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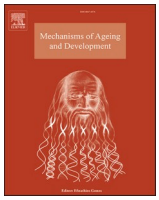

Sex/gender-related differences in inflammaging

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ABSTRACT

Geroscience puts mechanisms of aging as a driver of the most common age-related diseases and dysfunctions. Under this perspective, addressing the basic mechanisms of aging will produce a better understanding than addressing each disease pathophysiology individually. Worldwide, despite greater functional impairment, life expectancy is higher in women than in men. Gender differences in the prevalence of multimorbidity lead mandatory to the understanding of the mechanisms underlying gender-related differences in multimorbidity patterns and disability-free life expectancy. Extensive literature suggested that inflammaging is at the crossroad of aging and age-related diseases. In this review, we highlight the main evidence on sex/gender differences in the mechanisms that foster inflammaging, i.e. the age-dependent triggering of innate immunity, modifications of adaptive immunity, and accrual of senescent cells, underpinning some biomarkers of inflammaging that show sex-related differences. In the framework of the "gender medicine perspective", we will also discuss how sex/gender differences in inflammaging can affect sex differences in COVID-19 severe outcomes.

1. Introduction

With population ageing emerging as a world trend in the coming decades, the promotion of healthy longevity is the main aim for individuals and government policymakers. Since the life expectancy at birth is not able to fully describe health expectancy, other parameters, such as healthy life years, referred also as disability-free life expectancy, have been proposed (Kim et al., 2022). Health outcomes also depend upon social and economic factors that, in turn, are influenced by cultural and political conditions (Osypuk et al., 2014). Overall, to understand health and illness, both sex and gender must be considered (Vlassoff, 2007). Indeed, sex and/or gender differences in healthy life expectancy are well documented in all developed countries (Mauvais-Jarvis et al., 2020). Sex differences refer to biological variables, whereas gender differences refer to behavioral/life-habits issues. Sex and gender disparities have been extensively documented in epidemiology, pathophysiology, clinical manifestations, diagnosis, disease progression, and response to treatments, (Mauvais-Jarvis et al., 2020; Shannon et al., 2019). Life expectancy in women is higher than in men, even if the gender gap in life expectancy has narrowed during the last decades of the twentieth century in most countries (Barford et al., 2006; Van Oyen et al., 2010). Despite this mortality advantage of women, it is counter-balanced by a disability disadvantage, a phenomenon called the female–male health–survival paradox (Case and Paxson, 2005; Oksuzyan et al., 2008). This paradox was confirmed in hospitalized older adults (Gordon et al., 2018). Also, among the oldest old, the fastest-growing segment of the older population, sex differences in total life expectancy and disability-free life expectancy exist, suggesting that the male-female health-survival paradox persists at very old age (Hoogendijk et al., 2019). Increasing evidence confirmed the existence of gender differences in the prevalence of multimorbidity and coexistence of several chronic diseases, an important challenge facing healthcare systems in all developed countries (Abad-Diez et al., 2014; Almagro et al., 2020; Yao et al., 2020).

Overall, women had higher total life expectancies than men, but they have an increased risk to live an unhealthy longevity characterized by functional impairment. The most interesting hypothesis to explain this apparent paradox is based on hormonal and genetic sex-related

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differences. Age at natural menopause (ANM) is considered a marker of biological ageing and is increasingly recognized as a sentinel for chronic disease risk in later life and age-related morbidity and mortality outcomes (Finch, 2014; Schoenaker et al., 2014). A significant association between ANM and biological aging, measured using the epigenetic clock, was highlighted (Levine et al., 2016). The association between age at ANM and physical function in older women was confirmed in several international studies (Velez et al., 2019a,b). These data also revealed that socioeconomic conditions could play a role in such association. Women in socially disadvantaged areas may reach menopause with different physiological reserves than those from more advantaged settings, leading to worse physical function in postmenopausal years. Differences in gender in terms of social/cultural identification outcomes are of relevance, but we will focus this review on biological sex-dependent differences.

