Ageing Research Reviews 71 (2021) 101422

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Immunosenescence and inflammaging in the aging process: age-related diseases or longevity?

Aurelia Santoro [a], Elisa Bientinesi [b], Daniela Monti [b],*

[a] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, 40126, Italy
[b] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, 50134, Italy

ARTICLE INFO

Keywords:
Aging
Longevity
Centenarians
Innate immunity
Immunosenescence
Inflammaging
COVID-19

ABSTRACT

During aging the immune system (IS) undergoes remarkable changes that collectively are known as immunosenescence. It is a multifactorial and dynamic phenomenon that affects both natural and acquired immunity and plays a critical role in most chronic diseases in older people. For a long time, immunosenescence has been considered detrimental because it may lead to a low-grade, sterile chronic inflammation we proposed to call "inflammaging" and a progressive reduction in the ability to trigger effective antibody and cellular responses against infections and vaccinations. Recently, many scientists revised this negative meaning because it can be considered an essential adaptation/remodeling resulting from the lifelong immunological biography of single individuals from an evolutionary perspective. Inflammaging can be considered an adaptive process because it can trigger an anti-inflammatory response to counteract the age-related pro-inflammatory environment. Centenarians represent a valuable model to study the beneficial changes occurring in the IS with age. These extraordinary individuals reached the extreme limits of human life by slowing down the aging process and, in most cases, delaying, avoiding or surviving the major age-associated diseases. They indeed show a complex and heterogeneous phenotype determined by an improved ability to adapt and remodel in response to harmful stimuli. This review aims to point out the intimate relationship between immunosenescence and inflammaging and how these processes impact unsuccessful aging rather than longevity. We also describe the gut microbiota age-related changes as one of the significant triggers of inflammaging and the sex/gender differences in the immune system of the elderly, contributing to the sex/gender disparity in terms of epidemiology, pathophysiology, symptoms and severity of age-related diseases. Finally, we discuss how these phenomena could influence the susceptibility to COVID-19 infection.

1. Introduction

Demographic estimations predict that the coronavirus disease 2019 (COVID-19) pandemic will lower healthy life expectancy worldwide, particularly in socio-economic disadvantaged people (Harper, 2021). One hundred twenty-five million people were aged 80 years, and the oldest old and centenarians were the segment of the elderly population that was increasing the fastest. Until 2019, estimation reported that by 2050, the world's population aged 60 years and older is expected to total 2 billion, up from 900 million in 2015 (WHO, 2015). The COVID-19 virus pandemic has caused many deaths worldwide, and the oldest-old are the most vulnerable (Marcon et al., 2020), also considering that the total deaths have been underestimated by more than a factor of 1.5 (Modi et al., 2021). Supposing that the prevalence of the infection continues to grow, this could strongly impact life expectancy, breaking the secular trend and resulting in a decline in lifespan with different rates among countries (Marois et al., 2020; Andrasfay and Goldman, 2021). However, the aging of the population and the post-COVID-19 syndrome are currently two of the main socio-economic burdens that society and the healthcare system will have to manage over the following years.

Aging is one of the most intricate and complex biological phenomena that can impact many organ and systems' functions and represent the main risk factor for geriatric diseases (Kennedy et al., 2014). The recent conceptualization of Geroscience envisages that few selected and interconnected biological processes represent the critical pillars of aging and age-related diseases. Among these, inflammation, alteration of metabolic pathways and stress adaptation play a role (Kennedy et al.,

---

* Corresponding author at: Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Morgagni 50, 50134, Florence, Italy.
E-mail address: daniela.monti@unifi.it (D. Monti).

https://doi.org/10.1016/j.arr.2021.101422
Received 28 May 2021; Received in revised form 1 August 2021; Accepted 3 August 2021

2014). The immune system (IS) exhibits remarkable changes during aging called "immunosenescence", a multifactorial phenomenon that affects both natural and acquired immunity and play a critical role in most chronic diseases in the elderly (Franceschi et al., 1995a; De Martinis et al., 2005; Barbé-Tuana et al., 2020).

Immunosenescence is a dynamic process where several IS functions are reduced, whereas others remain unchanged or increased (Paolisso et al., 2000). For several years, immunosenescence has been considered detrimental because it may lead to a low-grade, sterile chronic inflammation we proposed to call "inflammaging" and a progressive reduction in the ability to trigger effective antibody and cellular responses against infections and vaccinations (Franceschi et al., 2000a; Franceschi and Campisi, 2014; Franceschi et al., 2017a; Fulop et al., 2018).

Moreover, inflammaging is crucially involved in the aetiology and progression of age-related diseases, often presented with multimorbidity and may finally lead to organ failure and death (Furman et al., 2019).

As immunosenescence proceeds, older people also become more susceptible to infectious diseases and cancer. Indeed, aged people and the oldest-old have an augmented risk for developing and dying from viral infections such as influenza and COVID-19 (Chen et al., 2021). Adults with chronic inflammatory conditions have a heightened risk for developing severe COVID-19 and dying (Huang et al., 2020). The interconnection between immunity and senescence is now receiving unprecedented emphasis during the COVID-19 pandemic, bringing to the fore the critical need to combat immunosenescence and improve older people's immune function and resilience.

Many gerontologists have now revised the negative meaning of immunosenescence (Pawelec et al., 2020a). From an evolutionary perspective, the age-related changes of the IS can indeed be considered an adaptation/remodeling rather than solely detrimental (Franceschi and Grignolio, 2010; Fulop et al., 2020). In this framework, aging represents a continuum without precise borders. The extremes are represented on one side by patients with age-associated diseases, where inflammation plays a pathogenic role. On the other side, long-lived individuals delayed or avoided such conditions due to an effective anti-inflammatory response (Franceschi et al., 2018a). Several factors, such as genetics, nutrition, exercise, exposure to microorganisms, sex (biological-related), gender (cultural-related) and human cytomegalovirus status, can influence immunosenescence. (Sansoni et al., 2014; Vescovini et al., 2007; Pawelec, 2020b). Therefore, it could be conceptualized that the age-related immune changes may be a mix of adaptation/resilience and maladaptation, closely related to the immunobiography (Franceschi et al., 2017a; Fulop et al., 2018). However, not the all-elderly population will suffer from these age-related diseases: more and more individuals are reaching very old age, such as centenarians (≥100 years old) having a relatively well-functioning IS (Monti et al., 2000; Sizzano et al., 2018). Centenarians show a complex and heterogeneous phenotype determined by an improved ability to adapt and remodel in response to physical and chemical agents, psychological stress and biological stimuli such as viral, bacterial and tumour antigens (Franceschi et al., 2017b, c). These extraordinary individuals reached the extreme limits of human life by slowing down the aging process and, in most cases, delaying, avoiding or surviving the major age-associated diseases. Centenarians show a lower prevalence of cancer (Salvioli et al., 2009), cardiovascular diseases (Olivieri et al., 2008), insulin resistance and diabetes (Paolisso et al., 2001), and they manage to delay the onset of dementia, Alzheimer's disease and osteoporotic fractures of about one or two decades on average (Evert et al., 2003; Passeri et al., 2003). On the other extreme, aging is accompanied by augmented morbidity due to a decreased ability of the IS to cope with new antigenic challenges and control chronic infections. Indeed, mortality due to infectious diseases continues to accelerate in very late life, different from all the other mortality causes (Pawelec et al., 2006). The age-associated immune deregulation is due to changes in innate and adaptive immunity (Franceschi et al., 1995b; Alberti et al., 2006; Nasi et al., 2006; Ostan et al., 2008; Sansoni et al., 2008) and is associated with chronically elevated markers of systemic inflammation (Cevenini et al., 2013).

The present review aims to summarise recent advancements in immunosenescence. Particular attention is devoted to the intimate relationship between immunosenescence and inflammaging and how these processes impact unsuccessful aging rather than longevity. We also describe the gut microbiota age-related changes as one of the significant triggers of inflammaging and the sex/gender differences in the immune system of the elderly, contributing to the sex/gender disparity in terms of epidemiology, pathophysiology, symptoms and severity of age-related diseases. Finally, we discuss how these phenomena could influence the susceptibility to COVID-19 infection.

2. Age-associated changes in innate immunity

The IS may schematically be divided into an ancestral/ innate part, mainly represented by neutrophils, monocytes, natural killer (NK) and dendritic cells (DC), and into a phylogenetically recent part represented by adaptive immunity (B and T lymphocytes). For a long time, innate immunity was considered unaffected by aging. Still, several studies have demonstrated that crucial components of the innate IS undergo profound changes related to an increased risk of infections and higher infection-related mortality. In fact, the aging process seems to hit both branches of the IS (Franceschi et al., 2000b), and innate cells play a crucial role in inducing inflammaging (Fig. 1). One hypothesis says that the constant immune challenges over the lifetime lead to a higher basal activation state of the innate IS (Fulop et al., 2018). In addition to exogenous antigens, damaged macromolecules, organelles, and cell debris can serve as damage-associated molecular patterns (DAMPs) to induce innate immunity through the NF-κB pathway and the induction of the canonical NLRP3 inflammasome (Youm et al., 2013).

2.1. *Neutrophils: age-related changes*

Neutrophils represent the first line of defence of the innate immune response and kill invading microbes. Neutrophils are recruited to the sites of infection to rapidly carry out their microbicidal activity, which relies on several mechanisms such as phagocytosis, degranulation of antimicrobial proteins, and the release of neutrophil extracellular traps (NETs) (Amulic et al., 2012).

Age-related profound alterations in functions of these cells have been described and account for the increased frequency of infection in the elderly (Brubaker et al., 2013). The microbicidal activity of neutrophils from elderly individuals is significantly reduced (Simell et al., 2011; Wenisch et al., 2000) due to impaired phagocytosis (Butcher et al., 2001; Wenisch et al., 2000), degranulation (McLaughlin et al., 1986), and ROS production (Fulop et al., 2004). Elderly individuals also display a reduced capability to NET formation owing to the increased release of neutrophil elastase via degranulation, an enzyme critical for NET formation. Moreover, a diminished respiratory burst of neutrophils from elderly subjects due to diminished NADPH oxidase and myeloperoxidase (MPO) activity can provide an additional explanation (Ortmann and Kolaczkowska, 2018). A decreased NETosis is frequently associated with sepsis, explaining why elderly individuals are more susceptible to invasive bacterial disease following skin and soft tissue infection. Excessive NETosis has been suggested to play an essential role in the pathogenesis of many infectious, inflammatory, and autoimmune diseases, but insufficient evidence supports this hypothesis (Vorobjeva and Chernyak, 2020). Recently, Rodriguez-Rosales have demonstrated that different neutrophils subsets resembling maturation stages are present in the blood of patients with psoriasis. The $CD10^{neg}CD16^{low}CD11b^{low}$ fraction increased in psoriatic patients, and this subset showed the morphology of aged neutrophils, though the lack of CD10 expression is associated with immaturity. The aged neutrophils ($CD10^{neg}$) are accumulated in the skin and have a pro-inflammatory effect on T cells mediated by NET formation. NET soluble mediators induce IL-17 release

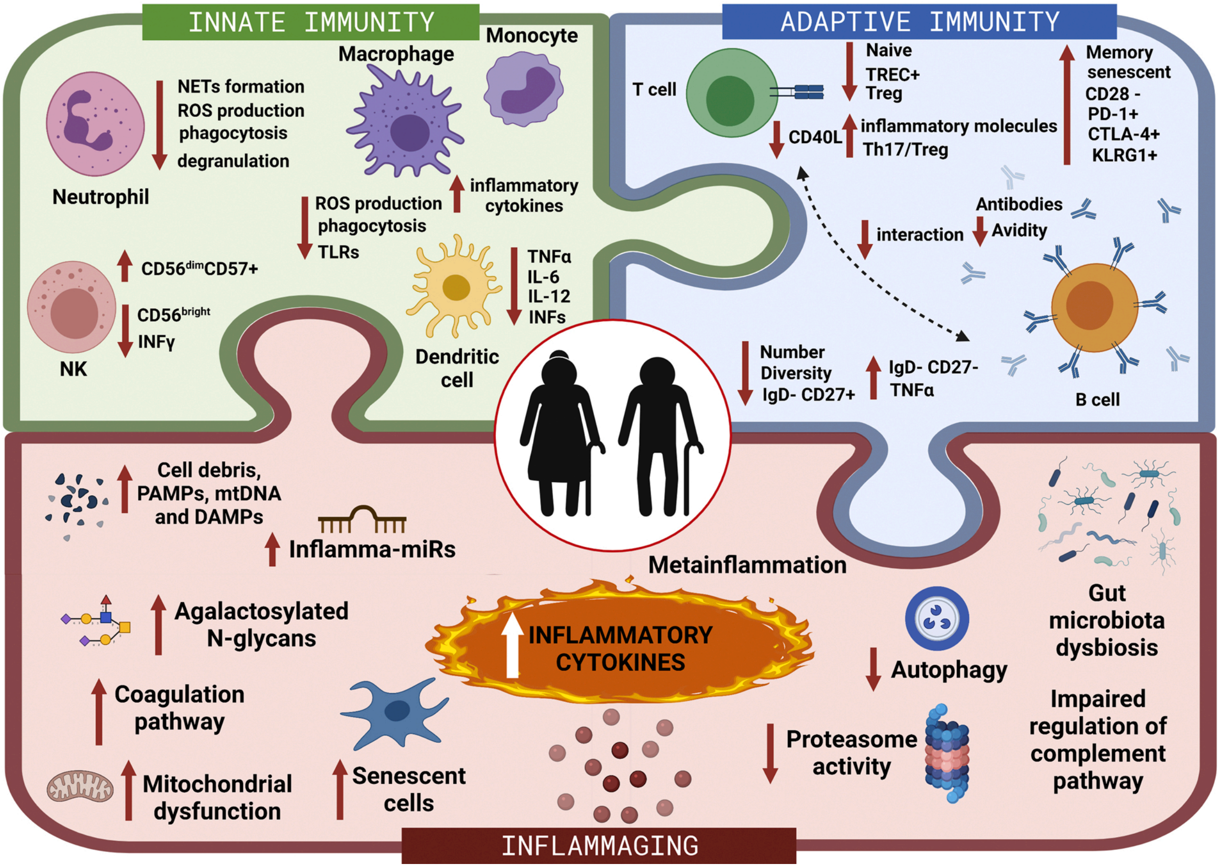

Fig. 1. Age-related changes in innate and adaptive immunity and their contribution to inflammaging. Crucial components of the innate IS such as neutrophils, NK, monocytes, macrophages and dendritic cells undergo profound modifications with age. Also, the function of T and B cells in adaptive immunity changes in the elderly. Both age-related changes in innate and adaptive IS trigger the increase of inflammatory mediators that together with other modifications such as increase of cell debris and damaged-associated molecular patterns (DAMPs), senescent cells, inflamma-miRs, coagulation pathway components, Agalactosylated N-glycans, metaflammation, decrease of disposal capability of proteasome and autophagy, gut microbiota dysbiosis and impaired regulation of complement, contribute to inflammaging. Created with BioRender.com.

by T cells and contribute to psoriasis development and inflammation (Rodriguez-Rosales et al., 2021).

Similarly, an increased number of immature neutrophils are associated with severe acute respiratory distress syndrome and could be a non-negligible source of IL-6 during COVID-19-induced cytokine storm (Carissimo et al., 2020). In addition, during SARS-CoV-19 infection, a substantial decrease in T-cells was observed, especially in subsets with cytolytic activity such as CD8 and $\gamma\delta$ T-cells. In particular, VD2, a $\gamma\delta$ T-cells subset, showed a general decrease in the periphery with disease severity. These cells can actively recruit and activate neutrophils to the site of infection or inflammation (Carissimo et al., 2020). In aging, a reduction of VD2 T-cell counts in blood have been shown, and the presence of inflammaging could explain why elderly individuals are more susceptible to severe COVID-19 (Carissimo et al., 2020).

Interestingly, centenarians show well-preserved neutrophil functions, such as bacterial phagocytosis, chemotaxis and superoxide production, comparable to those of young subjects (Alonso-Fernandez et al., 2008). Moreover, monocyte chemotaxis towards formyl-methionyl-leucyl-phenylalanine (f-MLP), adrenocorticotropic hormone (ACTH), and corticotrophin-releasing hormone (CRH) were well preserved in centenarians (Genedani et al., 2008).

2.2. Monocytes/macrophages: age-associated changes

The fundamental role of innate cells, in particular macrophages, is further supported by recent findings indicating that they also display a form of memory (trained immunity) so that these cells could be able to mount augmented inflammatory responses upon activation by recognition of DAMPs or alarmins (Franceschi et al., 2017a; Netea and van der Meer, 2017). At present, it is unknown whether cells of the innate IS undergo an age-related increase in such memory responses; however, it is possible to hypothesize a role for trained immunity in inflammaging (Franceschi et al., 2017a). Therefore, the progressive age-related up-regulation of macrophages and macrophages derived cells throughout the body could explain, at least in part, the pro-inflammatory status, which characteristically accompanies the aging process (Franceschi et al., 2000a). Thus, a reduced life span and health span can be envisaged with hyperactivation of the innate immunity response.

Aging has not been shown to significantly alter the absolute number and the frequency of overall monocytes in humans. However, it does determine significant changes in the relative distribution of their subsets and their functionality as a significant age-related reduction of reactive oxygen species (ROS) production and phagocytosis capability (Hearps et al., 2012). In addition, the macrophages show many age-related functional changes, among which a reduced expression of the principal Toll-Like Receptors (TLRs). TLRs can recognize pathogen patterns from viruses, bacteria, or fungi, induce NF-kB pro-inflammatory signalling, release different cytokines, and activate innate immunity to eliminate antigens (Panda et al., 2009; Shaw et al., 2011). Thus, age-associated reduction in TLR-induced IL-6 and TNF-α production, particularly in response to engagement of TLR1/2 and an increased release of TNF-α upon TLR4 stimulation, has been demonstrated (Panda et al., 2009).

Moreover, in human monocytes from aged people, the stimulation of TLR1/2, TLR2/6, TLR4, or TLR5 induces higher levels of IL-8 (Qian et al., 2012). Such dysregulation appears to be caused by alterations in surface TLR expression and downstream signalling: TLR1 expression declines with age, and activation of MAPK and ERK1/1 pathways by TLR1/2 triggering is severely reduced in cells from elderly subjects (van Duin et al., 2007). In contrast, downstream signalling of TLR5 has been shown to increase, leading to inflammatory responses in the elderly (Qian et al., 2012). However, findings of different research groups demonstrated a heightened pro-inflammatory milieu in old and long-lived individuals, with higher serum levels of pro-inflammatory cytokines such as TNF-α, IL-6 and IL- 1β, and other markers (C-reactive protein, clotting factors) (Fagiolo et al., 1993; Franceschi et al., 2007; Morrisette-Thomas et al., 2014). A possible explanation for this apparent paradox, i.e., augment of pro-inflammatory cytokines with concomitant defects of TLRs function, could be due to different tissue cell types, such as adipocytes, producing cytokines, also if the monocytes/macrophages are the primary sources of IL-6 (Maggio et al., 2006). In humans, adipose tissue undergoes substantial immune-metabolic changes with aging, increasing the pro-inflammatory pathways related to acquired and innate immunity (Trim et al., 2021). In visceral white adipose tissue and liver have been demonstrated an age-related accumulation of pro-inflammatory M1-like macrophages characterized by increased expression of CD38, a NAD-consuming enzyme able to reduce tissue NAD levels (Covarrubias et al., 2020). This polarization of macrophages can be due to increased inflammaging determined by the accumulation of senescent cells. These active metabolic cells produce immune-modulator factors that promote CD38 expression in M1 resident macrophages, thus regulating immune cell homing, innate immune responses (Covarrubias et al., 2020). In addition, an increased level of endotoxins and others PAMPS with aging can activate innate immune cells that promote inflammatory state and consequently the CD38 expression by tissue-resident M1-like macrophages, and hence enhanced NADase activity and contribute to the NAD decline associated with aging (Covarrubias et al., 2020). Therefore, the source of pro-inflammatory cytokines in aging might depend on the complex interplay of immunologic, hormonal, and neuroendocrine factors *in vivo* (Stout and Suttles, 2005; Straub and Mocchegiani, 2004). The release of cytokines by monocytes/macrophages might be modulated by adipokines (Lago et al., 2008), adrenal hormones (Jurberg et al., 2018), whose circulating levels are impaired with age (Sergio, 2008).

Three different monocyte subsets can be individuated based on their phenotype: classical ($CD14^+CD16^-$, which are 90% of circulating monocytes), intermediate ($CD14^+CD16^+$), and non-classical ($CD14^{dim}CD16^+$) monocytes (Hearps et al., 2012). Aging affects the relative distribution of monocyte subsets, with a marked reduction of the classical subset and an increase in the number of intermediate and non-classical monocytes with profound dysregulation in cytokines secretion after TLRs activation of monocytes (Hearps et al., 2012).

