoS One 14 (2019), e0225825.
[147] S.-J. Oh, J.K. Lee, O.S. Shin, Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity, Immune Netw. 19 (2019) e37.
[148] C. Solana, R. Tarazona, R. Solana, Immunosenescence of natural killer cells, inflammation, and alzheimer's disease, Int. J. Alzheimers Dis. 2018 (2018), https://doi.org/10.1155/2018/3128758.
[149] A. Larbi, C. Franceschi, D. Mazzatti, R. Solana, A. Wikby, G. Pawelec, Aging of the immune system as a prognostic factor for human longevity, Physiology 23 (2008) 64–74.
[150] G.C.L. Wong, M.C. Strickland, A. Larbi, Changes in t cell homeostasis and vaccine responses in old age. Vaccines for Older Adults: Current Practices and Future Opportunities, 2020, pp. 36–55, https://doi.org/10.1159/000504487.

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