Overall, a complex crosstalk between sex-related genetic makeup and environmental factors, including hormonal behavior, affects the health span of men and women differently. In this framework, it is mandatory to understand the mechanisms underlying gender differences in multimorbidity patterns and disability-free life expectancy. The central tenet of the "Geroscience hypothesis" is that since aging is at the crossroad for the development of the most common chronic diseases and conditions, addressing aging will produce a better outcome than addressing each disease individually (Austad, 2016; Ferrucci et al., 2020; Sierra and Kohanski, 2017). Extensive literature suggested that inflammaging is the real risk factor for both the aging process rate and age-related disease development and progression (Franceschi et al., 2018; Fulop et al., 2018). Inflammaging is the chronic, systemic, low-grade, and therefore subclinical for a long time, proinflammatory status that increases during aging (Franceschi et al., 2000a). Inflammaging is characterized by unbalanced systemic cytokine secretion, with increased levels of the most relevant pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α), and reduced levels of anti-inflammatory cytokines, such as IL-10, TGF-beta. This unbalanced inflammatory milieu contributes to a greater predisposition to illness and worsening of chronic diseases thus increasing morbidity and mortality risk in the elderly (Franceschi et al., 2000a; Xia et al., 2016). Two key cellular mechanisms are likely to foster inflammaging: innate immunity attrition/immunosenescence (Franceschi et al., 2000a; Prattichizzo et al., 2018) and cell senescence (Childs et al., 2015). Long-standing evidence highlighted sex-related differences in the activation of the innate immune system (Bonafè et al., 2001; Goetzl et al., 2010; Klein and Flanagan, 2016; Mauvais-Jarvis et al., 2020). New research on both human and animal models suggests sex differences also in the phenomena of immunosenescence and cellular senescence, but data are scarce and not adequately discussed and integrated into a holistic view.

In this review, we highlighted and critically discussed the main evidence on sex-dependent differences in inflammaging, with the aim to better understand the mechanisms impinging upon the sex/gender differences in immune and cellular senescence and the complex effects of such mechanisms on total life expectancy and disability-free life expectancy. In addition, in the framework of the "gender medicine perspective", sex differences in severe outcomes of the coronavirus disease-19 (COVID-19) will be presented (Bonafe and Olivieri, 2022).

2. Sex-dependent differences in immune functions

In humans, sexual dimorphism refers to the differences in male and female physiology, morphology, or behavior, and often extends far beyond this. Sexual dimorphism in the immune response has been extensively investigated, suggesting that females exhibit lower infection rates than males for a variety of bacterial, viral, and parasitic pathogens (Klein and Flanagan, 2016; Shepherd et al., 2020). This complex phenomenon probably arises not only from genetic differences between males and females but also from differences in sex hormones that alter the milieu in which immune cells live and work (Franceschi et al., 2000b; Ter Horst et al., 2016). Females on one side exhibit lower infection rates than males, on the other side, they have up to a fourfold increase in risk for autoimmune disease compared to men. Many explanations have been proposed for these unbalanced immune responses, including sex hormones, the X chromosome, microchimerism, environmental factors, and the microbiome (Kronzer et al., 2021). Sex hormones exert their immunomodulatory activity by binding hormone response elements in genes involved in innate immunity, such as MyD88, IRF7, and a number of toll-like receptors (TLRs), and by interacting with other DNA-binding transcription factors, including NF-kB and AP-1 (Jaillon et al., 2019). Notably, the latter mechanism is responsible for the estrogen-mediated repression of IL-6 synthesis (Klein and Flanagan, 2016).

Overall, these trends indicate that females have a heightened immune reactogenicity to both self and non-self-molecular patterns.

2.1. Innate immunity

The molecular mechanisms driving the sexually dimorphic immune response are currently under investigation. Regarding innate immunity, several differences in cytokine production, complement activation, and cell number and activity were reported.

The phagocytic activity of neutrophils, macrophages, and other types of antigen-presenting cells (APC) is higher in females compared to males (Bouman et al., 2005). In animal models affected by group B streptococcal (GBS)-induced pneumonia, it was recently demonstrated that with bacterial burdens being equal, males exhibited a more pronounced release of innate inflammatory cytokines and chemokines and a higher proportion of infiltrating monocytes/macrophages (Deny et al., 2022). The analysis of the distribution of macrophage subtypes M1 (pro-inflammatory) versus M2 (anti-inflammatory) yielded a higher M1/M2 ratio in infected males compared with females (Deny et al., 2022).

Neutrophils from reproductive-age males are more immature and less activated than their female counterparts. RNA sequencing on circulating neutrophils from healthy adults showed that female neutrophils displayed significant up-regulation of type I IFN (IFN)-stimulated genes (ISGs) and these differences seem to be neutrophil specific, driven by a distinct neutrophil subset and related to maturation status (Gupta et al., 2020).