On the contrary, Costantini et al. suggest that healthy aging is associated with a significantly increased proportion of total monocytes, without significant changes in the frequency of the three subsets (Costantini et al., 2018). These authors also investigated the inflammatory (M1) and anti-inflammatory (M2) profiles in the three monocyte subsets through the expression of CD80 and CD163. CD80 is expressed on M1 macrophages, whereas CD163 is expressed on M1. The results indicate a reduction in $CD163^+$ and $CD80^-CD163^-$ cells in classical monocytes and an increase in $CD163^+$cells in non-classical monocytes, suggesting different age-related trends for classical and non-classical M2 monocytes (Costantini et al., 2018). However, since classical monocytes account for 80–90% of circulating monocytes, healthy aging seems to be characterized by a reduced proportion of M2 monocytes. On the contrary, old patients with acute myocardial infarction showed in the classical monocyte subset a significant increase of $CD163^+$cells having an inflammatory role in atherosclerosis and cardiac remodeling. Moreover, $CD80^+$ monocytes (M1) increased significantly in intermediate and non-classical subsets, underlining as a pro-inflammatory polarization of monocytes and consequent M1/M2 imbalance could play a role in cardiovascular diseases' pathogenesis (Costantini et al., 2018).

Recently, an in-depth global analysis revealed alterations after stimulation of monocytes sorted from healthy adult and old individuals with TLR4, TLR7/8, and RIG-I agonists. A reduced release of IFN-α, IFN-γ, IL-1β, CCL20, and CCL8 and higher expression of CX3CR1 was observed, while no age effects on unstimulated monocyte subsets were evidenced (Metcalf et al., 2017). Besides, high TNF-α plasma levels promoted the egress of immature monocytes from bone marrow that can produce, when stimulated with bacterial products *in vivo*, high levels of TNF-α, thus reinforcing inflammaging (Puchta et al., 2016).

A key role in inflammaging might also be played by single nucleotide polymorphisms (SNPs) in the promoter regions of genes encoding for IL-6 and IFN-γ. Bonafè et al. found that the IL-6 promoter genetic variability at –174 C/G locus and its effect on IL-6 serum levels in older people, including centenarians, contribute to inflammaging. They demonstrated that genetically predisposed individuals to produce high levels of IL-6 during aging, *i.e.* C- men at IL-6 –174 C/G locus, have a reduced ability to reach the extreme limits of the human lifespan. On the other hand, the capability of producing low levels of IL-6 throughout the lifespan (C+ individuals) appears to be beneficial for longevity, at least in men. Women experience higher IL-6 serum levels later in life than men, and the age-related increase of IL-6 serum levels in women is entirely independent of –174 C/G locus activity (Bonafè et al., 2001). Moreover, the +874 A allele for the IFN-γ gene is associated with low IFN-γ production and is positively associated with longevity in male and female centenarians (Lio et al., 2002). Specifically, genetic variants that tend to increase anti-inflammatory cytokines and those that decrease pro-inflammatory cytokines have been associated with successful aging and are more common among persons attaining the oldest ages (Lio et al., 2002).

However, while the SNPs mentioned above may yield some insights into a person's predisposition for inflammaging, many other variables can play a role, and it is essential to consider them. The lifelong immunological experiences and stimuli that each individual was exposed to (Franceschi et al., 2017a), age (Sansoni et al., 2008), gender (Ostan et al., 2016), different geographical and historical settings, diet and stress levels (Calder et al., 2011; Franceschi et al., 2018b; Santoro et al., 2020a), as well as the composition of gut-associated commensal bacteria (i.e., the microbiome) (Kau et al., 2011; Santoro et al., 2020b) are key factors contributing to inflammaging. This condition is known with the term immunobiography, which should help understand the enormous heterogeneity of the immune phenotype in older adults (Franceschi et al., 2017a).

2.3. *NK cells: age-related changes*

NK cells are innate lymphoid cells (ILC) representing 10–15% of peripheral blood lymphocytes and participate in the early defense against intracellular pathogens and tumour cells. They are cytotoxic non-T lymphocytes characterized by the expression of CD56 and/or CD16 (Solana et al., 2012b) and share many features with them ILC1 such as their capacity to produce IFN-γ (Spits et al., 2016). According to differential expression of surface markers CD56 and CD16, three NK subsets can be identified. In $CD56^{bright}CD16^{neg/dim}$ subset, the cells are more immature and secrete cytokines and chemokines, whereas the main NK cell subset CD56^{dim}CD16^{+} is made up of mature NK cells with high cytotoxic capacity after direct contact with tumour or virus-infected target cells (Cooper et al., 2004). Furthermore, a scarce subset of NK cells, devoid of CD56 expression and displaying a reduced functional capacity, has been identified in healthy controls and chronic viral infections such as HIV and hepatitis C virus (Solana et al., 2012b). Many data of changes in NK-cell phenotype and function with old age have been reported but frequently inconsistent. An increase in the number of mature NK cells with a significant reduction in the immature NK cell subset probably due to the impaired production of new NK cells was observed with advanced age (Le Garff-Tavernier et al., 2010; Gayoso et al., 2011). Thus, the decline in CD56^{bright} NK cells and the increase in the CD56^{dim}CD57^{+} subset support that the population of NK cells suffers a process of remodeling with a reduction in the output of more immature CD56^{bright} cells and an accumulation of highly differentiated CD56^{dim}CD57^{+} NK cells (Solana et al., 2012b). Both age and persistent cytomegalovirus (CMV) infection contribute to the NK cell phenotypical and functional changes observed in the elderly.

Aging does not change total NK cell cytotoxicity, probably due to the increased frequencies of mature NK cells, but impairment of NK cell cytotoxicity on a per-cell basis due to the decreased expression of activating receptors has been reported (Hazeldine and Lord, 2013). In centenarians, the increase of the high-activity NK subset is mirrored by exceptionally well-preserved cytotoxicity, and it can be speculated that the preserved NK activity can help reach far advanced age in good conditions (Sansoni et al., 1992). The age-related increase of cells bearing NK markers and non-MHC-restricted T lymphocytes could be interpreted as an adaptative mechanism to cope with the decrease of T cells related to the thymic involution. Human NK cells from healthy subjects over 90 years of age, however, are still able to secrete the chemotactic cytokines MIP-1α, Rantes, and IL-8 and can also effectively release these chemokines in response to IL-12 and IL-2, but their production remains lower than that observed in young subjects (Mariani et al., 2002). Many studies have shown that the functions of NK cells extend, beyond their role in anti-viral and tumour immunity, into such areas as immune regulation, the initiation of adaptive immune responses, and the clearance of senescent cells (Hazeldine and Lord, 2013). Thus, several features of the aging process, such as the reduced efficacy of vaccination, the appearance of senescent cells and the higher rates of fungal infection, may be partly attributable to the decline in NK cell function that accompanies human aging.

2.4. *Dendritic cells: age-related changes*

Dendritic cells (DCs) are professional APCs classified as myeloid DCs (mDCs) or plasmacytoid DCs (pDCs) having different functional activities: mDCs, producing IL-12, induce helper T cell type 1 (Th1) and cytotoxic T lymphocyte (CTL) responses, whereas pDCs produce IFN-α/β in response to bacteria and viruses (Banchereau et al., 2000). Age-related changes in the number and frequency of mDCs and pDCs were discordantly reported (Jing et al., 2009; Perez-Cabezas et al., 2007). Both mDCs and pDCs from elderly individuals showed a significant impairment in secreting TNF-α, IL-6, and IL-12 (p40) in response to TLRs. Moreover, the lower release of IFNs and pro-inflammatory cytokines from pDCs have been associated with a reduced response to the influenza vaccine (Panda et al., 2010). However, basal production of pro-inflammatory cytokines in the absence of TLR engagement is higher in cells from older than young individuals, suggesting a dysregulation of cytokine production that may limit further activation through TLR engagement (Metcalf et al., 2017). In conclusion, the picture that emerges is a profound dysregulation of innate immune functions, with some functions down-regulated and others up-regulated or even enhanced. In particular, an increase in the basal production of pro-inflammatory cytokines, observed in different cell types, could be a significant contributor to the age-related increase of the levels of such molecules observed in several cohorts of elderly subjects (Salvioli et al., 2013)

3. Age-associated changes in adaptive immunity

Two types of responses constitute the adaptive IS: the cell-mediated immune response carried out by T cells and the humoral immune response controlled by activated B cells and antibodies. T cells play a crucial role in orchestrating the immune responses and are subdivided into CD4^{+} and CD8^{+} T cell populations with different functions (Das et al., 2017). CD4^{+}T cells are crucial in achieving a regulated effective immune response to pathogens and possess effector functions (Das et al., 2017). Naive CD4^{+} T cells may differentiate into one of several lineages of T helper (Th) cells, including Th1, Th2, Th17, and Treg, as defined by their pattern of cytokine production and function (Zhu et al., 2010). CD8^{+} T cells constitute an essential branch of adaptive immunity contributing to the clearance of intracellular pathogens and providing long-term protection (Mittrücker et al., 2014). Alterations of adaptive responses have been described in aging, and the T cells compartment is the most affected and contributes to inflammaging (Franceschi, 2017d; Tu and Rao, 2016). The T-lymphocyte compartment has been studied extensively concerning immunosenescence and will be treated in this paragraph.

Two main changes in the adaptive IS characterize aging: i) a decrease in naïve T cells that leads to the shrinking of the TCR repertoire, ii) an increase in memory T cells primed by different antigens and upregulation of pro-inflammatory molecules.

A decrease in regenerative capacity is one of aging hallmarks and contributes to reducing hematopoietic cells (López-Otín et al., 2013). A good example is an age-related decline in hematopoiesis, causing a diminished production of adaptive immune cells (López-Otín et al., 2013). An increase with age in the frequency of myeloid-biased differentiation at the expense of lymphoid specificity and function is demonstrated in humans (Pang et al., 2011). These changes influence the T and B repertoire and are partly responsible for reducing T and B cell number.

T cell repertoire is compounded by thymic involution and the decline in its function after puberty (Palmer, 2013). The release of new naïve cells by thymus is vanishingly rare in the elderly. The reduced thymus output seems to be the primary explanation for the increased incidence of infections, cancers, vaccination failure, and reduced capacity to respond to neoantigens (Appay and Sauce, 2014; Pawelec, 2017). Steinmann et al. observed that thymus atrophy begins at the age of one year, and shrinks in volume by about 3% per year until middle age, then shrinking by $<1\%$ per years through the rest of life, however, the presence of thymic tissue has been described in a 107 years old subject (Steinmann et al., 1985). An evaluation of thymic output is based on quantifying recent thymic emigrants characterized by the expression of TCR rearrangement excision circles (TRECs). TREC^{+} lymphocytes present in the periphery indicate the organ's functionality since mature T cells that leave the thymus and enter the circulation can display TRECs in more than 70% of the cases. They have been detected in older people, up to 80 years, indicating that there may be a continuous thymic output of naïve T cells, even in advanced age (Douek and Koup, 2000). Nasi et al. analyzed the content of TREC in peripheral blood mononuclear cells (PBMCs) from centenarians, compared with young and middle-aged donors, and found a dramatic reduction in the number of TREC$^+$ cells. However, a well detectable number of TREC$^+$ lymphocytes was present in 4 centenarians out of 25, suggesting that such cells could derive from residues of thymic lymphopoietic islets (Nasi et al., 2006).

Recent data show that mechanisms can partially maintain naïve T compartment as the homeostatic proliferation (Appay and Sauce, 2014). Homeostatic proliferation effectively maintains the naïve CD4$^+$ T cell pool in humans in healthy aging, but less so in respect of naïve CD8$^+$ T cells (Goronzy et al., 2015). It is clear that homeostatic proliferation does not allow the production of new specificities but can only maintain the repertoire's richness. Moreover, during homeostatic proliferation, the selected clones could have a higher affinity for self-antigens and lead to autoreactivity in older individuals (Goronzy and Weyand, 2012). Qi and colleagues have demonstrated that naive repertoire richness until 70 years old decline slowly, but age plays a role in the unequal size of the observed clones, which is more prevalent in naïve CD8$^+$ T cells than their CD4$^+$ T cells cell counterparts (Qi et al., 2014). In the past years, several studies, including ours (Cossarizza et al., 1997), used the expression of CD45 isoforms, CD45RA and CD45R0, to define naïve/-unprimed and memory/experienced T cells, respectively. Consequently, it was reported that a well-preserved number of naïve T cells can be still present in people of advanced age, including centenarians (Cossarizza et al., 1996, 1997).

With increasing age, our body tends to allocate resources differently, reducing the energy consumption of many metabolically active organs and tissues such as the thymus, muscles, bone marrow and redirect energy to other functions and activities to support the organism's survival.

Exposure to new pathogens is maximal during the first years of life but less likely in later life when immune memory for previously encountered pathogens is more prevalent and more important for survival (Pawelec, 2018; Shanley et al., 2009). Therefore, resources must be preferentially allocated to combat these "usual" related pathogens on the memory side of the IS rather than spending energy on a useless struggle, which can be interrupted in any case by the destruction of the invading organism.

The second hallmark of immunosenescence is the expansion of memory T cells in response to latent viruses affecting T cell repertoire diversity. The life-long chronic antigen load causes the filling of the immunological space by a T lymphocytes population with a late-differentiated phenotype and the T cell repertoire's shrinkage. The body hosts many latent infections, which can re-activate from time to time under specific conditions such as human CMV (Larbi and Fulop, 2014). CMV infection has a more significant impact than age in expanding CD4$^+$ and CD8$^+$ effector memory T cells, particularly the latter, increasing oligoclonality during normal human aging (Pawelec et al., 2001a,2001b, Hadrup et al., 2006; Vescovini et al., 2004; Sadighi Akha, 2018). We have seen that CMV-driven CD8$^+$ T cell reactivity is correlated with increasing numbers of late differentiated CD28$^-$CD8$^+$ T cells in the elderly, including centenarians (Fagnoni et al., 1996). This parameter makes up a substantial part of the highly discussed Immune Risk Phenotype (IRP) considered for the potential prediction of increased morbidity and death (Wikby et al., 2006). Pawelec, in collaboration with OCTO/NONA study group in Jönköping, Sweden, identified some simple immunological markers associated with the survival of the very elderly over 2, 4 and 6 years from baseline at 85 years of age (Pawelec et al., 2003). They found that a cluster of markers named IRP characterized by an excess of late-stage differentiated CD8$^+$CD27$^-$CD28$^-$ T cells reactive to CMV antigens, a reduced T cell proliferative response to mitogens, an inverted CD4:8 ratio and CMV-seropositivity together with a deficit of B cells, was weakly associated with 2, 4 and 6-year all-cause mortality at follow-up (Pawelec et al., 2001a,2001b)

Moreover, higher serum levels of IL-6 and cognitive impairment assessment were more closely associated with mortality than the IRP. However, the survival of those individuals from the OCTO/NONA studies who were both in the IRP and had higher IL 6 levels and cognitive impairment was the worst of any subjects studied (Wikby et al., 2006). Consistent with this, none of the OCTO/NONA subjects in the IRP group who survived become centenarians (Strindhall et al., 2007). However, the IRP is not widely accepted because it was not confirmed in the Leiden 85-Plus study, a prospective population-based cohort study of individuals aged 85 years living in Leiden (Derhovanessian et al., 2013). Thus, immune parameters associated with survival may vary in diverse populations at different ages (Pawelec, 2012a). These observations emphasize the concept that the immunosenescence and the consequent inflammaging are hugely heterogeneous and represent a continuum remodeling in response to unpredicted long-time exposures to external and/or internal stressors determining the so-called immunobiography. Consequently, the immunosenescence and inflammaging can be more or less severe, leading to a wide range of outcomes from overt diseases where inflammation plays a pathogenic role in successful aging (e.g., centenarians) (Franceschi et al., 2018a).

CMV chronic infection in nonagenarians and centenarians was characterized by highly variable frequency and an absolute number of CD8$^+$ T cells that, occasionally, were strikingly expanded. Moreover, most anti-CMV CD8$^+$ T cells did not bear the CD28 molecule, thus supporting the hypothesis that the age-related expansion of CD28$^-$ T cells may depend, at least in part, on repeated rounds of cellular replication for the ongoing immune response against CMV (Vescovini et al., 2004).

This determines the phenomenon of memory cell inflation, leading to the emergence of vast populations of resting effector CD8$^+$ and, to a lesser extent, CD4$^+$ cells. These inflated CMV-specific memory T cells maintain their efficient effector functions for the individual's lifetime, and they are not exhausted (Nikolich-Zugich et al., 2017).

Overall, CMV immune changes may play a role in immunological fitness and, particularly, during co-infection and vaccination. Additionally, a systematic review of the relation between CMV-infection and immunosenescence in western people aged fifty and older showed that CMV seems to enhance immunosenescence. This evidence is based on the high levels of the highly differentiated effector memory T cells and T effector memory re-expressing CD45RA cells (TEMRA) in the CD8$^+$ and CD4$^+$ T cell pools. At the same time, there is a decrease in central memory cells (Weltevrede et al., 2016). Although CMV was once considered the leading cause of age-related immune changes in the elderly, accumulating data are still quite contradictory. The current opinion is that CMV infection does not seem to be only detrimental (Derhovanessian et al., 2013; Solana et al., 2012a; Pawelec et al., 2012b), but it may be considered a recurrent stimulation that maintains sustained immunological alertness and favours a better immune response (Pawelec et al., 2012b). The global response to the many various CMV antigens has been linked to better survival (Bajwa et al., 2017), suggesting that the increased number of committed memory T cells may not be considered unequivocally detrimental or related only to aging.

One of the essential features of aging is the notion of senescent cells (Campisi and Robert, 2014). During aging, senescent cells, *i.e.* differentiated CD28$^-$ T cells, induced by a repeated pathogen encounter during chronological aging, and end-stage differentiated senescent T cells, are characterized by a progressive reduction of telomere length and a proliferative arrest, tend to accumulate (Akbar et al., 2016). These cells have been previously considered to be inactive. However, recent data have shown that they are metabolically active, arising with age in the body and produce large amounts of pro-inflammatory cytokines (a phenomenon called senescence-associated secretory phenotype, SASP) as stated by the inflammaging (Akbar et al., 2016). Thus, chronic antigenic stimulation leads both to the phenomenon of inflammaging and the increase of the number of senescent T cells (Callender et al., 2018). One additional consequence of chronic stimulation is the phenomenon of exhaustion, characterized by inadequate responses to proliferative stimuli and the expression of inhibitory receptors, such as PD-1, CTLA-4, KLRG1 and many others on T cell subsets (Vasudev et al., 2014).

Another component that may favour inflammaging is the compromised ability of $CD4^+$ T cells to differentiate into functional subsets, resulting in many dysregulated responses. Two of these are the reduced cognate help to B cells with consequent reduced humoral immunity and the increased ratio of the pro-inflammatory Th17 cells and the immunosuppressive T regulatory cells, favouring a basal pro-inflammatory status (Schmitt et al., 2013; Bektas et al., 2017).

Thus, changes in the TH17/Treg ratios and altered cytokine expression during aging may contribute to an imbalance between the pro-inflammatory and anti-inflammatory immune response (Schmitt et al., 2013), indicating higher susceptibility to developing inflammatory diseases with increasing age.

Like the T cell pools, the B cell compartment also undergoes age-related changes. Peripheral B cell number and percentages decline significantly, and specific humoral immune responses against extracellular pathogens and vaccines are impaired. In particular, B cell repertoire diversity, immunoglobulin isotypes and receptor repertoire are affected by age (Bulati et al., 2011; Frasca et al., 2020). In aging, the transcriptional factor E47 that controls B cell functions is down-regulated, reducing the activation-induced cytidine deaminase (AID), which induces class switch recombination and Ig somatic hypermutation. Moreover, it might also be responsible for diminished antibodies avidity and antibody-mediated protection (Frasca et al., 2016). However, this defect might be mainly linked to reduced B cells interaction with $CD40L^+$ T helper cells because, in older adults, the memory/effector T cells show a reduced expression of CD40 L, necessary for B cells cooperation (Colonna-Romano et al., 2003). As well-known and described above, T cell function impairment has *per se* paramount importance in immunosenescence and contribute to an age-related decrease in antibody responses of elderly individuals.

Furthermore, it has been reported that elevated levels of TNF-α, typical of inflammaging, can cause human unstimulated B cells from elderly individuals to release significantly higher levels of TNF-α than those from young subjects and render them unable to respond to exogenous antigens, mitogens or vaccines. (Frasca et al., 2014). Regarding the major circulating B-cell subsets have been identified four populations: naïve [IgD^+CD27^-], IgM memory [IgD^+CD27^+], switched memory [IgD^-CD27^+], and late/exhausted memory [IgD^-CD27^-] (Ademokun et al., 2010).

It has been shown that the percentage of switched memory B cells, the predictors of optimal antibody responses, decreases with age (Frasca et al., 2020), while the percentage of late/exhausted memory B cells, the antigen-experienced and pro-inflammatory B-cell subset, increases (Fecteau et al., 2006. Colonna-Romano et al., 2009). These senescent cells have stable cell cycle arrest, shorter telomeres, secrete pro-inflammatory cytokines before stimulation, and are "refractory" to undergo in vitro class switch when stimulated with antigens and mitogens (Fecteau et al., 2006; Colonna-Romano et al., 2009). For a detailed description of B-cell age-related changes, please refer to Frasca et al., 2020.

Finally, concerning sex, steroid hormones, few studies have analyzed post-menopausal IS. However, age-related changes in the IS are different between men and women, and some data show that immunosenescence develops earlier in men than in women, possibly because women have a higher life expectancy than men (Ostan et al., 2016). The IS changes related to sex/gender are described in detail in BOX 1 and Fig. 2.