Immune cells from females showed a stronger induction of genes associated with TLRs pathways and antiviral type I interferon (IFN) responses than cells from males (Klein et al., 2010; Pujantell and Altfeld, 2022). Accordingly, *ex vivo* studies demonstrated that women exhibit enhanced cellular responsiveness to the LPS-mediated stimulation of the TLR4 pathway, which may be related both to differences in TLR4 density and intracellular signaling (O'Connor et al., 2007). Conversely, in vitro treatment of macrophages with the male hormone testosterone reduced TLR4 expression and sensitivity to ligands (Rettew et al., 2008). Receptors for sex hormones, including estrogen receptors (ER) and androgen receptors (AR), are expressed by most immune cells, and sex hormones can therefore affect the function of many immune cells, including plasmacytoid DCs and their ability to produce Type I IFNs. It was reported that plasmacytoid DCs derived from females produced significantly more IFN-a in response to TLR7 ligands than plasmacytoid DCs derived from males, thus triggering a stronger immune activation (Griesbeck et al., 2015).

Regarding NK as innate immune cells, males have a higher count of total NK cells, a higher frequency of CD56dim NK cells and higher expression of CD57, which is found on NK and T cell surfaces (Phan et al., 2017). In women during reproductive age, estrogen inhibits NK cell cytotoxicity during the ovulatory phase (Giefing-Kroll et al., 2015). NK cells in postmenopausal women retain their sensitivity to sex hormones since estradiol enhances the proliferation of blood NK cells (Sho et al., 2017). With respect to cytotoxicity, the effects of age on the cytotoxic capacity of blood NK cells are unclear (Almeida-Oliveira et al.,

2011; Hazeldine et al., 2012). Despite NK cells from younger women upregulating IFNγ, MIP-1α, and IL-8 to a greater extent than cells from older women (Mariani et al., 2002a,b), women over the age of 70 have more vigorous NK cell cytotoxic activity relative to men (Al-Attar et al., 2016).

Sex-related differences in the complement system have also been demonstrated, including increased activity of the alternative pathway in males (Gaya da Costa et al., 2018; Kamitaki et al., 2020), contrasting to a greater dependence on the lectin pathway in females (Wu et al., 2021). In animal models, females have been shown to display reduced susceptibility to complement-mediated damage, suggesting that this phenomenon could contribute to increase male susceptibility to target organ damage (Kotimaa et al., 2016). The modulation of the innate and adaptive immune system in the female reproductive tract (FRT) changes across the menstrual cycle and pregnancy, but little is known about the alterations in mucosal immune protection and the potential systemic effects of these alterations in women following menopause, The immune system in the FRT has two key functions: the defense against pathogens and reproduction. However, after menopause, the reproductive function ends, and the two overlapping processes probably contribute to alterations in immune protection in aging women: menopause and immunosenescence (Rodriguez-Garcia et al., 2021). Some studies into innate and adaptive immune functions in the FRT following menopause indicated that immune protection by epithelial cells, stromal fibroblasts, T cells, and DC are compromised (Agrawal et al., 2017).

Emerging evidence is showing that perimenopause is pro-inflammatory and disrupts estrogen-regulated neurological systems (McCarthy and Raval, 2020). An interesting study on an animal model suggested for the first time an involvement of the inflammasome originating in the female reproductive system as a contributor to inflammation in the brain that makes the peri-menopausal women's brain more susceptible to neurodegenerative diseases such as stroke (Raval et al., 2019).

2.2. Adaptive immunity

A major contribution to the higher reactivity of females to immune challenges is provided also by adaptive immunity. In this regard, sex-related differences in both the number and relative proportions of specific B and T cell subsets, as well as in their antibody or cytotoxic responses have been described (Agrawal et al., 2021). Such differences begin to develop at the earliest stages of development, where a greater proportion of CD5 + naïve B cells and a slightly lower expression of B cell activating factor (BAFF) was described for males and become progressively more consistent in the reproductive ages (Fink and Klein, 2018). Most notably, aging represents a major factor accentuating sexual dimorphisms in acquired immunity (Marquez et al., 2020).

A higher CD4+T cell number and CD4/CD8 cell ratio have been reported for females of several ethnicities (Abdullah et al., 2012). In vitro studies confirmed that both CD4+ and CD8+ cells from women are more prone to activation and display a higher expression of genes related to antiviral and inflammatory responses (Hewagama et al., 2009). At the earliest ages, T cells are more skewed towards Th2 and Treg responses (Fink and Klein, 2018). In males, these cells tend to retain these properties for a longer time span, whereas in females, a switch towards the production of Th1 polarizing cytokines is sooner observed, which accounts for a greater degree of protection against viruses and other intracellular pathogens (Kollmann et al., 2017). Notably, this higher propensity of females to develop Th1 responses is partly attenuated by estrogens which, at high concentrations, sustain the activation of Th2 responses (Klein and Flanagan, 2016). On the contrary, low concentrations of estradiol are associated with an increase in the transcription of the interferon gamma gene (Lengi et al., 2006). In general, exposure to estradiol induces expansion of the Treg compartment and decline of Th17 cell number and function (Kim et al., 2019).

Data from transcriptomic studies, however, confirm that most of the sex-related differences in acquired immunity are dominated by the B cell gene expression landscape (Marquez et al., 2020). Whereas estrogens act as potent inhibitors of B cell lymphopoiesis by negatively affecting the viability and proliferation of precursors (Hill et al., 2011), estradiol increases immunoglobulin synthesis in mature B cells (Kanda and Tamaki, 1999). Nonetheless, prolonged exposure to estradiol is associated with production of antibodies against various self-antigens, such as DNA and phospholipids, and survival of self-reactive B cells (Khan and Ahmed, 2015). This dualistic effect of estrogens on B cells suggest that additional factors contribute to the hormone-mediated regulation of B cell function.

During aging, the decline of sex hormones is accompanied by a gradual functional decline of the immune system, which is particularly evident in females. Again, the most evident differences between sexes were described for B cells, while T cells follow a more uniform trajectory of aging across sexes. A multi-omic comparative analysis of human PBMCs showed a downregulation of genes specific to naïve B cells only in men which, together with the upregulation of genes associated with monocyte function, results in a more pronounced switch of the male immune system toward innate immunity (Marquez et al., 2020). At the same time, a reduced ability of the CD4+T cell compartment to respond to antigen exposure was reported (Moro-Garcia et al., 2013). Surprisingly, while it could be expected that the gradual age-associated decline in estrogen levels could lead to a reduction of sex-specific differences in the immune system, it was reported that aging is accompanied by a further increase in the sexual dimorphism of immune cells (Marquez et al., 2020), an observation that deserves further mechanistic investigations. In this regard, an interesting cell-extrinsic mechanism of antagonistic pleiotropy involving IL-7 signaling has been recently described to explain the age-associated sexual dimorphism in T cell function (Mkhikian et al., 2022). While IL-7 is crucial to maintain the function of naïve T cells throughout childhood and adulthood, its activation during aging was linked with increased N-glycan branching and reduced T naïve function, which was particularly evident in old females. (Mkhikian et al., 2022). This mechanism may explain some of the effects of age-related diseases characterized by increased circulating levels of N-glycans on the immune system, as well as the sex-dependent differences in the response of older individuals to specific vaccines, and may offer a potential therapeutic target to counteract T cell aging (McGill and Benayoun, 2022).

An intriguing subsect of B cells is represented by age-associated B cells (ABCs). ABCs constitute a population of naturally occurring B cells that are present at low frequencies in young animals and undergo a progressive expansion with aging, especially in the splenic compartment (Cancro, 2020). ABCs were shown to arise from naïve B cells upon exposure to exogenous or endogenous nucleic acids, which bind TLR7 and TLR9 (Phalke et al., 2022). In presence of appropriate survival signals, including T cell help and CD40 costimulation, these cells tend to acquire a B memory phenotype and persist as a distinct population (Russell Knode et al., 2017). This peculiar mechanism of activation, which dominates the conventional B-cell receptor cross-linking activation in these cells, prompts a specific link between ABCs and autoimmune manifestations such as systemic sclerosis and rheumatoid arthritis (Mouat et al., 2022). Indeed, upon activation, ABCs release high levels of IL-10 and reshape the naive CD4+ T cell population toward Th17 differentiation when acting as antigen-presenting cells (Rubtsov et al., 2011). Hence, it is not surprising that a faster accrual of ABCs was reported in patients with autoimmune disease, particularly among females (Rakhmanov et al., 2009). The sustained secretory and immunomodulatory activity of ABCs, along with the relative reduction in follicular B cells associated with their expansion in secondary lymphoid organs (Riley et al., 2017), suggest a central role of these cells in the progression of inflammaging.