Box 1

Inflammaging: also a matter of sex and gender?

Although women experienced almost five years of advantage in life expectancy, these are years of diseases and disability (Ostan et al., 2016; Gemmati et al., 2019), showing a higher prevalence of multimorbidity patterns than men (Abad-Díez et al., 2014). Inflammaging represents the common hub shared by the majority of the age-related diseases (ARDs) (Furman et al., 2019; Franceschi and Campisi, 2014) and likely contributing to the gender disparity in terms of epidemiology, pathophysiology, symptoms and severity of diseases (Franceschi et al., 2018a; Ostan et al., 2016). A complex interplay modulates the lifelong balance between inflammaging and anti-inflammaging among sex (genetics, epigenetics and hormones) and gender (environmental, lifestyle and socio-cultural) factors, profoundly affects aging trajectories and ARDs risk (Franceschi et al., 2007, 2018a). Differences between males and females in inflammaging have been reported with contradictory results likely due to the variety of factors modulating inflammaging in different experimental settings and human populations (Yang and Kozloski, 2011; Newman et al., 2016; Milan-Mattos et al., 2019; Di Benedetto et al., 2019,Márquez et al., 2020). During life, the IS evolves and changes, with marked sex differences (Fig. 2). Adult females have more robust innate and adaptive immune responses (Oertelt-Prigione, 2012) with higher $CD4^+$ T cell counts and $CD4^+$:$CD8^+$ ratios than males (Klein and Flanagan, 2016). Transcriptional data confirmed this pattern in women while suggesting a higher expression of genes related to myeloid cells in men (Bongen et al., 2019). The number and activity of B and T cells in aged males rapidly decline compared to females (Goetzl et al., 2010; Márquez et al., 2020). Age-related differences between the two sexes increase after age 65, with older men having higher monocytes activity and inflammation (Márquez et al., 2020). At variance, during menopause, females have higher pro-inflammatory markers such as CRP and GM-CSF than males (Furman et al., 2014). However, with age, some evidence shows that T cells from females produce more IL-10 than do males' T cells (Pietschmann et al., 2003), which may neutralize the adverse effects of inflammaging with age. Although these effects may contribute to an improved humoral response in women, at the same time, they can favour the appearance of autoreactive clones (Sakiani et al., 2013). Females are indeed 2–10-fold more prone to a series of disabling autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, systemic rheumatoid arthritis, myasthenia gravies, Hashimoto's thyroiditis and Sjogren's syndrome (Keestra et al., 2021). Female hormones decrease autoimmune regulator gene (AIRE) expression by triggering the negative selection of self-reactive T cells (Bakhru and Su, 2016) and Treg development, thus protecting against autoimmunity. Moreover, the cellular mosaicism resulting from the random inactivation of X chromosome loci in all mammal cells from females is likely to create a unique functional plasticity within female immune cells (Youness et al., 2021; Yu et al., 2021) and thus be involved in the aetiology of female autoimmune diseases. The better immune females' response is also evident after vaccinations when women reveal higher immunoglobulins and seroconversion and lower disease (Flanagan et al., 2017). Finally, it is important to stress that sex/gender differences in the IS cell number and function are not the sole contributor to the sex dimorphism in inflammaging, resulting from the sum of the age-related local, chronic inflammatory processes of multiple organs/systems.

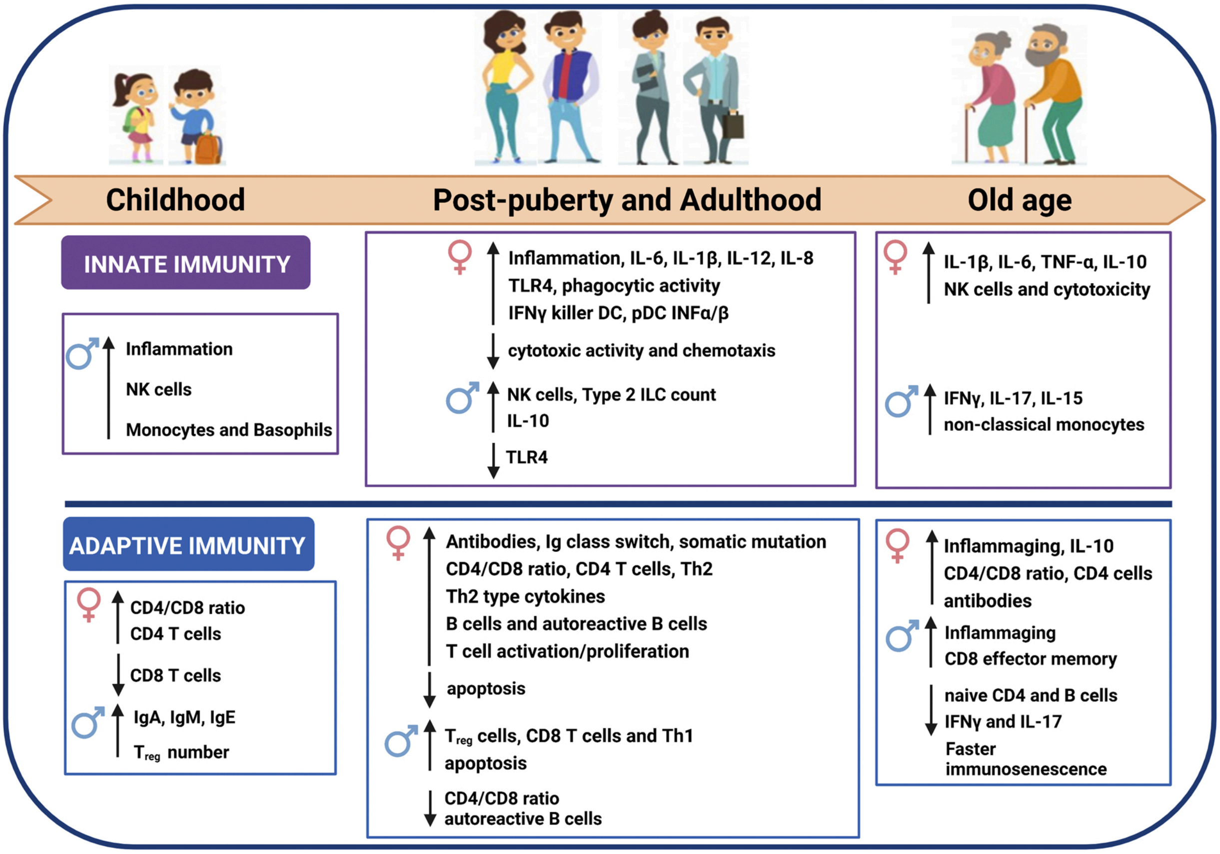

Fig. 2. Sex differences in innate and adaptive immunity throughout the life course. A series of immunological components differ between human females and males across the course of life. Besides genes and hormones, environmental factors can modulate the functioning of the immune system differentially between males and females. Men experience a faster progression to immunosenescence than women, highlighted by changes in immune cells and inflammatory mediators. **Abbreviations:** TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{reg}, regulatory T cells, IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; DC, dendritic cells; pDC, plasmacytoid dendritic cells; NK, Natural Killer cells; ILC, innate lymphoid cells; Th, T helper lymphocytes. Created with BioRender.com.

4. Inflammaging as the dark side of immunosenescence

The changes of the IS occurring with age and characterizing immunosenescence should be considered a dynamic process involved in the adaptation to exogenous and endogenous detrimental stimuli to which our body is exposed lifelong and the major contributor to inflammaging (Franceschi et al., 2000a; Shaw et al., 2011; Franceschi and Campisi, 2014; Franceschi et al., 2018a; Monti et al., 2017). Inflammaging is one of the seven pillars of the aging process described by Kennedy and collaborators and characterize the major age-related diseases (Kennedy et al., 2014; Franceschi and Campisi, 2014) and representing an example of remodeling because it could be considered as the result of the imbalance between inflammatory and anti-inflammatory networks (Franceschi et al., 2007). Over more than 20 years from its discovery, in addition to immunosenescence, several biological basic mechanisms that contribute to inflammaging have been described in Fig. 1 and can be summarised as follow: i) accumulation with age, in many tissues, of senescent cells secreting pro-inflammatory mediators that can spread the senescent phenotype to the neighbouring cells (Coppé et al., 2008; Song et al., 2020a,2020b) and promote age-related diseases (Campisi and d'Adda di Fagagna, 2007); ii) age-related increased production of cell debris and components resulting from cell death or damage, such as nucleic acids, mitochondrial DNA (mtDNA), cardiolipin, mitochondria, Heat Shock Proteins and other proteins, that collectively are known as DAMPs, and are recognized by innate immune receptors like TLRs, NOD-Like Receptors (NLR) and cGMP-AMP synthase (cGAS). The accumulation with age of DAMPs has been called "Garb-aging" and can trigger innate immunity and the production of pro-inflammatory cytokines (Pinti et al., 2014; Franceschi et al., 2017a,2017b,2017c); iii) the concurrently age-related decreased disposal capability (Franceschi et al., 2017a,2017b,2017c). With age, autophagy and other pathways regulating proteostasis, such as proteasome activity (Mishto et al., 2006a, b), are reduced, contributing to the accumulation of misfolded protein aggregates activating inflammatory pathways; iv) telomere shortening and nuclear DNA damage, mediated by ROS and other agents, trigger DNA repair response and the production of pro-inflammatory compounds (Vitale et al., 2013); v) pro-inflammatory circulating microRNA (inflammaMIR) (Olivieri et al., 2013); vi) age-related accumulation in the blood of pro-inflammatory agalactosylated N-glycans, which represent one of the most powerful markers of biological age in humans (Dall'Olio et al., 2013); vii) enhanced activation of the coagulation pathway contributes to the rise of inflammatory tone increasing the risk for arterial and venous thrombosis in older people; viii) impaired regulation of complement pathway may induce a local inflammatory reaction in many degenerative diseases (*i.e.* the age-related macular degeneration) (Gallenga et al., 2014); ix) excess of energy/nutrients that drives to an inflammatory process coordinated by metabolic cells called "metaflammation" (Franceschi et al., 2018b; Cevenini et al., 2013). x) age-related gut microbiota dysbiosis represents a driving force for the homeostasis of the IS and an important source of inflammatory stimuli during aging (Biagi et al., 2010,2016). An in-depth description of gut microbiota remodeling in aging and centenarians will be illustrated in the next section of this review.

The key player in this inflammatory response is represented by the macrophage, which expresses many receptors for DAMPs and is present in virtually all the organs and tissues of the body and thus likely is responsible for local inflammaging (Sochocka et al., 2017). Macrophages can acquire memory-like characteristics upon activation by recognizing DAMPs (trained immunity), responding to different antigen exposure, and modulating fibrotic and inflammatory processes (Jeljeli et al., 2019). Compared to young people elderly are characterized by increased production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (Fagiolo et al., 1993). Although these cytokines, together with IL-8 and CRP, can be considered the most relevant circulating biomarkers of inflammaging (Ferrucci and Fabbri, 2018), recently it has been identified an immune signature for age-related chronic inflammation (Sayed et al., 2021) able to track multiple diseases and immunosenescence and predict multimorbidity. A major contributor to this inflammatory clock is CXCL9, a T-cell chemoattractant produced by neutrophils, macrophages, and endothelial cells (Sayed et al., 2021).

Starting from the life in utero and lasting during the entire life, the IS starts to record all the immunological experiences and stimuli it was exposed to (immunobiography) and plays out inflammatory responses to cope with and neutralize the large variety of stressors (Franceschi et al., 2017a; Santoro et al., 2020a).

This could help understand and interpret the individual heterogeneity of immune responses (to infections and vaccinations) that becomes particularly evident at old age and could affect both immunosenescence and inflammaging (Franceschi et al., 2017a). The phenotype of older adults is very complex and dynamic, continuously balancing between adaptive robustness and accumulating frailty (Franceschi et al., 2000a, 2000b; Ginaldi et al., 2005).

When kept under a certain threshold, this chronic inflammatory stimulation should not be considered detrimental (Furman et al., 2019) because it pushes a secondary adaptive activation of anti-inflammatory networks (Franceschi et al., 2007, 2018a). The strength of the adaptive response is likely critical to determine different aging trajectories and the net outcome: unsuccessful aging and age-associated diseases rather than successful aging and longevity.

The anti-inflammatory response represents a dynamic and active process able to trigger specific molecular pathways aimed to inhibit and resolve dangerous inflammation (Perretti and D'Acquisto, 2006). Consistent with this, the development of age-related diseases and frailty is a result of excessive stimulation of pro-inflammatory responses but also an ineffective anti-inflammatory reaction (Morrisette-Thomas et al., 2014), while the attaining of longevity and successful aging is determined by a reduced predisposition to stimulate inflammatory pathways in addition to an effective anti-inflammatory response. In other words, individuals who have a very well preserved and organized anti-inflammatory activity are able to counteract the age-related increase of inflammatory markers (inflammaging), and the probability to develop age-related diseases is highly reduced or delayed or show less severe consequences (Franceschi et al., 2007) (Fig. 3).

Centenarians that represent the best example of successful aging have a large quantity of circulating anti-inflammatory molecules such as Transforming Growth Factor (TGF)-β1, IL-10, IL-1 receptor antagonist (IL-1Ra), adiponectin, cortisol, anti-inflammatory arachidonic acid compounds, including HETE and EET, mitokines (FGF21, GDF15 and HN) (Salvioli et al., 2009; Gerli et al., 2000; Genedani et al., 2008; Meazza et al., 2011; Collino et al., 2013; Morrisette-Thomas et al., 2014; Conte et al., 2019). However, this anti-inflammatory state is effectively triggered to counterbalance the concomitant increased levels of inflammatory molecules in plasma, such as IL-6, IL-15, IL-18, IL-18 binding protein, IL-22, CRP, serum-amyloid A, fibrinogen, Von Willebrand factor, resistin and leukotrienes (Bonafè et al., 2001; Franceschi et al., 2007; Gangemi et al., 2005; Collino et al., 2013; Basile et al.,

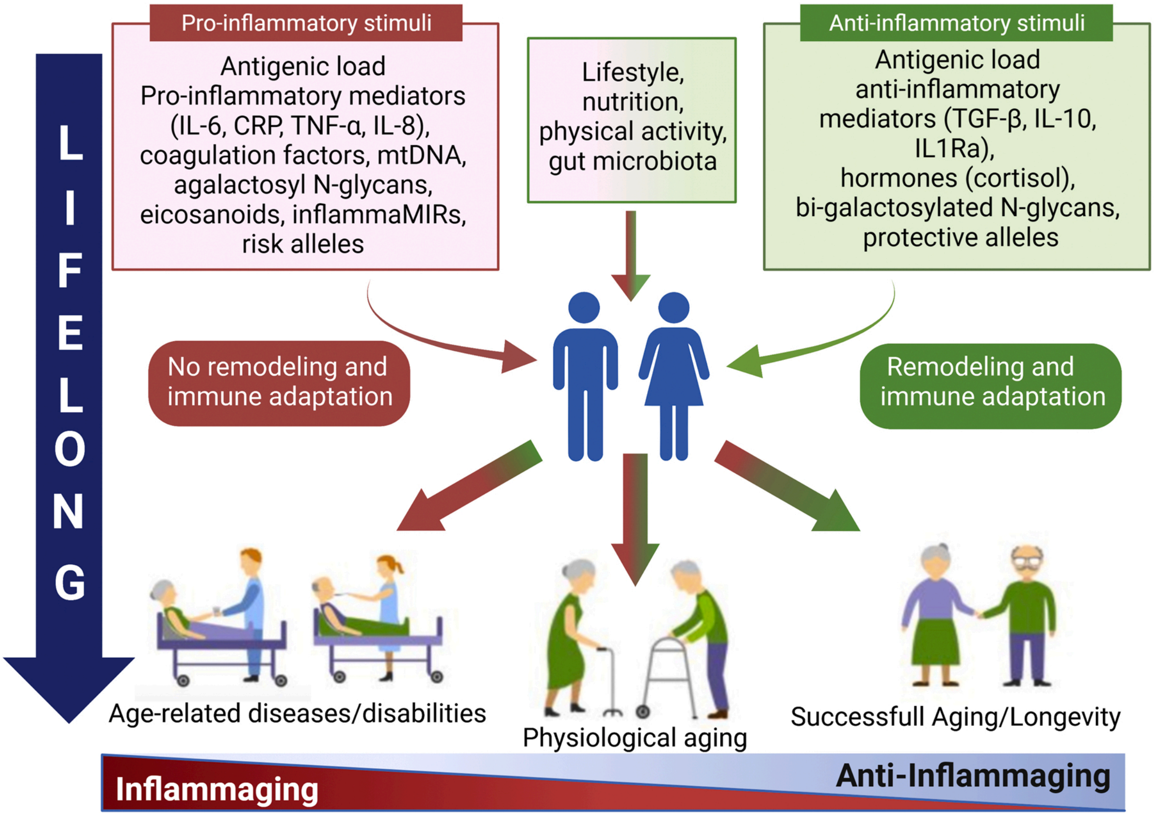

Fig. 3. Adaptation or maladaptation to lifelong pro- and anti-inflammatory stimuli leads to longevity or diseases. The pro- and anti-inflammatory stimuli that our organism is exposed to lifelong combined with a healthy or unhealthy lifestyle (nutrition and physical activity) and gut microbiota affect the IS remodeling triggering an adaptive or a maladaptive response. Excessive stimulation of pro-inflammatory pathways and an ineffective anti-inflammatory response constitutes a driving force for developing age-related diseases and disabilities. Instead, achieving successful aging and longevity is determined by a lower predisposition to mount inflammatory response combined with an efficient anti-inflammatory network. Created with BioRender.com.

2012). For a detailed review on inflammaging and longevity, please refer to Monti et al. (2017). It is still unknown whether this optimal balance is a characteristic of these individuals during their entire life due to both lifestyle and genetic background or if they acquire this ability in the later phase of life due to an adaptive strategy. A recent whole-genome sequencing analysis from our group showed that individuals aged more than 105 years have a peculiar genetic background associated with DNA repair system and clonal haematopoiesis that could likely represent important factors for healthy aging (Garagnani et al., 2021).

Inflammaging is a systemic physiological process involving most of the cells and the organs of the body (Cevenini et al., 2010, 2013). A variety of tissues (adipose tissue, muscle), organs (brain, liver), systems (immune system) and ecosystems (skin, oral, lung, gut and genito- urinary tract microbiota) contributes differently to the onset and progression of inflammaging with specific site organs-restricted and/or systemic effects (Cevenini et al., 2013; Santoro et al., 2020b). For instance, it is well known that adipose tissue (Franceschi, 2017d) not only increases quantitatively with age throughout the body with marked differences between males and females (Ponti et al., 2020; Santoro et al., 2018a) but also has been recognized as an endocrine source of mediators (hormones, acute-phase proteins, cytokines, adipokines and growth factors) (Calder et al., 2011). In particular, the accumulation of abdominal fat (visceral rather than subcutaneous) can establish and sustain a chronic low-grade inflammation (Santoro et al., 2018a) and contributing to metabolic diseases (Ostan et al., 2013). Obesity-associated inflammation has also been an additional factor for COVID-19 patients (Frasca et al., 2021). Interestingly, it has been found that single nucleotide polymorphism R293Q in the cGAS/STING pathway is associated with a decreased risk for obesity-associated cardiovascular disease in age-advanced subjects (Hamann et al., 2020), suggesting that this STING variant decreases the sensitivity of the innate IS towards DAMPS reducing the risk of age-related diseases.

Aging is not uniform, neither across tissues nor among individuals. People at the same chronological age could possess different aging rates due to a unique complex interaction among intrinsic and extrinsic factors (genetic *vs* environment) determining the so-called "biological age" (Hamczyk et al., 2020). Several studies are currently investigating the biomarkers defining biological age (Cohen et al., 2020). However, what is becoming more evident is that the level of inflammaging (tightly associated with biological age rather than chronological age) represents a critical factor in the large inter-individual variability of the elderly and predicting the development of age-related diseases (Franceschi et al., 2018b, Lehallier et al., 2019; Deelen et al., 2019).

The most common triggers of inflammaging include chronic infections (e.g. persistent viral infection by CMV; Sansoni et al., 2014), physical inactivity, (visceral) obesity, intestinal dysbiosis, diet, social isolation, psychological stress, early life adversity (Merz and Turner, 2021), disturbed sleep and disrupted circadian rhythm, and exposure to xenobiotics such as air pollutants, hazardous waste products, industrial chemicals and tobacco smoking (Furman et al., 2019). Therefore, the biological markers of inflammaging can vary according to environmental, cultural, and geographical settings that reflect worldwide (Batista et al., 2020; Franceschi et al., 2018c), and there is an urgent need to find tools to investigate inflammaging at personal level. Interestingly, several data report that sex and gender impact the immune response at old age and, consequently, on inflammaging (see BOX 1). In this framework, it is easy to understand that personalized strategies are needed to counteract inflammaging. Among the non-pharmacological approaches, dietary and physical activity interventions are the most encouraged. Accordingly, calorie restriction, intermitting fasting, adherence to healthy dietary patterns such as Mediterranean diet, meal timing, and frequency combined with an adequate amount of physical activity have likely advantageous effects on health (Marseglia et al., 2018; Jennings et al., 2018, 2019) and longevity (Santoro et al., 2020a) also because they directly increase the abundance of specific taxa of the gut microbiota and of specific microbial metabolites associated with reduced frailty and pro-inflammatory markers and improved cognitive function (Ghosh et al., 2020).

4.1. Gut microbiota: at the crossroad among inflammaging, immunosenescence and longevity

The commensal microbiota associated with the intestinal tract (GM) is currently the most studied in humans. Microbes in the gut are fundamental for the digestion function, the biosynthesis of vitamins and amino acids (Mardinoglu et al., 2015; Soto-Martin et al., 2020) and the modulation of fat storage and improve the ability of our body to extract nutrients from food (Martinez-Guryn et al., 2018); moreover, they can strongly control innate and specific immunity.

GM alterations in composition and function occurring during aging and as a consequence of age-related diseases (Lakshminarayanan et al., 2014), called dysbiosis, could impact on inflammaging due to the continuous stimulation of the IS, which causes immunosenescence (Santoro et al., 2020a,2020b). Overall, this inflammatory environment contributes to the progression of various pathological conditions in older adults and makes the host more susceptible to dangerous bacteria (Bischoff, 2016). The synergism between GM and immune cells has a remarkable impact on the host's health and immune defense. The microbiota is continuously adapting to its environment throughout the lifetime and is largely heterogeneous among individuals due to genetics and lifestyle factors. Diet, place and country of residence (Claesson et al., 2012; Ghosh et al., 2020), physical activity (Huang et al., 2019), smoking (Lee et al., 2018), sleep quality (Smith et al., 2019), mental health (Barandouzi et al., 2020) and medication (Sun et al., 2019) are key factors able to modulate GM from birth to advanced age. The GM composition of healthy adults is constituted at 90% by Bacteroidetes (Bacteroides, Prevotella) and Firmicutes (Clostridium, Faecalibacterium, Lactobacilli, Ruminococcus), and the residual 10% by Actinobacteria (Bifidobacterium), Proteobacteria (Escherichia, Helicobacter,

Table 1
Age-related changes in GM and its metabolites in Italian Elderly and Centenarians.

	Elderly	Centenarians	References
Biodiversity	Decreased biodiversity	Increased biodiversity	Biagi et al., 2016
Composition	**Increase of pathobionts** (*Enterobacteriaceae* and *Desulfovibrionaceae*)	**Increase of probiotic bacteria** *Bifidobacterium* and higher abundance of *Akkermansia* and *Christensenellaceae*	Biagi et al., 2010, 2012,2013, 2016
Adaptation	**Maladaptation**	**Good adaptation**	Biagi et al., 2016
Function	• Progressive loss of SCFA producing bacteria (*Faecalibacterium, Roseburia, Coprococcus*)	• Augmented capability for glycolysis and SCFA production	Biagi et al., 2010; Wu et al., 2019; Rampelli et al., 2020
		• Decrease in circulating tryptophan concentrations	Collino et al., 2013
		• Specific signature of glycerophospholipids and sphingolipids	Collino et al., 2013
		• Increased excretion of urine phenylacetylglutamine (PAG) and p-cresol sulfate (PCS)	Montoliu et al., 2014
		• Specific profile of Volatile Organic Compounds (VOCs) in urine and feces	Conte et al., 2020

Shigella) and Verrucomicrobia (Akkermansia) phyla (Qin et al., 2010). This composition drastically changes with aging. Indeed, pathophysiological changes in the gastrointestinal tract, lifestyle modification, nutrition (Claesson et al., 2012), behaviour, immunosenescence, and inflammaging strongly impact GM, eventually pushing maladaptive variants (Claesson et al., 2011). Specifically, the main age-associated changes of GM (summarized in Table 1) regard a decrease in biodiversity with a progressive loss of Short Chain Fatty Acids (SCFAs) producing bacteria with anti-inflammatory abilities and an increase of pathobionts (potential harmful bacteria). On the whole, these modifications set a vicious circle, further boosting inflammation and reduce the capability of older people to positively adapt to the different environmental events because of the decline of metabolic alternatives, for example, for SCFAs production.

Centenarians, the best example of successful adaptation, represent a valuable model to explore how the microbiota component can successfully maintain or re-establish a mutualistic relationship with the human host, along with the occurrence of age-related variations. Indeed, the gut microbiota of centenarians emerges as a peculiar ecosystem, different from that of elderly and adults, specifically adapted to a highly aged host (Biagi et al., 2017; Biagi and Santoro, 2021). Interestingly, the comparison of GM composition of centenarians from different countries has shown that while lifestyle, ethnicity and geography undoubtedly impact such extreme microbiota adaptive variations, common signatures of longevity emerge among the studied populations (Santoro et al., 2018b).

Our group studied the microbiota of centenarians for the first time in 2010 and revealed that centenarians (almost all women) showed all the modifications associated with aging itself (Biagi et al., 2010, 2012, 2013). Moreover, an increase of pro-inflammatory IL-6 and IL-8 was found (Biagi et al., 2010). The typical age modification above described, *i.e.* the reduction in the abundance of known health-promoting bacteria belonging to the genera *Faecalibacterium, Roseburia, Coprococcus*, and an increase in the proportion of subdominant species, including putative pro-inflammatory bacteria (*Enterobacteriaceae* and *Desulfovibrionaceae* families) were also present in centenarians. At the same time, the gut microbiota of centenarians and, especially, semi-supercentenarians (>105 years old) showed some peculiarities that might be able to contribute somehow to the maintenance of health during the extreme phases of life. Indeed, the GM of the exceptional survivors presented a higher prevalence of *Bifidobacterium*, a long time a known probiotic group of bacteria, as well as higher abundances of subdominant members of the human gut ecosystem that have been explored only recently, such as *Akkermansia* and *Christensenellaceae* (Biagi et al., 2016).

Akkermansia muciniphila is a mucin-degrading bacterium whose abundance in the human gut has been inversely correlated to several metabolic disease states (Geerlings et al., 2018). Also, *Christensenellaceae* has been associated with a state of metabolic health for the host, notably correlated to a lean phenotype and a reduced visceral adipose tissue (Oki et al., 2016; Tavella et al., 2021). Other Authors came to similar results when analyzing the microbiota of centenarians living in rural or isolated areas of China and Japan (Kong et al., 2016; Odamaki et al., 2016). Recently, studies involving centenarians from a rural area of India (Tuikhar et al., 2019) and Russia (Kashtanova et al., 2020) have been published, and the results were similar to those Italian, Chinese and Japanese populations in terms of increased biodiversity but with some peculiarities owing to the different lifestyle and nutritional habits.

The neutralization of inflammaging is one of the most hypothesized methods by which the microbiota is supposed to contribute to healthy aging (Biagi et al., 2013; Franceschi et al., 2018b). In a recent study using germ-free mice, the microbiota of old mice was transferred into young mice inducing inflammation in the young ones. However, the levels of inflammation were negatively correlated with the abundance of *Akkermansia* in the original microbiota (Fransen et al., 2017). Moreover, metagenomics studies exploring the function of the GM of centenarians conducted on two different Italian cohorts of centenarians from Sardinia and Bologna showed an augmented capability for glycolysis and SCFA production (Wu et al., 2019; Rampelli et al., 2020) also associated with functions related to the degradation of xenobiotics (Rampelli et al., 2020). Metabolomics approaches revealed that centenarians display a marked decrease in tryptophan concentration with a unique alteration of specific glycerophospholipids and sphingolipids and increased excretion of urine phenylacetylglutamine (PAG) and p-cresol sulfate (PCS) (Collino et al., 2013; Montoliu et al., 2014).

Furthermore, centenarians and their offspring are characterized by a specific profile of Volatile organic compounds (VOCs) in urine and faeces (Conte et al., 2020). In the authors' opinion, such features of microbial metabolisms might be involved in maintaining and prolonging metabolic and immunological health, adapting to the environment, and ultimately favouring longevity. The possibilities to exploit such data for human health maintenance during aging are still being explored, and exciting scenarios can be envisaged. *Akkermansia* and *Christensenella* represent promising health-promoting strategies and have been listed among the so-called "next-generation probiotics", *i.e.* bacteria other than the traditional *Lactobacillus* and *Bifidobacterium*, which could become part of more innovative and targeted probiotic strategies (O'Toole et al., 2017; Chang et al., 2019). In addition, the possibility of using microbiota transplantation to promote those features in the gut ecosystem that are known to be linked to longevity could be another possibility to sustain the IS to counteract inflammation and promote or restore healthiness.

5. Can immunosenescence and inflammaging increase COVID-19 susceptibility?

One of the most important observations in the COVID-19 pandemic is the differential susceptibility to illness. We know that individuals at the greatest risk are older persons (mainly men) affected by multimorbidities, including hypertension, diabetes, and/or obesity (Zhou et al., 2020; Gemmati et al., 2020). However, not all infected aged people will progress to the severe stage and will not die, but as yet, the why is not clear. Understanding the remodeling and adaptation or maladaptation of IS with age during the COVID-19 pandemic is fundamental because it could explain the different susceptibility among aged people and the different responses to vaccines (Ciabattini et al., 2020). In other words, it could help us to distinguish better which changes of IS may be detrimental or beneficial. As we highlighted several times in this review, older people are characterized by extreme heterogeneity due to the numerous and different exposure factors encountered lifelong that can determine each individual's different immune responses (immunobiography) (Franceschi et al., 2017a). With aging, these factors capable of eliciting inflammatory responses increase unabated, leading to high levels of pro-inflammatory mediators, which are believed to contribute to the pathogenesis of many, if not all, age-associated diseases and the progression of the aging process. (Franceschi and Campisi, 2014). Age-related gut microbiota dysbiosis represents a source of pro-inflammatory factors and may play an essential role in determining the course of COVID-19 (Ferreira et al., 2020). Inflammaging, associated with immunosenescence, likely results from the imbalance between the production of pro-and anti-inflammatory mediators. This is a sort of adaptive mechanism to a person's lifelong exposure to stressors, whereby inflammation continuously triggers anti-inflammatory responses (Spazzafumo et al., 2013). Inflammation could, in turn, be considered a sort of hormetic response, having positive outcomes at low doses (physiological inflammation) at young and adult ages and becoming detrimental during the postreproductive period, especially in people who, as a result of genetic background and/or unhealthy lifestyle, are not able to maintain an optimal balance between inflammaging and anti-inflammaging (Santoro et al., 2020a; Martucci et al., 2017).

Thus, inflammaging and immunosenescence, characterized by a loss in adaptive immune functions, could be predisposing conditions that sustain the mechanism by which the SARS-CoV-2 escape the immune surveillance and leads to serious COVID-19. This reinforces the need to find treatments that stimulate the innate immune response to protect the

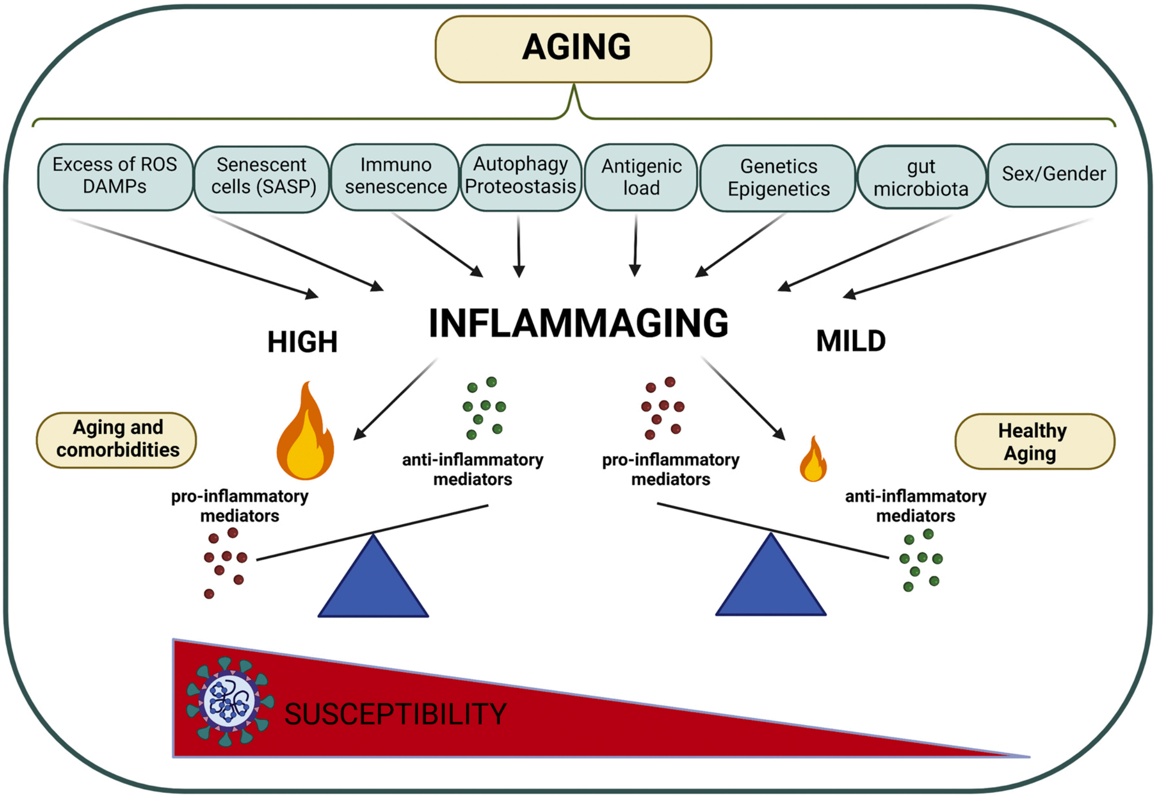

Fig. 4. Inflammaging and susceptibility to COVID 19. Aging is characterized by extreme heterogeneity due to the numerous and different exposures to lifelong factors determining each individual's different immune responses. The different remodeling and adaptive reaction of the immune system triggered by inflammaging could explain the different susceptibility to COVID-19 among aged people. The adaptive anti-inflammatory response triggered by a mild inflammaging could reduce the susceptibility to COVID-19 or the disease severity. A poor remodeling and the consequent maladaptation of the immune system, triggered by a high inflammaging, could increase the risk of SARS-CoV-2 infection and the severity of the disease. Created with BioRender.com.

organism from infections.

In other words, the aged persons who have developed a phenotype characterized by a higher level of plasma inflammatory mediators leading to comorbidities (e.g., hypertension, cardiovascular diseases, obesity, diabetes) could present higher COVID-19 susceptibility with severe complications and explain the high mortality rates in this cohort (Fig. 4). In addition, to systemic risk factors for higher COVID-19 severity in the elderly, it is also essential to consider changes that occur locally in the lung with age. Data regarding the aging human lung's transcriptomic features and cellular landscape concerning SARS-CoV-2 have recently been obtained (Chow et al., 2021). Lung aging is transcriptionally characterized by increased cell adhesion and heightened stress responses, along with reduced mitochondria and diminished cellular replication. Moreover, many age-related alterations in cellular composition, including cells implicated in response to SARS-COV-2, have been demonstrated. These changes highlighted reduced regenerative capacity, progressive lung parenchyma loss during aging, and an augmented risk for chronic obstructive pulmonary disease and pulmonary fibrosis. Furthermore, proliferating natural killer (NK)/T cells among immune cells decreased with age, whereas IGSF21+ dendritic cells increased with age. NK and T cells are fundamental in response to SARS-COV-2, and their decrease may contribute to the increased risk of COVID-19 morbidity and mortality in older patients. Chow et al. have also demonstrated that some age-associated genes are enriched among genes directly regulated by SARS-COV-2 infection in vitro and in vivo, suggesting transcriptional parallels between the aging lung and SARS-COV-2 infection (Chow et al., 2021).

Moreover, a central lesson from aging medicine suggests that the biological age, rather than chronological age, of affected patients, might be critical in systematically assessing COVID-19 infections to avoid excess mortality. At present, it is possible to quantify biological age using various proteomic, epigenetic and inflammatory biomarkers, which should help us predict the risk of developing major age-related diseases and susceptibility to COVID-19. (Sayed et al., 2021; Lehallier et al., 2019; Horvath et al., 2015).

Centenarians have a peculiar state/degree of inflammaging, which is much lower than predicted by their chronological age and is biased toward anti-inflammaging. The production of anti-inflammatory molecules and cells formed lifelong represent an adaptive, compensatory mechanism to continuously down-regulate the inflammatory process and avoid its chronic detrimental effects (Franceschi et al., 2007; Sayed et al., 2021; Storci et al., 2019).

In the era of COVID-19, it is interesting to underline that centenarians showed a remarkable capacity to recover after coronavirus infection. To this regard, there are anecdotal observations that centenarians and sometimes supercentenarians (people over 110 years old) survived and recovered after SARS-CoV-2 infection (Abbatecola and Antonelli-Incalzi, 2020), as confirmed in a group of centenarians belonging to "Centenari a Trieste (CaT) study" (Marcon et al., 2020). Centenarians have better resilience and biological reserves to better cope with inflammaging as they can mount a robust anti-inflammaging response neutralizing the overall presence of inflammatory processes.

Finally, it is essential to emphasize the crucial role of inflammaging and immunosenescence in post-covid syndrome or long-covid, one of the major health burdens in the following years. Nearly a third of individuals discharged from hospital after acute COVID-19 need to be re-admitted to hospitals after few months (and more than 1 in 10 died after discharge); two-thirds had increased rates of multiorgan dysfunction and respiratory diseases, diabetes and cardiovascular diseases compared with the expected risk in the general population (Ayoubkhani et al., 2021).

Consequently, to SARS-CoV-2 infection, the IS underwent complex testing, and the recovery is highly heterogeneous depending also on the personal background, the severity of disease, pharmacological treatments and the total capacity of long-term adaptation and resilience.

6. Conclusions and perspectives

Aging is one of the most intricate and complex biological phenomena and represents the major risk factor for all age-related diseases, such as infections, cancer, autoimmune disorders, and chronic inflammatory diseases. A significant characteristic of older people is their heterogeneity regarding their health status (presence/absence of comorbidities, frailty, cognitive impairment) and their different capability to mount an immune response to pathogens and vaccines (Franceschi et al., 2017a, 2017b,2017c,2017d; Ciabattini et al., 2018)

Aging is not uniform among individuals and can be considered a continuum with the extreme phenotypes represented by diseases and disabilities on one side and healthy aging and longevity on the other side. Several factors, such as genetics, nutrition, exercise, previous exposure to microorganisms, sex (biological-related), gender (cultural-related) and human cytomegalovirus status, can influence immunosenescence. Many age-related changes in IS have been described, and most of them have been considered harmful and causes many age-related diseases.

Changes occur in both the innate and the adaptive IS, but not with the same extent or the same consequences. Therefore, it could be conceptualized that the age-related immune changes may be a mix of adaptation/resilience and maladaptation, closely related to the immunobiography (Franceschi et al., 2017a; Fulop et al., 2018).The balance between these two processes will establish how the person will age (Fig. 3).

Moreover, sex and gender strictly impact the IS of the elderly, likely contributing to the sex/gender disparity in terms of epidemiology, pathophysiology, symptoms, and severity of age-related diseases such as autoimmune diseases. There is an intricate interrelationship between immunosenescence and inflammaging able to generate a complex network of adaptive mechanisms that can favor longevity when able to counteract the injuries individuals are exposed lifelong (adaptation) or, on the opposite side, increase the susceptibility to diseases when inadequate (maladaptation) (Fig. 3).

The study of this interconnection is now becoming of particular interest during the COVID-19 pandemic, bringing to the fore the critical need to combat immunosenescence and inflammaging and improve older people's immune function and resilience. Future studies are necessary to elucidate these interactions and increase targets for new interventions to decrease the deleterious effects of aging and use the beneficial effects for a better health span in the elderly. The gut microbiota dysbiosis occurring during aging plays an essential role in modulating inflammaging, and information gathered from the studies on centenarians could represent a valuable health-promoting strategy to encourage treatments with longevity-associated probiotics. The rapid advancement of knowledge and technologies to study the IS and the integration of omics such as genetic/epigenetic/metabolic and environmental factors (nutrition and physical activity) will pave the way to improve the insight on the beneficial effects of immunosenescence and inflammaging as processes triggered to adapt and counteract aging also at personal level.

Author Contributions

DM and AS contributed to the concept, writing and critical discussion of the manuscript. EB contributed to the critical discussion of the manuscript and the revision of the literature. All authors reviewed and/or edited the manuscript before submission.

Funding

This work has been partially supported by: the Roberto and Cornelia Pallotti legacy for cancer research and the JPI-HDHL-Metadis, "EURO-DIET" project (ID: 1164; 2020–2023) to AS; by the Fondazione CR Firenze (2019) n. 24,213-(2018.1015) and Project of Excellence "Gender Medicine" 2020, Department of Experimental and Clinical Biomedical Sciences "Mario Serio to DM.

Declaration of Competing Interest

The authors have no conflicts of interest

References

Abad-Díez, J.M., Calderón-Larrañaga, A., Poncel-Falcó, A., Poblador-Plou, B., Calderón-Meza, J.M., Sicras-Mainar, A., Clerencia-Sierra, M., Prados-Torres, A., 2014. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. BMC Geriatr. 14, 75. https://doi.org/10.1186/1471-2318-14-75.