2.3. Immunosenescence

When people age, the capacity of their immune system for immunosurveillance gradually declines, a phenomenon called immunosenescence (Walford, 1969). Immunosenescence is multifactorial and affects both natural and acquired immunity (Pawelec, 2012, 2018). Even if the post-menopausal modulation/alteration of the immune system was not extensively investigated, increasing evidence suggests that immunosenescence develops earlier in men than in women, and this phenomenon has been related to a longer life expectancy of women (Dudkowska et al., 2017; Hirokawa et al., 2013; Ostan et al., 2016; Caruso et al., 2013) .

Regarding the biological mechanisms that could modulate immunosenescence differently in men and women, it has been highlighted that in the reproductive age steroids can differentially modulate the immune system; while estrogens increase the immune response, progesterone and androgens exert immune suppressive actions (Oertelt-Prigione, 2012). Estrogen receptors are expressed not only in reproductive tissues but also in immune cells, such as lymphocytes, monocytes, macrophages and dendritic cells, so that a reduction in estrogen levels can be associated with imbalanced immune cell activation and function (Calippe et al., 2010; Candore et al., 2010; Laffont et al., 2017). Therefore, the post-menopausal period could be characterized by an increased rate of immunosenescence in females compared to males of the same age, so that the advantage in terms of immune system efficiency that women experience in the reproductive period is lost in the post-reproductive period.

3. Sex-dependent differences in cellular senescence

If the reshaping of innate and adaptive immunity, i.e., immunosenescence, is one of the main culprits of inflammaging, robust data also highlighted the contribution of different types of senescent cells, including senescent immune cells, showing that progressive accrual of senescent cells in aging and chronic diseases is associated with detrimental effects in tissue homeostasis (Fulop et al., 2018). Senescent cells lost their replicative ability and change their morphology and functions, acquiring a characteristic phenotype called the senescence-associated secretory phenotype (SASP). The SASP program includes a plethora of pro-inflammatory and pro-resolving molecules so that SASP can play opposite effects on tissue health. When senescence is circumscribed and limited in time, it exerts beneficial effects on health, promoting tissue repair and extracellular matrix remodeling (Di Micco et al., 2021; Pazolli et al., 2012). When senescent cells are chronically present, SASP factors are continually secreted, generating a chronic inflammatory state associated with both inflammaging (Sharma, 2021) and pro-oncogenic effects (Di Micco et al., 2021; Kuilman et al., 2010). Differential rates of cellular senescence drive unique organ ageing and numerous chronic diseases, such as CVD, metabolic diseases, and neurodegenerative diseases (Childs et al., 2016; Guerrero et al., 2021). Notably, senescence is responsible for a 'contagious aging': senescent cells can release molecules and/or vesicles containing a plethora of different types of molecules, that affects senescence in neighboring or distant young cells, thus yield to bystander senescence (Bonafe et al., 2012; da Silva et al., 2019; Mensà et al., 2020; Nelson et al., 2012).

Since many inducers of cellular senescence are known to generate DNA damage and initiate the DNA damage response (DDR), sex differences in cellular senescence could be induced by molecular mechanisms that respond to genotoxic insults (Ng and Hazrati, 2022). Current studies show that the female sex is associated with greater susceptibility to DNA damage and a greater likelihood of senescence onset, despite additional evidence showing that estrogen protects against genotoxic insult and inhibits senescence regulatory proteins (Ng and Hazrati, 2022). Increasing evidence suggests that estrogen primarily prevents the onset of cellular senescence and its pro-inflammatory effects by protecting against DNA damage and inhibiting senescence regulatory proteins (Rall-Scharpf et al., 2021). However, there is also evidence that estrogen is equally capable of doing the opposite (i.e., generating DNA damage; stimulating senescence regulatory pathways) (Rall-Scharpf et al., 2021).

Immunosenescence obviously contributes to the accumulation of senescent cells during aging, reducing the efficiency of senescent cell clearance. Senescent cells recruit and make immune cells senescent and dysfunctional via SASP, leading in turn to persistent and excessive accumulation of senescent cells (Prata et al., 2018). It was recently reported that senescent fibroblasts and epithelia were not only refractory to macrophage-mediated engulfment and removal, but they also paralyzed the ability of macrophages to remove bystander apoptotic corpses, suggesting that the longer the life span or more severe the disease, efferocytotic corpses would accrue and be linked to inflammation perpetuation and/or other disease consequences (Schloesser et al., 2023). It was hypothesized that males and females might differ in the rate at which they produce or clear senescent cells, thus leading to different rates at which senescent cells accumulate in various tissues (Bronikowski et al., 2022).