Abbatecola, A.M., Antonelli-Incalzi, R., 2020. Editorial: COVID-19 spiraling of frailty in older Italian patients. J. Nutr. Health Aging 24 (5), 453–455. https://doi.org/10.1007/s12603-020-1357-9.

Ademokun, A., Wu, Y.C., Dunn-Walters, D., 2010. The ageing B cell population: composition and function. Biogerontology 11, 125–137. https://doi.org/10.1007/s10522-009-9256-9.

Akbar, A.N., Henson, S.M., Lanna, A., 2016. Senescence of T lymphocytes: implications for enhancing human immunity. Trends Immunol. 37 (12), 866–876. https://doi.org/10.1016/j.it.2016.09.002.

Alberti, S., Cevenini, E., Ostan, R., Capri, M., Salvioli, S., Bucci, L., Ginaldi, L., DeMartinis, M., Franceschi, C., Monti, D., 2006. Age-dependent modifications of type 1 and type 2 cytokines within virgin and memory CD4+ T cells in humans. Mech. Ageing Dev. 127 (6), 560–566. https://doi.org/10.1016/j.mad.2006.01.014.

Alonso-Fernandez, P., Puerto, M., Mate, I., Ribera, J.M., de la Fuente, M., 2008. Neutrophils of centenarians show function levels similar to those of young adults. J. Am. Geriatr. Soc. 56, 2244–2251. https://doi.org/10.1111/j.1532-5415.2008.02018.x.

Amulic, B., Cazalet, C., Hayes, G.L., Metzler, K.D., Zychlinsky, A., 2012. Neutrophil function: from mechanisms to disease. Annu. Rev. Immunol. 30, 459–489. https://doi.org/10.1146/annurev-immunol-020711-074942.

Andrasfay, T., Goldman, N., 2021. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. Proc. Natl. Acad. Sci. U. S. A. 118 (5) https://doi.org/10.1101/2020.07.12.20148387 e2014746118.

Appay, V., Sauce, D., 2014. Naive T cells: the crux of cellular immune aging? Exp. Gerontol. 54, 90–93. https://doi.org/10.1016/j.exger.2014.01.003.

Ayoubkhani, D., Khunti, K., Nafilyan, V., Maddox, T., Humberstone, B., Diamond, I., Banerjee, A., 2021. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ 372. https://doi.org/10.1136/bmj.n693 n693.

Bajwa, M., Vita, S., Vescovini, R., Larsen, M., Sansoni, P., Terrazzini, N., Caserta, S., Thomas, D., Davies, K.A., Smith, H., Kern, F., 2017. CMV-specific T-cell responses at older ages: broad responses with a large central memory component may be key to long-term survival. J. Infect. Dis. 215 (8), 1212–1220. https://doi.org/10.1093/infdis/jix080.

Bakhru, P., Su, M.A., 2016. Estrogen turns down "the AIRE". J. Clin. Invest. 126, 1239–1241. https://doi.org/10.1172/JCI86800.

Banchereau, J., Briere, F., Caux, C., Davoust, J., Lebecque, S., Liu, Y.J., Pulendran, B., Palucka, K., 2000. Immunobiology of dendritic cells. Annu. Rev. Immunol. 18, 767–811. https://doi.org/10.1146/annurev.immunol.18.1.767.

Barandouzi, Z.A., Starkweather, A.R., Henderson, W.A., Gyamfi, A., Cong, X.S., 2020. Altered composition of gut microbiota in depression: a systematic review. Front. Psychiatry 11, 541. https://doi.org/10.3389/fpsyt.2020.00541.

Barbé-Tuana, F., Funchal, G., Schmitz, C.R.R., Maurmann, R.M., Bauer, M.E., 2020. The interplay between immunosenescence and age-related diseases. Semin. Immunopathol. 42 (5), 545–557. https://doi.org/10.1007/s00281-020-00806-z.

Basile, G., Paffumi, I., D'Angelo, A.G., Figliomeni, P., Cucinotta, M.D., Pace, E., Ferraro, M., Saitta, S., Lasco, A., Gangemi, S., 2012. Healthy centenarians show high levels of circulating interleukin-22 (IL-22). Arch. Gerontol. Geriatr. 54, 459–461. https://doi.org/10.1016/j.archger.2011.05.004.

Batista, M.A., Calvo-Fortes, F., Silveira-Nunes, G., Camatta, G.C., Speziali, E., Turroni, S., Teixeira-Carvalho, A., Martins-Filho, O.A., Neretti, N., Maioli, T.U., Santos, R.R., Brigidi, P., Franceschi, C., Faria, A.M.C., 2020. Inflammaging in endemic areas for infectious diseases. Front. Immunol. 11, 579972 https://doi.org/10.3389/fimmu.2020.579972.

Bektas, A., Schurman, S.H., Sen, R., Ferrucci, L., 2017. Human T cell immunosenescence and inflammation in aging. J. Leukoc. Biol. 102, 977–988. https://doi.org/10.1189/jlb.3RI0716-335R.

Biagi, E., Santoro, A., 2021. A trait of longevity: the microbiota of centenarians (2021). Comprehensive Gut Microbiota edited Elsevier https://doi.org/10.1016/B978-0-12-819265-8.00052-8 in press.

Biagi, E., Nylund, L., Candela, M., Ostan, R., bucci, L., Pini, E., Nikkïla, J., Monti, D., Satokari, R., Franceschi, C., Brigidi, P., De Vos, W., 2010. Through aging, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One 5 (5), e10667. https://doi.org/10.1371/journal.pone.0010667.

Biagi, E., Candela, M., Fairweather-Tait, S., Franceschi, C., Brigidi, P., 2012. Aging of the human metaorganism: the microbial counterpart. Age (Dordr). 34 (1), 247–267. https://doi.org/10.1007/s11357-011-9217-5.

Biagi, E., Candela, M., Turroni, S., Garagnani, P., Franceschi, C., Brigidi, P., 2013. Aging and gut microbes: perspectives for health maintenance and longevity. Pharmacol. Res. 69 (1), 11–20. https://doi.org/10.1016/j.phrs.2012.10.005.

Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C., Quercia, S., Scurti, M., Monti, D., Capri, M., Brigidi, P., Candela, M., 2016. Gut microbiota and extreme longevity. Curr. Biol. 26 (11), 1480–1485. https://doi.org/10.1016/j.cub.2016.04.016.

Biagi, E., Rampelli, S., Turroni, S., Quercia, S., Candela, M., Brigidi, P., 2017. The gut microbiota of centenarians: signatures of longevity in the gut microbiota profile. Mech. Ageing Dev. 165 (Pt B), 180–184. https://doi.org/10.1016/j.mad.2016.12.013.

Bischoff, S.C., 2016. Microbiota and aging. Curr. Opin. Clin. Nutr. Metab. Care 19, 26–30. https://doi.org/10.1097/MCO, 0000000000000242.

Bonafè, M., Olivieri, F., Cavallone, L., Giovagnetti, S., Mayegiani, F., Cardelli, M., Pieri, C., Marra, M., Antonicelli, R., Lisa, R., Rizzo, M.R., paolisso, G., Monti, D., Franceschi, C., 2001. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. Eur. J. Immunol. 31, 2357–2361. https://doi.org/10.1002/1521-4141 (200108)31:83.0.co;2-x.

Bongen, E., Lucian, H., Khatri, A., Fragiadakis, G.K., Bjornson, Z.B., Nolan, G.P., Utz, P.J., Khatri, P., 2019. Sex differences in the blood transcriptome identify robust changes in immune cell proportions with aging and influenza infection. Cell Rep. 29 (7), 1961–1973. https://doi.org/10.1016/j.celrep.2019.10.019 e4.

Brubaker, A.L., Rendon, J.L., Ramirez, L., Choudhry, M.A., Kovacs, E.J., 2013. Reduced neutrophil chemotaxis and infiltration contributes to delayed resolution of cutaneous wound infection with advanced age. J. Immunol. 190, 1746–1757. https://doi.org/10.4049/jimmunol.1201213.

Bulati, M., Buffa, S., Candore, G., Caruso, C., Dunn-Walters, D.K., Pellicanò, M., Wu, Y.C., Colonna Romano, G., 2011. B cells and immunosenescence: a focus on IgG+ IgD−CD27− (DN) B cells in aged humans. Ageing Res. Rev. 10, 274–284. https://doi.org/10.1016/j.arr.2010.12.002.

Butcher, S., Chahal, H., Savey, E., Killampalli, V.V., Alpar, E.K., Lord, J.M., 2001. Functional decline in human neutrophils with age. Sci. World J. 1, 67. https://doi.org/10.1100/TSW.2001.105.

Calder, P.C., Ahluwalia, N., Brouns, F., Buetler, T., Clement, K., Cunningham, K., Esposito, K., Jönsson, L.S., Kolb, H., Lansink, M., Marcos, A., Margioris, A., Matusheski, N., Nordmann, H., O'Brien, J., Pugliese, G., Rizkalla, S., Schalkwijk, C., Tuomilehto, J., Wärnberg, J., Watzl, B., Winklhofer-Roob, B.M., 2011. Dietary factors and low-grade inflammation in relation to overweight and obesity. Br. J. Nutr. 106, S5–78. https://doi.org/10.1017/S0007114511005460.

Callender, L.A., Carroll, E.C., Beal, R.W.J., Chambers, E.S., Nourshargh, S., Akbar, A.N., Henson, S.M., 2018. Human CD8(+) EMRA T cells display a senescence-associated secretory phenotype regulated by p38 MAPK. Aging Cell 17 (1), e12675. https://doi.org/10.1111/acel.12675.

Campisi, J., d'Adda di Fagagna, F., 2007. Cellular senescence: when bad things happen to good cells. Nat. Rev. Mol. Cell Biol. 8 (9), 729–740. https://doi.org/10.1038/nrm2233.

Campisi, J., Robert, L., 2014. Cell senescence: role in aging and age-related diseases. Interdiscip. Top. Gerontol. 39, 45–61. https://doi.org/10.1159/000358899.

Carissimo, G., Xu, W., Kwok, I., Abdad, M.Y., Chan, Y.H., Fong, S.W., Puan, K.J., Lee, C. Y.P., Yeo, N.K.W., Amrun, S.N., Chee, R.S.L., How, W., Chan, S., Fan, B.E., Andiappan, A.K., Lee, B., Rötzschke, O., Young, B.E., Leo, Y.S., Lye, D.C., Renia, L., Ng, L.G., Larbi, A., Ng, L.F., 2020. Whole blood immunophenotyping uncovers immature neutrophil-to-VD2 T-cell ratio as an early marker for severe COVID-19. Nat. Commun. 11 (1), 1–12. https://doi.org/10.1038/s41467-020-19080-6.

Cevenini, E., Caruso, C., Candore, G., Capri, M., Nuzzo, D., Duro, G., Rizzo, C., Colonna-Romano, G., Lio, D., Di Carlo, D., Palmas, M.G., Scurti, M., Pini, E., Franceschi, C., Vasto, S., 2010. Age-related inflammation: the contribution of different organs, tissues and systems. How to face it for therapeutic approaches. Curr. Pharm. Des. 16 (6), 609–618. https://doi.org/10.2174/138161210790883840.

Cevenini, E., Monti, D., Franceschi, C., 2013. Inflamm-ageing. Curr. Opin. Clin. Nutr. Metab. Care 16 (1), 14–20. https://doi.org/10.1097/MCO.0b013e32835ada13.

Chang, C.J., Lin, T.L., Tsai, Y.L., Wu, T.R., Lai, W.F., Lu, C.C., lai, H.C., 2019. Next generation probiotics in disease amelioration. J. Food Drug Anal. 27 (3), 615–622. https://doi.org/10.1016/j.jfda.2018.12.011.

Chen, Y., Klein, S.L., Garibaldi, B.T., Li, H., Wu, C., Osevala, N.M., Li, T., Margolick, J.B., Pawelec, G., Leng, S.X., 2021. Aging in COVID-19: vulnerability, immunity and intervention. Ageing Res. Rev. 65, 101205 https://doi.org/10.1016/j.arr.2020.101205.

Chow, R.D., Majety, M., Chen, S., 2021. The aging transcriptome and cellular landscape of the human lung in relation to SARS-CoV-2. Nat. Commun. 12 (1) https://doi.org/10.1038/s41467-020-20323-9.

Ciabattini, A., Nardini, C., Santoro, F., Garagnani, P., Franceschi, C., Medaglini, D., 2018. Vaccination in the elderly: the challenge of immune changes with aging. Semin. Immunol. 40, 83–94. https://doi.org/10.1016/j.smim.2018.10.010.

Ciabattini, A., Garagnani, P., Santoro, F., Rappuoli, R., Franceschi, C., Medaglini, D., 2020. Shelter from the cytokine storm: pitfalls and prospects in the development of SARS-CoV-2 vaccines for an elderly population. Semin. Immunopathol. 42 (5), 619–634. https://doi.org/10.1007/s00281-020-00821-0.

Claesson, M.J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., Marchesi, J.R., Falush, D., Dinan, T., Fitzgerald, G., Stanton, C., van Sinderen, D., O'Connor, M., Harnedy, N., O'Connor, K., Henry, C., O'Mahony, D., FitzGerald, A.P., Shanahan, F., Twomey, C., Hill, C., Ross, R.P., O'Toole, P.W., 2011. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. PNAS 108 (Suppl 1), 4586–4591. https://doi.org/10.1073/pnas.1000097107.

Claesson, M.J., Jeffery, I.B., Conde, S., Power, S.E., O'Connor, E.M., Cusack, S., Harris, H. M.B., Coakley, M., Lakshminarayanan, B., O'Sullivan, O., Fitzgerald, G.F., Deane, J., O'Connor, M., Harnedy, N., O'Connor, K., O'Mahony, D., van Sinderen, D., Wallace, M., Brennan, L., Stanton, C., Marchesi, J.R., Fitzgerald, A.P., Shanahan, F., Hill, C., Ross, R.P., O'Toole, P.W., 2012. Gut microbiota composition correlates with diet and health in the elderly. Nature 488, 178–184. https://doi.org/10.1038/nature11319.

Cohen, A.A., Kennedy, B.K., Anglas, U., Bronikowski, A.M., Deelen, J., Dufour, F., Ferbeyre, G., Ferrucci, L., Franceschi, C., Frasca, D., Friguet, B., Gaudreau, P., Gladyshev, V.N., Gonos, E.S., Gorbunova, V., Gut, P., Ivanchenko, M., Legault, V., Lemaitre, J.F., Liontis, T., Liu, G.H., Liu, M., Maier, A.B., Nobrega, O.T., Olde Rikkert, M.G.M., Pawelec, G., Rheault, S., Senior, A.M., Simm, A., Soo, S., Traa, A., Ukraintseva, S., Vanhaelen, Q., Van Raamsdonk, J.M., Witkowski, J.M., Yashin, A.I., Ziman, R., Fulop, T., 2020. Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework. Mech. Ageing Dev. 191, 111316 https://doi.org/10.1016/j.mad.2020.111316.

Collino, S., Montoliu, I., Martin, F.P., Scherer, M., Mari, D., Salvioli, S., Bucci, L., Ostan, R., Monti, D., Biagi, E., Brigidi, P., Franceschi, C., Rezzi, S., 2013. Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PLoS One 8, e56564. https://doi.org/10.1371/journal.pone.0056564.

Colonna-Romano, G., Bulati, M., Aquino, A., Scialabba, G., Candore, G., Lio, D., Motta, M., Malaguarnera, M., Caruso, C., 2003. B cells in the aged: CD27, CD5, and CD40 expression. Mech. Ageing Dev. 124, 389–393. https://doi.org/10.1016/s00476374(03)00013-00017.

Colonna-Romano, G., Bulati, M., Aquino, A., Pellicano, M., Vitello, S., Lio, D., Candore, G., Caruso, C., 2009. A double-negative (IgD-CD27-) B cell population is increased in the peripheral blood of older adults. Mech. Ageing Dev. 130, 681–690. https://doi.org/10.1016/j.mad.2009.08.003.

Conte, M., Ostan, R., Fabbri, C., Santoro, A., Guidarelli, G., Vitale, G., Mari, D., Sevini, F., Capri, M., Sandri, M., Monti, D., Franceschi, C., Salvioli, S., 2019. Human aging and longevity are characterized by high levels of Mitokines. J. Gerontol. A Biol. Sci. Med. Sci. 74 (5), 600–607. https://doi.org/10.1093/gerona/gly153.

Conte, M., Conte, G., Martucci, M., Monti, D., Casarosa, L., Serra, A., Mele, M., Franceschi, C., Salvioli, S., 2020. The smell of longevity: a combination of Volatile Organic Compounds (VOCs) can discriminate centenarians and their offspring from age-matched subjects and young controls. Geroscience 42 (1), 201–216. https://doi.org/10.1007/s11357-019-00143-6.

Cooper, M.A., Fehniger, T.A., Fuchs, A., Colonna, M., Caligiuri, M.A., 2004. NK cell and DC interactions. Trends Immunol. 25, 47–52. https://doi.org/10.1016/j.it.2003.10.012.

Coppé, J.P., Patil, C.K., Rodier, F., Sun, Y., Munoz, D.P., Goldstein, J., Nelson, P.S., Desprez, P.Y., Campisi, J., 2008. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 6, 2853–2868. https://doi.org/10.1371/journal.pbio.0060301.

Cossarizza, A., Ortolani, C., Paganelli, R., Barbieri, D., Monti, D., Sansoni, P., Fagiolo, U., Castellani, G., Bersani, F., Londei, M., Franceschi, C., 1996. CD45 isoforms expression on CD4+ and CD8+ T cells throughout life, from newborns to centenarians: implications for T cell memory. Mech. Ageing Dev. 86 (3), 173–195. https://doi.org/10.1016/0047-6374(95)01691-0.

Cossarizza, A., Ortolani, C., Monti, D., Franceschi, C., 1997. Cytometric analysis of immunosenescence. Cytometry 27, 297–313. https://doi.org/10.1002/(sici)1097-0320(19970401)27:4<297::aid-cyto1>3.0.co;2-a.

Costantini, A., Viola, N., Berretta, A., Galeazzi, R., Matacchione, G., Sabbatinelli, J., Storci, G., De Matteis, S., Butini, L., Rippo, M.R., Procopio, A.D., Caraceni, D., Antonicelli, R., Olivieri, F., Bonafè, M., 2018. Age-related M1/M2 phenotype changes in circulating monocytes from healthy/unhealthy individuals. Aging 10 (6), 1268–1280. https://doi.org/10.18632/aging.101465.

Covarrubias, A.J., Kale, A., Perrone, R., Lopez-Dominguez, J.A., Pisco, A.O., Kasler, H.G., Schmidt, M.S., Heckenbach, I., Kwok, R., Wiley, C.D., Wong, H.S., Gibbs, E., Iyer, S. S., Basisty, N., Wu, Q., Kim, I.J., Silva, E., Vitangcol, K., Shin, K.O., Lee, Y.M., Riley, R., Ben-Sahra, I., Ott, M., Schilling, B., Scheibye-Knudsen, M., Ishihara, K., Quake, S.R., Newman, J., Brenner, C., Campisi, J., Verdin, E., 2020. Senescent cells promote tissue NAD+ decline during ageing via the activation of CD38+ macrophages. Nature Metab. 2 (11), 1265–1283. https://doi.org/10.1038/s42255-020-00305-3.

Dall'Olio, F., Vanhooren, V., Chen, C.C., Slagboom, P.E., Wuhrer, M., Franceschi, C., 2013. N-glycomic biomarkers of biological aging and longevity: a link with inflammaging. Ageing Res. Rev. 12 (2), 685–698. https://doi.org/10.1016/j.arr.2012.02.002.

Das, A., Ranganathan, V., Umar, D., Thukral, S., George, A., Rath, S., Bal, V., 2017. Effector/memory CD4 T cells making either Th1 or Th2 cytokines commonly co-express T-bet and GATA-3. PLoSOne. 12 (10), e0185932. https://doi.org/10.1371/journal.pone.0185932.

De Martinis, M., Franceschi, C., Monti, D., Ginaldi, L., 2005. Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. FEBS Lett. 579, 2035–2039. https://doi.org/10.1016/j.febslet.2005.02.055.

Deelen, J., Kettunen, J., Fischer, K., van der Spek, A., Trompet, S., Kastenmuller, G., Boyd, A., Zierer, J., van den Akker, E.B., Ala-Korpela, M., Amin, N., Demirkan, A., Ghanbari, M., van Heemst, D., Ikram, M.A., van Klinken, J.B., Mooijaart, S.P., Peters, A., Salomaa, V., Sattar, N., Spector, T.D., Tiemeier, H., Verhoeven, A., Waldenberger, M., Wurtz, P., Davey Smith, G., Metspalu, A., Perola, M., Menni, C., Geleijnse, J.M., Drenos, F., Beekman, M., Jukema, J.W., van Duijn, C.M., Slagboom, P.E., 2019. A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. Nat. Commun. 10, 3346. https://doi.org/10.1038/s41467-019-11311-9.

Derhovanessian, E., Maier, A.B., Hähnel, K., Zelba, H., de Craen, A.J., Roelofs, H., Slagboom, E.P., Westendorp, R.G.J., Pawelec, G., 2013. Lower proportion of naïve peripheral CD8+ T cells and an unopposed proinflammatory response to human Cytomegalovirus proteins in vitro are associated with longer survival in very elderly people. Age Dordr. (Dordr) 35 (4), 1387–1399. https://doi.org/10.1007/s11357-012-9425-7.

Di Benedetto, S., Gaetjen, M., Muller, L., 2019. The modulatory effect of gender and cytomegalovirus- seropositivity on circulating inflammatory factors and cognitive performance in elderly individuals. Int. J. Mol. Sci. 20 (4), 990. https://doi.org/10.3390/ijms20040990.

Douek, D.C., Koup, R.A., 2000. Evidence for thymic function in the elderly. Vaccine. 16, 1638–1641. https://doi.org/10.1016/s0264-410x(99)00499-5.

Evert, J., Lawler, E., Bogan, H., Perls, T., 2003. Morbidity profiles of centenarians: survivors, delayers, and escapers. J. Gerontol. A Biol. Sci. Med. Sci. 58 (3), 232–237. https://doi.org/10.1093/gerona/58.3.m232.

Fagiolo, U., Cossarizza, A., Scala, E., Fanales-Belasio, E., Ortolani, C., Cozzi, E., Monti, D., Franceschi, C., Paganelli, R., 1993. Increased cytokine production in mononuclear cells of healthy elderly people. Eur. J. Immunol. 23, 2375–2378. https://doi.org/10.1002/eji.1830230950.

Fagnoni, F.F., Vescovini, R., Mazzola, M., Bologna, G., Nigro, E., Lavagetto, G., Franceschi, C., Passeri, M., Sansoni, P., 1996. Expansion of cytotoxic CD8+ CD28− T cells in healthy ageing people, including centenarians. Immunology. 88 (4), 501–507. https://doi.org/10.1046/j.1365-2567.1996.d01-689.x.

Fecteau, J.F., Cote, G., Neron, S., 2006. A new memory CD27-IgG+ B cell population in peripheral blood expressing VH genes with low frequency of somatic mutation. J. Immunol. 177, 3728–3736. https://doi.org/10.4049/jimmunol.177.6.3728.

Ferreira, C., Viana, S.D., Reis, F., 2020. Is gut microbiota dysbiosis a predictor of increased susceptibility to poor outcome of COVID-19 patients? An update. Microorganisms 9 (1), 53. https://doi.org/10.3390/microorganisms9010053.

Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15 (9), 505–522. https://doi.org/10.1038/s41569-018-0064-2.

Flanagan, K.L., Fink, A.L., Plebanski, M., Klein, S.L., 2017. Sex and gender differences in the outcomes of vaccination over the life course. Annu. Rev. Cell Dev. Biol. 33, 577–599. https://doi.org/10.1146/annurev-cellbio-100616-060718.

Franceschi, C., 2017d. Healthy ageing in 2016: obesity in geroscience - is cellular senescence the culprit? Nat. Rev. Endocrinol. 13 (2), 76–78. https://doi.org/10.1038/nrendo.2016.213.

Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A Biol. Sci. Med. Sci. 69 (Suppl 1), S4–S9. https://doi.org/10.1093/gerona/glu057.

Franceschi, C., Grignolio, A., 2010. Immunosenescence within an evolutionary perspective. In: Grignolio, A. (Ed.), Immunology Today: Three Historical Perspectives Under Three Theoretical Horizons. Bononia University Press, Bologna, pp. 79–99.

Franceschi, C., Monti, D., Barbieri, D., Grassilli, E., Troiano, L., Salvioli, S., Negro, P., Capri, M., Guido, M., Azzi, R., Sansoni, P., Paganelli, R., Fagiolo, U., Baggio, G., Donazzan, S., Mariotti, S., D'Addato, S., Gaddi, A., Ortolani, C., Cossarizza, A., 1995a. Immunosenescence in humans: deterioration or remodelling? Int. Rev. Immunol. (Paris) 12, 57–74. https://doi.org/10.3109/08830189509056702.

Franceschi, C., Monti, D., Sansoni, P., Cossarizza, A., 1995b. The immunology of exceptional individuals: the lesson of centenarians. Immunol. Today 16 (1), 12–16. https://doi.org/10.1016/0167-5699(95)80064-6.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000a. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Franceschi, C., Bonafè, M., Valensin, S., 2000b. Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine 18 (16), 1717–1720. https://doi.org/10.1016/s0264-410x(99)00513-7.

Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., Panourgia, M.P., Invidia, L., Celani, L., Scurti, M., Cevenini, E., Cstellani, G.C., Salvioli, S., 2007. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech. Ageing Dev. 128, 92–105. https://doi.org/10.1016/j.mad.2006.11.016.

Franceschi, C., Salvioli, S., Garagnani, P., de Eguileor, M., Monti, D., Capri, M., 2017a. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front. Immunol. 8, 982. https://doi.org/10.3389/fimmu.2017.00982.

Franceschi, C., Garagnani, P., Vitale, G., Capri, M., Salvioli, S., 2017b. Inflammaging and' Garb-aging'. Trends Endocrinol. Metab. 28 (3), 199–212. https://doi.org/10.1016/j.tem.2016.09.005.

Franceschi, C., Passarino, G., Mari, D., Monti, D., 2017c. Centenarians as a 21st century healthy aging model: a legacy of humanity and the need for a world-wide consortium (WWC100+). Mech. Ageing Dev. 165 (Pt B), 55–58. https://doi.org/10.1016/j.mad.2017.06.002.

Franceschi, C., Garagnani, P., Morsiani, C., Conte, M., Santoro, A., Grignolio, A., Monti, D., Capri, M., Salvioli, S., 2018a. The continuum of aging and age-related diseases: common mechanisms but different rates. Front. Med. 5, 61. https://doi.org/10.3389/fmed.2018.00061.

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018b. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat. Rev. Endocrinol. 14 (10), 576–590. https://doi.org/10.1038/s41574-018-0059-4.

Franceschi, C., Ostan, R., Santoro, A., 2018c. Nutrition and inflammation: are centenarians similar to individuals on calorie-restricted diets? Annu. Rev. Nutr. 38, 329–356. https://doi.org/10.1146/annurev-nutr-082117-051637.

Fransen, F., van Beek, A.A., Borghuis, T., El Aidy, S., Hugenholtz, F., van der-Gaast-de Jongh, C., Savelkoul, H.F.J., De Jonge, M.I., Boekschoten, M.V., Smidt, H., Faas, M.M., de Vos, P., 2017. Aged gut microbiota contributes to systemical inflammaging after transfer to germ-free mice. Front. Immunol. 8, 1385. https://doi.org/10.3389/fimmu.2017.01385.

Frasca, D., Diaz, A., Romero, M., Landin, A.M., Blomberg, B.B., 2014. High TNF-alpha levels in resting B cells negatively correlate with their response. Exp. Gerontol. 54, 116–122. https://doi.org/10.1016/j.exger.2014.01.004.

Frasca, D., Diaz, A., Romero, M., Blomberg, B.B., 2016. The generation of memory B cells is maintained, but the antibody response is not, in the elderly after repeated influenza immunizations. Vaccine 34, 2834–2840. https://doi.org/10.1016/j.vaccine.2016.04.023.

Frasca, D., Diaz, A., Romero, M., Garcia, D., Blomberg, B.B., 2020. B cell immunosenescence. Annu. Rev. Cell Dev. Biol. 36, 551–574. https://doi.org/10.1146/annurev-cellbio-011620-034148.

Frasca, D., Reidy, L., Cray, C., Diaz, A., Romero, M., Kahl, K., Blomberg, B.B., 2021. Influence of obesity on serum levels of SARS-CoV-2-specific antibodies in COVID-19 patients. PLoS One 16 (3), e0245424. https://doi.org/10.1371/journal.pone.0245424.

Fulop, T., Larbi, A., Douziech, N., Fortin, C., Guérard, K.P., Lesur, O., Khalil, A., Dupuis, G., 2004. Signal transduction and functional changes in neutrophils with aging. Aging Cell 3 (4), 217–226. https://doi.org/10.1111/j.1474-9728.2004.00110.x.

Fulop, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E.H., Cohen, A.A., Witkowski, J.M., Franceschi, C., 2018. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front. Immunol. 8, 1960. https://doi.org/10.3389/fimmu.2017.01960.

Fulop, T., Larbi, A., Hirokawa, K., Cohen, A.A., Witkowski, J.M., 2020. Immunosenescence is both functional/adaptive and dysfunctional/maladaptive. Semin. Immunopathol. 42 (5), 521–536. https://doi.org/10.1007/s00281-020-00818-9.

Furman, D., Hejblum, B.P., Simon, N., Jojic, V., Dekker, C.L., Thiébaut, R., Tibshirani, R.J., Davis, M.M., 2014. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc. Natl. Acad. Sci. 111, 869–874. https://doi.org/10.1073/pnas.1321060111.

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstreuer, N., Slavich, G.M., 2019. Chronic inflammation in the etiology of disease across the life span. Nat. Med. 25, 1822–1832. https://doi.org/10.1038/s41591-019-0675-0.

Gallenga, C.E., Parmeggiani, F., Costagliola, C., Sebastiani, A., Gallenga, P.E., 2014. Inflammaging: should this term be suitable for age related macular degeneration too? Inflamm. Res. 63, 105–107. https://doi.org/10.1007/s00011-013-0684-2.

Gangemi, S., Basile, G., Monti, D., Merendino, R.A., Di Pasquale, G., Bisignano, U., Nicita-Mauro, V., Franceschi, C., 2005. Age-related modifications in circulating IL-15 levels in humans. Mediators Inflamm. 2005 (4), 245–247. https://doi.org/10.1155/MI.2005.245.

Garagnani, P., Marquis, J., Delledonne, M., Pirazzini, C., Marasco, E., Kwiatkowska, K.M., Iannuzzi, V., Bacalini, M.G., Valsesia, A., Carayol, J., Raymond, F., Ferrarini, A., Xumerle, L., Collino, S., Mari, D., Arosio, B., Casati, M., Ferri, E., Monti, D., Nacmias, B., Sorbi, S., Luiselli, D., Pettener, D., Castellani, G., Sala, C., Passarino, G., De Rango, F., D'Aquila, P., Bertamini, L., Martinelli, N., Girelli, D., Olivieri, O., Giuliani, C., Descombes, P., Franceschi, C., 2021. Whole-genome sequencing analysis of semi-supercentenarians. Elife 10, e57849. https://doi.org/10.7554/eLife.57849.

Gayoso, I., Sanchez-Correa, B., Campos, C., Alonso, C., Pera, A., Casado, J.G., Morgado, S., tarazona, R., Solana, R., 2011. Immunosenescence of human natural killer cells. J. Inn. Immun. 3, 337–343. https://doi.org/10.1159/000328005.

Geerlings, S.Y., Kostopoulos, I., de Vos, W.M., Belzer, C., 2018. Akkermansia muciniphila in the human gastrointestinal tract: when, where, and how? Microorganisms 6 (3), 75. https://doi.org/10.3390/microorganisms6030075.

Gemmati, D., Varani, K., Bramanti, B., Piva, R., Bonaccorsi, G., Trentini, A., Manfrinato, M.C., Tisato, V., Carè, A., Bellini, T., 2019. Bridging the gap" everything that could have been avoided if we had applied gender medicine, pharmacogenetics and personalized medicine in the gender-omics and sex-omics era. Int. J. Mol. Sci. 21 (1), 296. https://doi.org/10.3390/ijms21010296.

Gemmati, D., Bramanti, B., Serino, M.L., Secchiero, P., Zauli, G., Tisato, V., 2020. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? Int. J. Mol. Sci. 21 (10), 3474. https://doi.org/10.3390/ijms21103474.

Genedani, S., Filaferro, M., Carone, C., Ostan, R., Bucci, L., Cevenini, E., Franceschi, C., Monti, D., 2008. Influence of f-MLP, ACTH(1-24) and CRH on in vitro chemotaxis of monocytes from centenarians. Neuroimmunomodulation 15 (4-6), 285–289. https://doi.org/10.1159/000156472.

Gerli, R., Monti, D., Bistoni, O., Mazzone, A.M., Peri, G., Cossarizza, A., Di Gioacchino, M., Cesarotti, M.E., Doni, A., Mantovani, A., Franceschi, C., Paganelli, R., 2000. Chemokines, sTNF-Rs and sCD30 serum levels in healthy aged people and centenarians. Mech. Ageing Dev. 121 (1-3), 37–46. https://doi.org/10.1016/s0047-6374(00)00195-0.

Ghosh, T.S., Rampelli, S., Jeffery, I.B., Santoro, A., Neto, M., Capri, M., Giampieri, E., Jennings, A., Candela, M., Turroni, S., Zoetendal, E.G., Hermes, G.D.A., Elodie, C., Meunier, N., Brugere, C.M., Pujos-Guillot, E., Berendsen, A.M., De Groot, L.C.P.G.M., Feskins, E.J.M., Kaluza, J., Pietruszka, B., Bielak, M.J., Comte, B., Maijo-Ferre, M., Nicoletti, C., De Vos, W.M., Fairweather-Tait, S., Cassidy, A., Brigidi, P., Franceschi, C., O'Toole, P.W., 2020. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut 69 (7), 1218–1228. https://doi.org/10.1136/gutjnl-2019-319654.

Ginaldi, L., De Martinis, M., Monti, D., Franceschi, C., 2005. Chronic antigenic load and apoptosis in immunosenescence. Trends Immunol. 26 (2), 79–84. https://doi.org/10.1016/j.it.2004.11.005.

Goetzl, E.J., Huang, M.C., Kon, J., Patel, K., Schwartz, J.B., Fast, K., Ferrucci, L., Madara, K., Taub, D.D., Longo, D.L., 2010. Gender specificity of altered human immune cytokine profiles in aging. FASEB J. 24 (9), 3580–3589. https://doi.org/10.1096/fj.10-160911.

Goronzy, J.J., Weyand, C.M., 2012. Immune aging and autoimmunity. Cell. Mol. Life Sci. 69, 1615–1623. https://doi.org/10.1007/s00018-012-0970-0.

Goronzy, J.J., Fang, F., Cavanagh, M.M., Qi, Q., Weyand, C.M., 2015. Naive T cell maintenance and function in human aging. J. Immunol. 194, 4073–4080. https://doi.org/10.4049/jimmunol.1500046.

Hadrup, S.R., Strindhall, J., Kollgaard, T., Seremet, T., Johansson, B., Pawelec, G., Thor Straten, P., Wikby, A., 2006. Longitudinal studies of clonally expanded CD8 T cells reveal a repertoire shrinkage predicting mortality and an increased number of dysfunctional cytomegalovirus-specific T cells in the very elderly. J. Immunol. 176, 2645–2653. https://doi.org/10.4049/jimmunol.176.4.2645.

Hamann, L., Szwed, M., Mossakowska, M., Chudek, J., Puzianowska-Kuznicka, M., 2020. First evidence for STING SNP R293Q being protective regarding obesity-associated cardiovascular disease in age-advanced subjects - a cohort study. Immun. Ageing 17, 7. https://doi.org/10.1186/s12979-020-00176-y.

Hamczyk, M.R., Nevado, R.M., Barettino, A., Fuster, V., Andres, V., 2020. Biological versus chronological aging: JACC focus seminar. J. Am. Coll. Cardiol. 75, 919–930. https://doi.org/10.1016/j.jacc.2019.11.062.

Harper, S., 2021. The impact of the Covid-19 pandemic on global population ageing. J. Popul. Ageing 22 (May), 1–6. https://doi.org/10.1007/s12062-021-09330-w. Epub ahead of print. PMID: 34055101; PMCID: PMC8140566.

Hazeldine, J., Lord, J.M., 2013. The impact of ageing on natural killer cell function and potential consequences for health in older adults. Ageing Res. Rev. 12 (4), 1069–1078. https://doi.org/10.1016/j.arr.2013.04.003.

Hearps, A.C., Martin, G.E., Angelovich, T.A., Cheng, W.J., Maisa, A., Landay, A.L., Jaworowski, A., Crowe, S.M., 2012. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. Aging Cell 11, 867–875. https://doi.org/10.1111/j.1474-9726.2012.00851.x.

Horvath, S., Pirazzini, C., Bacalini, M.G., Gentilini, D., Di Blasio, A.M., Delledonne, M., Mari, D., Arosio, B., Monti, D., Passarino, G., De Rango, F., D'Aquila, P., Giuliani, C., Marasco, E., Collino, S., Descombes, P., Garagnani, P., Franceschi, C., 2015. Decreased epigenetic age of PBMCs from Italian semi- supercentenarians and their offspring. Aging (Albany NY) 7, 1159–1170. https://doi.org/10.18632/aging.100861.

Huang, W.C., Chen, Y.H., Chuang, H.L., Chiu, C.C., Huang, C.C., 2019. Investigation of the effects of microbiota on exercise physiological adaption, performance, and energy utilization using a gnotobiotic animal model. Front. Microbiol. 10, 1906. https://doi.org/10.3389/fmicb.2019.01906.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395, 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

Jeljeli, M., Riccio, L.G.C., Doridot, L., Chêne, C., Nicco, C., Chouzenoux, S., Deletang, Q., Allanore, Y., Kavian, N., Batteux, F., 2019. Trained immunity modulates inflammation-induced fibrosis. Nat. Commun. 10 (1), 5670. https://doi.org/10.1038/s41467-019-13636-x.

Jennings, A., Cashman, K.D., Gillings, R., Cassidy, A., Tang, J., Fraser, W., Dowling, K.G., Hull, G.L.J., Berendsen, A.A.M., de Groot, L.C.P.G.M., Pietruszka, B., Wierzbicka, E., Ostan, R., Bazzocchi, A., Battista, G., Caumon, E., Meunier, N., Malpuech-Brugère, C., Franceschi, C., Santoro, A., Fairweather-Tait, S.J., 2018. A Mediterranean-like dietary pattern with vitamin D3 (10 µg/d) supplements reduced the rate of bone loss in older Europeans with osteoporosis at baseline: results of a 1-y randomized controlled trial. Am. J. Clin. Nutr. 108 (3), 633–640. https://doi.org/10.1093/ajcn/nqy122.

Jennings, A., Berendsen, A.M., de Groot, L.C.P.G.M., Feskens, E.J.M., Brzozowska, A., Sicinska, E., Pietruszka, B., Meunier, N., Caumon, E., Malpuech-Brugère, C., Santoro, A., Ostan, R., Franceschi, C., Gillings, R., O' Neill, C.M., Fairweather-Tait, S. J., Minihane, A.M., Cassidy, A., 2019. Mediterranean-style diet improves systolic blood pressure and arterial stiffness in older adults. Hypertension 73 (3), 578–586. https://doi.org/10.1161/HYPERTENSIONAHA.118.12259.

Jing, Y., Shaheen, E., Drake, R.R., Chen, N., Gravenstein, S., Deng, Y., 2009. 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, 777–784. https://doi.org/10.1016/j.humimm.2009.07.005.

Jurberg, A.D., Cotta-de-Almeida, V., Temerozo, J.R., Savino, W., Bou-Habib, D.C., Riederer, I., 2018. Neuroendocrine control of macrophage development and function. Front. Immunol. 9, 1440. https://doi.org/10.3389/fimmu.2018.01440.

Kashtanova, D.A., Klimenko, N.S., Strazhesko, I.D., Starikova, E.V., Glushchenko, O.E., Gudkov, D.A., Tkacheva, O.N., 2020. A cross-sectional study of the gut microbiota composition in Moscow long-livers. Microorganisms 8 (8), 1162. https://doi.org/10.3390/microorganisms8081162.

Kau, A.L., Ahern, P.P., Griffin, N.W., Goodman, A.L., Gordon, J.I., 2011. Human nutrition, the gut microbiome and the immune system. Nature 474, 327–336. https://doi.org/10.1038/nature10213.

Keestra, S.M., Male, V., Salali, G.D., 2021. Out of balance: the role of evolutionary mismatches in the sex disparity in autoimmune disease. Med. Hypotheses 151, 110558. https://doi.org/10.1016/j.mehy.2021.110558.

Kennedy, B.K., Berger, S.L., Brunet, A., Campisi, J., Cuervo, A.M., Epel, E.S., Franceschi, C., Lithgow, G.J., Morimoto, R.I., Pessin, J.E., Rando, T.A., Richardson, A., Schadt, E.E., Wyss-Coray, T., Sierra, F., 2014. Geroscience: linking aging to chronic disease. Cell 159, 709–713. https://doi.org/10.1016/j.cell.2014.10.039.

Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16 (10), 626–638. https://doi.org/10.1038/nri.2016.90.

Kong, F., Hua, Y., Zeng, B., Ning, R., Li, Y., Zhao, J., 2016. Gut microbiota signatures of longevity. Curr. Biol. 26 (18), R832–R833. https://doi.org/10.1016/j.cub.2016.08.015.

Lago, R., Gómez, R., Lago, F., Gómez-Reino, J., Gualillo, O., 2008. Leptin beyond body weight regulation–current concepts concerning its role in immune function and inflammation. Cell. Immunol. 252, 139–145. https://doi.org/10.1016/j.cellimm.2007.09.004.

Lakshminarayanan, B., Stanton, C., O'Toole, P.W., Ross, R.P., 2014. Compositional dynamics of the human intestinal microbiota with aging: implications for health. J. Nutr. Health Aging 18, 773–786. https://doi.org/10.1007/s12603-014-0549-6.

Larbi, A., Fulop, T., 2014. From "truly naïve" to "exhausted senescent" T cells: when markers predict functionality. Cytometry A. 85 (1), 25–35. https://doi.org/10.1002/cyto.a.22351.

Le Garff-Tavernier, M., Beziat, V., Decocq, J., Siguret, V., Gandjbakhch, F., Pautas, E., Debré, P., Merle-Beral, H., Vieillard, V., 2010. Human NK cells display major phenotypic and functional changes over the lifespan. Aging Cell 9, 527–535. https://doi.org/10.1111/j.1474-9726.2010.00584.x.

Lee, S.H., Yun, Y., Kim, S.J., Lee, E.J., Chang, Y., Ryu, S., Shin, H., Kim, H.L., Kim, H.N., Lee, J.H., 2018. Association between cigarette smoking status and composition of gut microbiota: population-based cross-sectional study. J. Clin. Med. 7, 282. https://doi.org/10.3390/jcm7090282.

Lehallier, B., Gate, D., Schaum, N., Nanasi, T., Lee, S.E., Yousef, H., Moran Losada, P., Berdnik, D., Keller, A., Verghese, J., Sathyan, S., Franceschi, C., Milman, S., Barzilai, N., Wyss-Coray, T., 2019. Undulating changes in human plasma proteome profiles across the lifespan. Nat. Med. 25, 1843–1850. https://doi.org/10.1038/s41591-019-0673-2.

Lio, D., Scola, L., Crivello, A., Bonafè, M., Franceschi, C., Olivieri, F., Colonna-Romano, G., Candore, G., Caruso, C., 2002. Allele frequencies of +874T→A single nucleotide polymorphism at the first intron of interferon-γ gene in a group of Italian centenarians. Exp. Gerontol. 37, 315–319. https://doi.org/10.1016/s0531-5565(01)00198-x.

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.

Maggio, M., Guralnik, J.M., Longo, D.L., Ferrucci, L., 2006. Interleukin-6 in aging and chronic disease: a magnificent pathway. J. Gerontol. A Biol. Sci. Med. Sci. 61, 575–584. https://doi.org/10.1093/gerona/61.6.575.

Marcon, G., Tettamanti, M., Capacci, G., Fontanel, G., Spanò, M., Nobili, A., Forloni, G., Franceschi, C., 2020. COVID-19 mortality in Lombardy: the vulnerability of the oldest old and the resilience of male centenarians. Aging 12 (15), 15186–15195. https://doi.org/10.18632/aging.103872.

Mardinoglu, A., Shoaie, S., Bergentall, M., Ghaffari, P., Zhang, C., Larsson, E., Bäckhed, F., Nielsen, J., 2015. The gut microbiota modulates host amino acid and glutathione metabolism in mice. Mol. Syst. Biol. 11, 834. https://doi.org/10.15252/msb.20156487.

Mariani, E., Meneghetti, A., Neri, S., Ravaglia, G., Forti, P., Cattini, L., Facchini, A., 2002. Chemokine production by natural killer cells from nonagenarians. Eur. J. Immunol. 32, 1524–1529. https://doi.org/10.1002/1521-4141 (200206)32:6<1524::AID-IMMU1524>3.0.CO;2-E.

Marois, G., Muttarak, R., Scherbov, S., 2020. Assessing the potential impact of COVID-19 on life expectancy. PLoSONE 15 (9), e0238678. https://doi.org/10.1371/journal.pone.0238678.

Márquez, E.J., Chung, C.H., marches, R., Rossi, R.J., Nehar-Belaid, D., Eroglu, A., Mellert, D.J., kuchel, G.A., Banchereau, J., Ucar, D., 2020. Sexual-dimorphism in human immune system aging. Nat. Commun. 11, 751. https://doi.org/10.1038/s41467-020-14396-9.

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A.A.M., Bialecka-Debek, A., Jennings, A., Gillings, R., Meunier, N., Caumon, E., Fairweather-Tait, S., Pietruszka, B., De Groot, L.C.P.G.M., Santoro, A., Franceschi, C., 2018. Effect of the NU-AGE diet on cognitive functioning in older adults: a randomized controlled trial. Front. Physiol. 9, 349. https://doi.org/10.3389/fphys.2018.00349.

Martinez-Guryn, K., Hubert, N., Frazier, K., Urlass, S., Musch, M.W., Ojeda, P., Pierre, J. F., Miyoshi, J., Sontag, T., Cham, C., Reardon, C., Leone, V., Chang, E.B., 2018. Small intestine microbiota regulate host digestive and absorptive adaptive responses to dietary lipids. Cell Host Microbe 23, 458–469. https://doi.org/10.1016/j.chom.2018.03.011.

Martucci, M., Ostan, R., Biondi, F., Bellavista, E., Fabbri, C., Bertarelli, C., Salvioli, S., Capri, M., Franceschi, C., Santoro, A., 2017. Mediterranean diet and inflammaging within the hormesis paradigm. Nutr. Rev. 75 (6), 442–455. https://doi.org/10.1093/nutrit/nux013.

McLaughlin, M.E., Kao, R., Liener, I.E., Hoidal, J.R., 1986. A quantitative in vitro assay of polymorphonuclear leukocyte migration through human amnion membrane utilizing 111in-oxine. J. Immunol. Methods 95 (1), 89–98. https://doi.org/10.1016/0022-1759(86)90321-2.

Meazza, C., Vitale, G., Pagani, S., Castaldi, D., Ogliari, G., Mari, D., Laarej, K., Tinelli, C., Bozzola, M., 2011. Common adipokine features of neonates and centenarians. J. Pediatr. Endocrinol. Metab. 24 (11-12), 953–957. https://doi.org/10.1515/jpem.2011.373.

Merz, M.P., Turner, J.D., 2021. Is early life adversity a trigger towards inflammageing? Exp. Gerontol. 150, 111377 https://doi.org/10.1016/j.exger.2021.111377.

Metcalf, T.U., Wilkinson, P.A., Cameron, M.J., Ghneim, K., Chiang, C., Wertheimer, A.M., Hiscott, J.B., Nikolich-Zugich, J., Haddad, E.K., 2017. Human monocyte subsets are transcriptionally and functionally altered in aging in response to pattern recognition receptor agonists. J. Immunol. 199 (4), 1405–1417. https://doi.org/10.4049/jimmunol.1700148.

Milan-Mattos, J.C., Anibal, F.F., Perseguini, N.M., Minatel, V., Rehder-Santos, P., Castro, C.A., Vasilceac, F.A., Mattiello, S.M., Faccioli, L.H., Catai, A.M., 2019. Effects of natural aging and gender on pro-inflammatory markers. Braz. J. Med. Biol. Res. 52, e8392. https://doi.org/10.1590/1414-431X20198392.

Mishto, M., Santoro, A., Bellavista, E., Sessions, R., Textoris-Taube, K., Dal Piaz, F., Carrard, G., Forti, K., Salvioli, S., Friguet, B., Kloetzel, P.M., Rivett, A.J., Franceschi, C., 2006a. A structural model of 20S immunoproteasomes: effect of LMP2 codon 60 polymorphism on expression, activity, intracellular localisation and insight into the regulatory mechanisms. Biol. Chem. 387 (4), 417–429. https://doi.org/10.1515/BC.2006.056.

Mishto, M., Bellavista, E., Santoro, A., Stolzing, A., Ligorio, C., Nacmias, B., Spazzafumo, L., Chiappelli, M., Licastro, F., Sorbi, S., Pession, A., Ohm, T., Grune, T., Franceschi, C., 2006b. Immunoproteasome and LMP2 polymorphism in aged and Alzheimer's disease brains. Neurobiol. Aging 27 (1), 54–66. https://doi.org/10.1016/j.neurobiolaging.2004.12.004.

Mittrücker, H.W., Visekruna, A., Huber, M., 2014. Heterogeneity in the differentiation and function of CD8$^+$ T cells. Arch. Immunol. Ther. Exp. 62 (6), 449–458. https://doi.org/10.1007/s00005-014-0293-y.

Modi, C., Böhm, V., Ferraro, S., Stein, G., Seljak, U., 2021. Estimating COVID-19 mortality in Italy early in the COVID-19 pandemic. Nat. Commun. 12 (1 May), 2729. https://doi.org/10.1038/s41467-021-22944-0, 12PMID: 33980836; PMCID: PMC8115692.

Monti, D., Salvioli, S., Capri, M., Malorni, W., Straface, E., Cossarizza, A., Botti, B., Piacentini, M., Baggio, G., Barbi, C., Valensin, S., Bonafè, M., Franceschi, C., 2000. Decreased susceptibility to oxidative stress-induced apoptosis of peripheral blood mononuclear cells from healthy elderly and centenarians. Mech. Ageing Dev. 121 (1-3), 239–250. https://doi.org/10.1016/s0047-6374(00)00220-7.

Monti, D., Ostan, R., Borelli, V., Castellani, G., Franceschi, C., 2017. Inflammaging and human longevity in the omics era. Mech. Ageing Dev. 165 (Pt B), 129–138. https://doi.org/10.1016/j.mad.2016.12.008.

Montoliu, I., Scherer, M., Beguelin, F., DaSilva, L., Mari, D., Salvioli, S., Martin, F.P., Capri, M., Bucci, L., Ostan, R., Garagnani, P., Monti, D., Biagi, E., Brigidi, P., Kussmann, M., Rezzi, S., Franceschi, C., Collino, S., 2014. Serum profiling of healthy aging identifies phospho- and sphingolipid species as markers of human longevity. Aging (Albany NY). 6 (1), 9–25. https://doi.org/10.18632/aging.100630.

Morrisette-Thomas, V., Cohen, A.A., Fülöp, T., Riesco, É., Legault, V., Li, Q., Milot, E., Dusseault-Bélanger, F., Ferrucci, L., 2014. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mech. Ageing Dev. 139, 49–57. https://doi.org/10.1016/j.mad.2014.06.005.

Nasi, M., Troiano, L., Lugli, E., Pinti, M., Ferraresi, R., Monterastelli, E., Mussi, C., Salvioli, G., Franceschi, C., Cossarizza, A., 2006. Thymic output and functionality of the IL-7/IL-7 receptor system in centenarians: implications for the neo-lymphogenesis at the limit of human life. Aging Cell 5, 167–175. https://doi.org/10.1111/j.1474-9726.2006.00204.x.

Netea, M.G., van der Meer, J.W., 2017. Trained immunity: an ancient way of remembering. Cell Host Microbe 21 (3), 297–300. https://doi.org/10.1016/j.chom.2017.02.003.

Newman, A.B., Sanders, J.L., Kizer, J.R., Boudreau, R.M., Odden, M.C., Zeki Al Hazzouri, A., Arnold, A.M., 2016. Trajectories of function and biomarkers with age: the CHS All Stars Study. Int. J. Epidemiol. 45 (4), 1135–1145. https://doi.org/10.1093/ije/dyw092.

Nikolich-Zugich, J., Goodrum, F., Knox, K., Smithey, M.J., 2017. Known unknowns: how might the persistent herpesvirome shape immunity and aging? Curr. Opin. Immunol. 48, 23–30. https://doi.org/10.1016/j.coi.2017.07.011.

O'Toole, P.W., Marchesi, J.R., Hill, C., 2017. Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. Nat. Microbiol. 2, 17057. https://doi.org/10.1038/nmicrobiol.2017.57.

Odamaki, T., Kato, K., Sugahara, H., Hashikura, N., Takahashi, S., Xiao, J.Z., Abe, F., Osawa, R., 2016. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol. 16, 90. https://doi.org/10.1186/s12866-016-0708-5.

Oertelt-Prigione, S., 2012. Immunology and the menstrual cycle. Autoimm. Rev. 11 (6-7), A486–492. https://doi.org/10.1016/j.autrev.2011.11.023.

Oki, K., Toyama, M., Banno, T., Chonan, O., Benno, Y., Watanabe, K., 2016. Comprehensive analysis of the fecal microbiota of healthy Japanese adults reveals a new bacterial lineage associated with a phenotype characterized by a high frequency of bowel movements and a lean body type. BMC Microbiol. 16 (1), 284. https://doi.org/10.1186/s12866-016-0898-x.

Olivieri, F., Spazzafumo, L., Antonicelli, R., Marchegiani, F., Cardelli, M., Sirolla, C., Galeazzi, R., Giovagnetti, S., Mocchegiani, E., Franceschi, C., 2008. Combination of biomarkers to predict mortality in elderly patients with myocardial infarction. Mech. Ageing Dev. 129 (4), 231–237. https://doi.org/10.1016/j.mad.2008.01.002.

Olivieri, F., Rippo, M.R., Monsurrò, V., Salvioli, S., Capri, M., Procopio, A.D., Franceschi, C., 2013. MicroRNAs linking inflamm-aging, cellular senescence and cancer. Ageing Res. Rev. 12 (4), 1056–1068. https://doi.org/10.1016/j.arr.2013.05.001.

Ortmann, W., Kolaczkowska, E., 2018. Age is the work of art? Impact of neutrophil and organism age on neutrophil extracellular trap formation. Cell Tissue Res. 371, 473–488. https://doi.org/10.1007/s00441-017-2751-4.

Ostan, R., Bucci, L., Capri, M., Salvioli, S., Scurti, M., Pini, E., Monti, D., Franceschi, C., 2008. Immunosenescence and immunogenetics of human longevity. Neuroimmunomodulation 15 (4–6), 224–240. https://doi.org/10.1159/000156466.

Ostan, R., Bucci, L., Cevenini, E., Palmas, M.G., Pini, E., Scurti, M., Vescovini, R., Caruso, C., Mari, D., Vitale, G., Franceschi, C., Monti, D., 2013. Metabolic syndrome in the offspring of centenarians: focus on prevalence, components, and adipokines. Age (Dordr) 35 (5), 1995–2007. https://doi.org/10.1007/s11357-012-9483-x.

Ostan, R., Monti, D., Gueresi, P., Bussolotto, M., Franceschi, C., Baggio, G., 2016. Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine. Clin. Sci. 130 (19), 1711–1725. https://doi.org/10.1042/CS20160004.

Palmer, D.B., 2013. The effect of age on thymic function. Front. Immunol. 4, 316. https://doi.org/10.3389/fimmu.2013.00316.

Panda, A., Arjona, A., Sapey, E., Bai, F., Fikrig, E., Montgomery, R.R., Lord, J.M., Shaw, A.C., 2009. Human innate immunosenescence: causes and consequences for immunity in old age. Trends Immunol. 30 (7), 325–333. https://doi.org/10.1016/j.it.2009.05.004.

Panda, A., Qian, F., Mohanty, S., van Duin, D., Newman, F.K., Zhang, L., Chen, S., Towle, V., Belshe, R.B., Fikrig, E., Allore, H.G., Montgomery, R.R., Shaw, A.C., 2010. Age-associated decrease in TLR function in primary human dendritic cells predicts influenza vaccine response. J. Immunol. 184 (5), 2518–2527. https://doi.org/10.4049/jimmunol.0901022.

Pang, W.W., Price, E.A., Sahoo, D., Beerman, I., Maloney, W.J., Rossi, D.J., Schrier, S.L., Weissman, I.L., 2011. Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. Proc. Natl. Acad. Sci. U. S. A. 108, 20012–20017. https://doi.org/10.1073/pnas.1116110108.

Paolisso, G., Barbieri, M., Bonafè, M., Franceschi, C., 2000. Metabolic age modelling: the lesson from centenarians. Eur. J. Clin. Invest. 30 (10), 888–894. https://doi.org/10.1046/j.1365-2362.2000.00729.x.

Paolisso, G., Barbieri, M., Rizzo, M.R., Carella, C., Rotondi, M., Bonafè, M., Franceschi, C., Rose, G., De Benedictis, G., 2001. Low insulin resistance and preserved beta-cell func- tion contribute to human longevity but are not associated with TH-INS genes. Exp. Gerontol. 37 (1), 149–156. https://doi.org/10.1016/s0531-5565(01)00148-6.

Passeri, G., Pini, G., Troiano, L., Vescovini, R., Sansoni, P., Passeri, M., Gueresi, P., Delsignore, R., Pedrazzoni, M., Franceschi, C., 2003. Low vitamin D status, high bone turnover, and bone fractures in centenarians. J. Clin. Endocrinol. Metab. 88 (11), 5109–5115. https://doi.org/10.1210/jc.2003-030515.

Pawelec, G., 2012a. Hallmarks of human "immunosenescence": adaptation or dysregulation? Immun. Ageing 9, 15. https://doi.org/10.1186/1742-4933-9-15.

Pawelec, G., 2017. Immunosenescence and cancer. Biogerontol 18, 717–721. https://doi.org/10.1007/s10522-017-9682-z.

Pawelec, G., 2018. Age and immunity: what is "immunosenescence"? Exp. Gerontol. 105, 4–9. https://doi.org/10.1016/j.exger.2017.10.024.

Pawelec, G., 2020b. The human immunosenescence phenotype: does it exist? Semin. Immunopathol. 42 (5), 537–544. https://doi.org/10.1007/s00281-020-00810-3.

Pawelec, G., Hirokawa, K., Fülöp, T., 2001a. Altered T cell signalling in ageing. Mech. Ageing Dev. 122 (14), 1613–1637. https://doi.org/10.1016/s0047.

Pawelec, G., Müller, L., Wagner, W., 2001b. MHC class II-restricted tumor antigens and CD4+ T cells play a role in hematological malignancies as well as solid tumors. Trends Immunol. 22 (8), 422–423. https://doi.org/10.1016/s1471-4906(01)01987-1.

Pawelec, G., Ouyang, Q., Wagner, W., Biol, D., Wikby, A., 2003. Pathways to a robust immune response in the elderly. Immunol. Allergy Clin. N. Am. 23 (1), 1–13. https://doi.org/10.1016/s0889-8561(02)00075-9.

Pawelec, G., Koch, S., Franceschi, C., Wikby, A., 2006. Human immunosenescence: does it have an infectious component? Ann. N. Y. Acad. Sci. 1067, 56–65. https://doi.org/10.1196/annals.1354.009.

Pawelec, G., McElhaney, J.E., Aiello, A.E., Derhovanessian, E., 2012b. The impact of CMV infection on survival in older humans. Curr. Opin. Immunol. 24, 507–511. https://doi.org/10.1016/j.coi.2012.04.002.

Pawelec, G., Bronikowski, A., Cunnane, S.C., Ferrucci, L., Franceschi, C., Fülöp, T., Gaudreau, P., Gladyshev, V.N., Gonos, E.S., Gorbunova, V., Kennedy, B.K., Larbi, A., Lemaître, J.F., Liu, G.H., Maier, A.B., Morais, J.A., Nóbrega, O.T., Moskalev, A., Rikkert, M.O., Seluanov, A., Senior, A.M., Ukraintseva, S., Vanhaelen, Q., Witkowski, J., Cohen, A.A., 2020a. The conundrum of human immune system "senescence". Mech. Ageing Dev. 192, 111357. https://doi.org/10.1016/j.mad.2020.111357.

Perez-Cabezas, B., Naranjo-Gomez, M., Fernandez, M.A., Grifols, J.R., Pujol-Borrell, R., Borras, F.E., 2007. Reduced numbers of plasmacytoid dendritic cells in aged blood donors. Exp. Gerontol. 42, 1033–1038. https://doi.org/10.1016/j.exger.2007.05.010.

Perretti, M., D'Acquisto, F., 2006. Novel aspects of annexin 1 and glucocorticoid biology: intersection with nitric oxide and the lipoxin receptor. Inflamm. Allergy Drug Targets 5 (2), 107–114. https://doi.org/10.2174/187152806776383170.

Pietschmann, P., Gollob, E., Brosch, S., Hahn, P., Kudlacek, S., Willheim, M., Woloszczuk, W., Peterlik, M., Tragl, K.H., 2003. The effect of age and gender on cytokine production by human peripheral blood mononuclear cells and markers of bone metabolism. Exp. Gerontol. 38, 1119–1127. https://doi.org/10.1016/s0531-5565(03)00189-x.

Pinti, M., Cevenini, E., Nasi, M., De Biasi, S., Salvioli, S., Monti, D., Benatti, S., Gibellini, L., Cotichini, R., Stazi, M.A., Trenti, T., Franceschi, C., Cossarizza, A., 2014. Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging". Eur. J. Immunol. 44 (5), 1552–1562. https://doi.org/10.1002/eji.201343921.

Ponti, F., Santoro, A., Mercatelli, D., Gasperini, C., Conte, M., Martucci, M., Sangiorgi, L., Franceschi, C., Bazzocchi, A., 2020. Aging and imaging assessment of body composition: from fat to facts. Front. Endocrinol. (Lausanne) 10, 861. https://doi.org/10.3389/fendo.2019.00861. PMID: 31993018; PMCID: PMC6970947.

Puchta, A., Naidoo, A., Verschoor, C.P., Loukov, D., Thevaranjan, N., Mandur, T.S., Nguyen, P.S., Jordana, M., Loeb, M., Xing, Z., Kobzik, L., Larché, M.J., Bowdish, D.M., 2016. TNF drives monocyte dysfunction with age and results in impaired anti-pneumococcal immunity. PLoS Pathog. 12 (1), e1005368. https://doi.org/10.1371/journal.ppat.1005368.

Qi, Q., Liu, Y., Cheng, Y., Glanville, J., Zhang, D., Lee, J.Y., Olshen, R.A., Weyand, C.M., Boyd, S.D., Goronzy, J.J., 2014. Diversity and clonal selection in the human T-cell repertoire. Proc. Natl. Acad. Sci. U. S. A. 111, 13139–13144. https://doi.org/10.1073/pnas.1409155111.

Qian, F., Wang, X.M., Zhang, L., Chen, S., Piecychna, M., Allore, H., Bockenstedt, L., Malawista, S., Bucala, R., Shaw, A.C., Fikrig, E., Montgomery, R.R., 2012. Age-associated elevation in TLR5 leads to increased inflammatory responses in the elderly. Aging Cell 11, 104–110. https://doi.org/10.1111/j.1474-9726.2011.00759.x.

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdof, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D.R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., Xie, Y., Tap, J., Lepage, P., Bertalan, M., Batto, J.M., Hansen, T., Le Paslier, D., Linneberg, A., Nielsen, H.B., Pelletier, E., Renault, P., Sicheritz-Ponten, T., Turner, K., Zhu, H., Yu, C., Li, S., Jian, M., Zhou, Y., Li, Y., Zhang, X., Li, S., Qin, N., Yang, H., Wang, J., Brunak, S., Doré, J., Guarner, F., Kristiansen, K., Pedersen, O., Parkhill, J., Weissenback, J., Meta HIT Consortium, Bork, P., Ehrlich, S.D., Wang, J., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65. https://doi.org/10.1038/nature08821.

Rampelli, S., Soverini, M., D'Amico, F., Barone, M., Tavella, T., Monti, D., Capri, M., Astolfi, A., Brigidi, P., Biagi, E., Franceschi, C., Turroni, S., Candela, M., 2020. Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. mSystems. 5 (2) https://doi.org/10.1128/mSystems.00124-20 e00124-20.

Rodriguez-Rosales, Y.A., Langereis, J.D., Gorris, M.A.J., van den Reek, J.M.P.A., Fasse, E., Netea, M.G., de Vries, I.J.M., Gomez-Muñoz, L., van Cranenbroek, B., Körber, A., Sonderman, W., Joosten, I., de Jong, E.M.G.J., Koenen, H.J.P.M., 2021. Immunomodulatory aged neutrophils are augmented in blood and skin of psoriasis patients. J. Allergy Clin. Immunol. 1–11. https://doi.org/10.1016/j.jaci.2021.02.041.

Sadighi Akha, A.A., 2018. Aging and the immune system: an overview. J. Immunol. Methods 463, 21–26. https://doi.org/10.1016/j.jim.2018.08.005.

Sakiani, S., Olsen, N.J., Kovacs, W.J., 2013. Gonadalsteroids and humoral immunity. Nat. Rev. Endocrinol. 9, 56–62. https://doi.org/10.1038/nrendo.2012.206.

Salvioli, S., Capri, M., Bucci, L., Lanni, C., Racchi, M., Uberti, D., Memo, M., Mari, D., Govoni, S., Franceschi, C., 2009. Why do centenarians escape or postpone cancer? The role of IGF-1, inflammation and p53. Cancer Immunol. Immunother. 58, 1909–1917. https://doi.org/10.1007/s00262-008-0639-6.

Salvioli, S., Monti, D., Lanzarini, C., Conte, M., Pirazzini, C., Bacalini, M.G., Garagnani, P., Giuliani, C., Fontanesi, E., Ostan, R., Bucci, L., Sevini, F., Yani, S.L., Barbieri, A., Lomartire, L., Borelli, V., Vianello, D., Bellavista, E., Martucci, M., Cevenini, E., Pini, E., Scurti, M., Biondi, F., Santoro, A., Capri, M., Franceschi, C., 2013. Immune system, cell senescence, aging and longevity—inflamm-aging reappraised. Curr. Pharm. Des. 19 (9), 1675–1679. https://doi.org/10.2174/138161213805219531.

Sansoni, P., Brianti, V., Fagnoni, F., Snelli, G., Marcato, A., Passeri, G., Monti, D., Cossarizza, A., Franceschi, C., 1992. NK cell activity and T-lymphocyte proliferation in healthy centenarians. Ann. N. Y. Acad. Sci. 663, 505–507. https://doi.org/10.1111/j.1749-6632.1992.tb38717.x.

Sansoni, P., Vescovini, R., Fagnoni, F., Biasini, C., Zanni, F., Zanlari, L., Telera, A., Lucchini, G., Passeri, G., Monti, D., Franceschi, C., Passeri, M., 2008. The immune system in extreme longevity. Exp. Gerontol. 43, 61–65. https://doi.org/10.1016/j.exger.2007.06.008.

Sansoni, P., Vescovini, R., Fagnoni, F.F., Akbar, A., Arens, R., Chiu, Y.L., Cičin-Šain, L., Dechanet-Merville, J., Derhovanessian, E., Ferrando-Martinez, S., Franceschi, C., Frasca, D., Fulöp, T., Furman, D., Gkrania-Klotsas, E., Goodrum, F., Grubeck-Loebenstein, B., Hurme, M., Kern, F., Lilleri, D., López-Botet, M., Maier, A.B., Marandu, T., Marchant, A., Matheï, C., Moss, P., Muntasell, A., Remmerswaal, E.B., Riddell, N.E., Rothe, K., Sauce, D., Shin, E.C., Simanek, A.M., Smithey, M.J., Söderberg-Nauclér, C., Solana, R., Thomas, P.G., van Lier, R., Pawelec, G., Nikolich-Zugich, J., 2014. New advances in CMV and immunosenescence. Exp. Gerontol. 55, 54–62. https://doi.org/10.1016/j.exger.2014.03.020.

Santoro, A., Bazzocchi, A., Guidarelli, G., Ostan, R., Giampieri, E., Mercatelli, D., Scurti, M., Berendsen, A., Surala, O., Jennings, A., Meunier, N., Caumon, E., Gillings, R., Kadi, F., Capel, F., Cashman, K.D., Pietruszka, B., Feskens, E.J.M., De Groot, L.C.P.G.M., Battista, G., Salvioli, S., Franceschi, C., 2018a. A cross-sectional analysis of body composition among healthy elderly from the european NU-AGE study: sex and country specific features. Front. Physiol. 9, 1693. https://doi.org/10.3389/fphys.2018.01693.

Santoro, A., Ostan, R., Candela, M., Biagi, E., Brigidi, P., Capri, M., Franceschi, C., 2018b. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell. Mol. Life Sci. 75 (1), 129–148. https://doi.org/10.1007/s00018-017-2674-y.

Santoro, A., Martucci, M., Conte, M., Capri, M., Franceschi, C., Salvioli, S., 2020a. Inflammaging, hormesis and the rationale for anti-aging strategies. Ageing Res. Rev. 64, 101142. https://doi.org/10.1016/j.arr.2020.101142.

Santoro, A., Zhao, J., Wu, L., Carru, C., Biagi, E., Franceschi, C., 2020b. Microbiomes other than the gut: inflammaging and age-related diseases. Semin. Immunopathol. 42 (5), 589–605. https://doi.org/10.1007/s00281-020-00814-z.

Sayed, N., Huang, Y., Nguyen, K., Krejciova-Rajaniemi, Z., Grawe, A.P., Gao, T., Tibshirani, R., Hastie, T., Alpert, A., Cui, L., Kuznetsova, T., Rosenberg-Hasson, Y., Ostan, R., Monti, D., Lehallier, B., Shen-Orr, S.S., Maecker, H.T., Dekker, C.L., Wyss-Coray, T., Franceschi, C., Jojic, V., Haddad, F., Montoya, J.G., Wu, J.C., Davis, M.M., Furman, D., 2021. Deep learning identifies an inflammatory clock which predicts multimorbidity, immunosenescence, frailty and cardiovascular aging in humans. Nature Aging 1, 598–615. https://doi.org/10.1038/s43587-021-00082-y.

Schmitt, V., Rink, L., Uciechowski, P., 2013. The Th17/Treg balance is disturbed during aging. Exp. Gerontol. 48, 1379–1386. https://doi.org/10.1016/j.exger.2013.09.003.

Sergio, G., 2008. Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm- aging, from robustness to frailty. Inflamm. Res. 57, 558–563. https://doi.org/10.1007/s00011-008-7243-2.

Shanley, D.P., Aw, D., Manley, N.R., Palmer, D.B., 2009. An evolutionary perspective on the mechanisms of immunosenescence. Trends Immunol. 30, 374–381. https://doi.org/10.1016/j.it.2009.05.001.

Shaw, A.C., Panda, A., Joshi, S.R., Qian, F., Allore, H.G., Montgomery, R.R., 2011. Dysregulation of human Toll-like receptor function in aging. Ageing Res. Rev. 10 (3), 346–353. https://doi.org/10.1016/j.arr.2010.10.007.

Simell, B., Vuorela, A., Ekström, N., Palmu, A., Reunanen, A., Meri, S., Käyhty, H., Väkeväinen, M., 2011. Aging reduces the functionality of anti-pneumococcal antibodies and the killing of Streptococcus pneumoniae by neutrophil phagocytosis. Vaccine 29 (10), 1929–1934. https://doi.org/10.1016/j.vaccine.2010.12.121.

Sizzano, F., Collino, S., Cominetti, O., Monti, D., Garagnani, P., Ostan, R., Pirazzini, C., Bacalini, M.G., Mari, D., Passarino, G., Franceschi, C., Palini, A., 2018. Evaluation of lymphocyte response to the induced oxidative stress in a cohort of ageing subjects, including semisupercentenarians and their offspring. Mediators Inflamm. 2018, 7109312. https://doi.org/10.1155/2018/7109312.

Smith, R.P., Easson, C., Lyle, S.M., Kapoor, R., Donnelly, C.P., Davidson, E.J., Parikh, E., Lopez, J.V., Tartar, J.L., 2019. Gut microbiome diversity is associated with sleep physiology in humans. PLoS One 14, e0222394. https://doi.org/10.1371/journal.pone.0222394.

Sochocka, M., Diniz, B.S., Leszek, J., 2017. Inflammatory response in the CNS: friend or foe? Mol. Neurobiol. 54 (10), 8071–8089. https://doi.org/10.1007/s12035-016-0297-1.

Solana, R., Tarazona, R., Gayoso, I., Lesur, O., Dupuis, G., Fulop, T., 2012. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin. Immunol. 24 (5), 331–341. https://doi.org/10.1016/j.smim.2012.04.008.

Solana, R., Tarazona, R., Aiello, A.E., Akbar, A.N., Appay, V., Beswick, M., Bosch, J.A., Campos, C., Cantisán, S., Cicin-Sain, L., Derhovanessian, E., Ferrando-Martínez, S., Frasca, D., Fulöp, T., Govind, S., Grubeck-Loebenstein, B., Hill, A., Hurme, M., Kern, F., Larbi, A., López-Botet, M., Maier, A.B., McElhaney, J.E., Moss, P., Naumova, E., Nikolich-Zugich, J., Pera, A., Rector, J.L., Riddel, N., Sanchez-Correa, B., Sansoni, P., Sauce, D., van Lier, R., Wang, G.C., Wills, M.R., Zieliński, M., Pawelwc, G., 2012a. CMV and immunosenescence: from basics to clinics. Immun. Ageing 9 (1), 23. https://doi.org/10.1186/1742-4933-9-23.

Song, P., An, J., Zou, M.H., 2020a. Immune clearance of senescent cells to combat ageing and chronic diseases. Cells 9 (3), 671. https://doi.org/10.3390/cells9030671.

Song, S., Lam, E.W., Tchkonia, T., Kirkland, J.L., Sun, Y., 2020b. Senescent cells: emerging targets for human aging and age-related diseases. Trends Biochem. Sci. 45, 578–592. https://doi.org/10.1016/j.tibs.2020.03.008.

Soto-Martin, E.C., Warnke, I., Farquharson, F.M., Christodoulou, M., Horgan, G., Derrien, M., Faurie, J.M., Flint, H.J., Duncan, S.H., Louis, P., 2020. Vitamin biosynthesis by human gut butyrate-producing bacteria and cross-feeding in synthetic microbial communities. mBio 11, e00886–e00920. https://doi.org/10.1128/mBio.00886-20.

Spazzafumo, L., Olivieri, F., Abbatecola, A.M., Castellani, G., Monti, D., Lisa, R., Galeazzi, R., Sirolla, C., Testa, R., Ostan, R., Scurti, M., Caruso, C., Vasto, S., Vescovini, R., Ogliari, G., Mari, D., Lattanzio, F., Franceschi, C., 2013. Remodelling of biological parameters during human aging: evidence for complex regulation in longevity and in type 2 diabetes. Age (Dordr) 35, 419–429. https://doi.org/10.1007/s11357-011-9348-8.

Spits, H., Bernink, J.H., Lanier, L., 2016. NK cells and type 1 innate lymphoid cells: partners in host defense. Nat. Immunol. 17, 758–764. https://doi.org/10.1038/ni.3482.

Steinmann, G.G., Klaus, B., Muller-Hermelink, H.K., 1985. The involution of the ageing human thymic epithelium is independent of puberty. A morphometric study. Scand. J. Immunol. 22, 563–575. https://doi.org/10.1111/j.1365-3083.1985.tb01916.x.

Storci, G., De Carolis, S., Papi, A., Bacalini, M.G., Gensous, N., Marasco, E., Tesei, A., Fabbri, F., Arienti, C., Zanoni, M., Sarnelli, A., Santi, S., Olivieri, F., Mensà, E., Latini, S., Ferracin, M., Salvioli, S., Garagnani, P., Franceschi, C., Bonafè, M., 2019. Genomic stability, anti-inflammatory phenotype, and up-regulation of the RNAseH2 in cells from centenarians. Cell Death Differ. 26, 1845–1858. https://doi.org/10.1038/s41418-018-0255-8.

Stout, R.D., Suttles, J., 2005. Immunosenescence and macrophage functional plasticity: dysregulation of macrophage function by age- associated microenvironmental changes. Immunol. Rev. 205, 60–71. https://doi.org/10.1038/s41418-018-0255-8.

Straub, R.H., Mocchegiani, E. (Eds.), 2004. The NeuroendoCrine Immune Network in Ageing Neuroimmune Biology, Vol. 4. Elsevier.

Strindhall, J., Nilsson, B.O., Lofgren, S., Ernerudh, J., Pawelec, G., Johansson, B., Wikby, A., 2007. No immune risk profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. Exp. Gerontol. 42 (8), 753–761. https://doi.org/10.1016/j.exger.2007.05.001.

Sun, J., Xu, J., Ling, Y., Wang, F., Gong, T., Yang, C., Ye, S., Ye, K., Wei, D., Song, Z., Chen, D., Liu, J., 2019. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl. Psychiatry 9, 189. https://doi.org/10.1038/s41398-019-0525-3.

Tavella, T., Rampelli, S., Guidarelli, G., Bazzocchi, A., Gasperini, C., Pujos-Guillot, E., Comte, B., Barone, M., Biagi, E., Candela, M., Nicoletti, C., Kadi, F., Battista, G., Salvioli, S., O'Toole, P.W., Franceschi, C., Brigidi, P., Turroni, S., Santoro, A., 2021. Elevated gut microbiome abundance of Christensenellaceae, Porphyromonadaceae and Rikenellaceae is associated with reduced visceral adipose tissue and healthier metabolic profile in Italian elderly. Gut Microbes 13 (1), 1–19. https://doi.org/10.1080/19490976.2021.1880221.

Trim, W.V., Walhin, J.P., Koumanov, F., Bouloumié, A., Lindsay, M.A., Chen, Y.C., Travers, R.L., Turner, J.E., Thompson, D., 2021. Divergent immunometabolic changes in adipose tissue and skeletal muscle with ageing in healthy humans. J. Physiol. (Paris). https://doi.org/10.1113/JP280977.

Tu, W., Rao, S., 2016. Mechanisms underlying T cell immunosenescence: aging and Cytomegalovirus infection. Front. Microbiol. 7, 2111. https://doi.org/10.3389/fmicb.2016.02111.

Tuikhar, N., Keisam, S., Labala, R.K., Imrat Ramakrishnan, P., Arunkumar, M.C., Ahmed, G., Biagi, E., Jeyaram, K., 2019. Comparative analysis of the gut microbiota in centenarians and young adults shows a common signature across genotypically non-related populations. Mech. Ageing Dev. 179, 23–35. https://doi.org/10.1016/j.mad.2019.02.001.

van Duin, D., Mohanty, S., Thomas, V., Ginter, S., Montgomery, R.R., Fikrig, E., Allore, H. G., Medzhitov, R., Shaw, A.C., 2007. Age-associated defect in human TLR-1/2 function. J. Immunol. 178, 970–975. https://doi.org/10.4049/jimmunol.178.2.970.

Vasudev, A., Ying, C.T., Ayyadhury, S., Puan, K.J., Andiappan, A.K., Nyunt, M.S., Shadan, N.B., Mustafa, S., Low, I., Rotzschke, O., Fulop, T., Ng, T.P., Larbi, A., 2014. γ/δ T cell subsets in human aging using the classical α/β T cell model. J. Leukoc. Biol. 96 (4), 647–655. https://doi.org/10.1189/jlb.5A1213-650RR.

Vescovini, R., Telera, A., Fagnoni, F.F., Biasini, C., Medici, M.C., Valcavi, P., di Pede, P., Lucchini, G., Zanlari, L., Passeri, G., Zanni, F., Chezzi, C., Franceschi, C., Sansoni, P., 2004. Different contribution of EBV and CMV infections in very long-term carriers to age- related alterations ofCD8+ T cells. Exp. Gerontol. 39, 1233–1243. https://doi.org/10.1016/j.exger.2004.04.004.

Vescovini, R., Biasini, C., Fagnoni, F.F., Telera, A.R., Zanlari, L., Pedrazzoni, M., Bucci, L., Monti, D., Medici, M.C., Chezzi, C., Franceschi, C., Sansoni, P., 2007. Massive load of functional effector CD4+ and CD8+ T cells against cytomegalovirus in very old subjects. J. Immunol. 179 (6), 4283–4291. https://doi.org/10.4049/jimmunol.179.6.4283.

Vitale, G., Salvioli, S., Franceschi, C., 2013. Oxidative stress and the ageing endocrine system. Nat. Rev. Endocrinol. 9 (4), 228–240. https://doi.org/10.1038/nrendo.2013.29.

Vorobjeva, N.V., Chernyak, B.V., 2020. NETosis: molecular mechanisms, role in physiology and pathology. Biochem. Mosc. 85, 1178–1190. https://doi.org/10.1134/S0006297920100065.

Weltevrede, M., Eilers, R., de Melker, H.E., van Baarle, D., 2016. Cytomegalovirus persistence and T-cell immunosenescence in people aged fifty and older: a systematic review. Exp. Gerontol. 77, 87–95. https://doi.org/10.1016/j.exger.2016.02.005.

Wenisch, C., Patruta, S., Daxböck, F., Krause, R., Hörl, W., 2000. Effect of age on human neutrophil function. J. Leukoc. Biol. 67 (1), 40–45. https://doi.org/10.1002/jlb.67.1.40.

Wikby, A., Nilsson, B.O., Forsey, R., Thompson, J., Strindhall, J., Lofgren, S., Ernerudh, J., Pawelec, G., Ferguson, F., Johansson, B., 2006. The immune risk phenotype is associated with IL-6 in the terminal decline stage: findings from the Swedish NONA immune longitudinal study of very late life func- tioning. Mech. Ageing Dev. 127 (8), 695–704. https://doi.org/10.1016/j.mad.2006.04.003.

World Health Organization, 2015. World Report on Ageing and Health. World Health Organization. https://www.who.int/health-topics/ageing#tab=tab_1.

Wu, L., Zeng, T., Zinellu, A., Rubino, S., Kelvin, D.J., Carru, C., 2019. A cross-sectional study of compositional and functional profiles of gut microbiota in sardinian centenarians. mSystems. 4 (4) https://doi.org/10.1128/mSystems.00325-19 e00325-19.

Yang, Y., Kozloski, M., 2011. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. J. Gerontol. A Biol. Sci. Med. Sci. 66 (5), 493–500. https://doi.org/10.1093/gerona/glr003.

Youm, Y.H., Grant, R.W., McCabe, L.R., Albarado, D.C., Nguyen, K.Y., Ravussin, A., Pistell, P., Newman, S., Carter, R., Laque, A., Munzberg, H., Rosen, C.J., Ingram, D. K., Salbaum, J.M., Dixit, V.D., 2013. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. Cell Metab. 18, 519–532. https://doi.org/10.1016/j.cmet.2013.09.010.

Youness, A., Miquel, C.H., Guéry, J.C., 2021. Escape from X chromosome inactivation and the female predominance in autoimmune diseases. Int. J. Mol. Sci. 22 (3), 1114. https://doi.org/10.3390/ijms22031114.

Yu, B., Qi, Y., Li, R., Shi, Q., Satpathy, A.T., Chang, H.Y., 2021. B cell-specific XIST complex enforces X-inactivation and restrains atypical B cells. Cell 184 (7), 1790–1803. https://doi.org/10.1016/j.cell.2021.02.015 e17.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.

Zhu, J., Yamane, H., Paul, W.E., 2010. Differentiation of effector CD4 T cell populations (*). Annu. Rev. Immunol. 28, 445–489. https://doi.org/10.1146/annurev-immunol-030409-101212.