4. Sex-dependent genetic and transcriptional differences related to aging and age-related disease

Increasing evidence suggested that sex differences in age-related diseases susceptibility are genotype-dependent, both in human and animal models, thus reinforcing the notion that genetic association studies need to consider sex as a covariate (Lipoldovà and Demant, 2021; Sabikunnahar et al., 2022). A recent sex-stratified genome-wide association study (GWAS) meta-analysis of blood lipids showed that 3–5 % of autosomal lipid-associated loci are characterized by sex-biased effects (Kanoni et al., 2022). In addition, 21 novel lipid loci were identified on the X chromosome, many of them showing pleiotropic associations with sex hormones (Kanoni et al., 2022). The search for novel genes and pathways associated with sex and frailty in diverse middle-aged cohorts using RNA sequencing led to the identification of sex-specific transcriptional changes associated with frailty, highlighting the relevance of epigenetic mechanisms in age- and sex-related differential risk of disease (Pacheco et al., 2022). When human RNA sequencing data from 53 tissues were analyzed in more than 500 adults, thousands of genes emerged as differentially expressed in the reproductive tracts and tissues common to both sexes (Gershoni and Pietrokovski, 2017). Sex-differential genes were related to various biological systems, including pathways related to mutation accumulation, which might reduce selection efficiency and thus affect the prevalence of different traits and diseases. Interestingly, many of the sex-specific genes that also undergo reduced selection efficiency are essential for successful reproduction in men or women (Gershoni and Pietrokovski, 2017). Regarding inflammaging, an epigenetic origin was invoked for the different manifestations in nonagenarian men and women (Nevalainen et al., 2015). These differences point to the genomic regulation of inflammatory response and suggest that the gender-specific immune system dimorphism in older individuals could be ascribed, almost in part, to DNA methylation (Nevalainen et al., 2015). Tissue- and sex-specific transcriptomic changes were observed in resident macrophages of peritoneum, liver, and brain during physiological aging in animal models, reinforcing this hypothesis (Babagana et al., 2021). Recently, an *in silico* approach highlighted sex-based differential mechanisms in typical Parkinson's disease hallmarks, including pathways related to inflammaging, such as inflammation, mitochondrial dysfunction, and oxidative stress (Lopez-Cerdan et al., 2022).

5. Sex-dependent differences in selected biomarkers of inflammaging

While increasing evidence is accumulating on the relevance of biomarkers of aging in human health and mortality, understanding the sex-specific features of these biomarkers is lagging. The effect of sex has

been largely ignored, considered a confounder rather than a source of biological variation, and therefore most of the results obtained on the biomarkers of aging/inflammaging are not biologically relevant to either sex (Hagg and Jylhava, 2021). This issue could have clinical relevance, as recently demonstrated by the need for sex-specific inflammatory biomarkers in predicting anti-inflammatory pharmacological responses (Lombardo et al., 2022).

IL-1β, IL-6, TNF-α, and C-reactive Protein (CRP) are the most extensively investigated circulating biomarkers of inflammaging, and their circulating levels are associated with an increased risk to develop all the most common age-related diseases. Sex seems to influence the levels of these cytokines in healthy adults, being IL-1β, IL-6, and TNF-α significantly higher in men as compared to women and this relationship was only partly explained by hormone levels (Bernardi et al., 2020). This is consistent with the higher cardiovascular risk exhibited by the male sex as compared to the female sex (Regitz-Zagrosek and Gebhard, 2022).

IL-6 is the most investigated cytokine released by innate immune cells and endothelial cells in the framework of inflammaging. IL-6 is defined as a Janus-faced cytokine since it can play both pro- and anti-inflammatory effects. Circulating IL-6 levels increase with age both in healthy men and women (Ferrucci et al., 2005), but differences between sexes remain largely unexplored. A genetic predisposition to produce high levels of IL-6 during aging was observed prevalently in men, and it seems to be associated with a longevity disadvantage (Bonafè et al., 2001). IL-6 was associated with all-cause mortality in men (Baune et al., 2011) and increased risk of developing the most common age-related diseases and their severe complications among apparently healthy men (Bernardi et al., 2020; Ridker et al., 2000). These observations prompted the hypothesis that IL-6, besides its role as a feasible and cost-effective biomarker of inflammaging, could represent a druggable target to reduce the residual inflammatory risk explaining the adverse cardiovascular outcomes after aggressive reduction of blood lipids (Aday and Ridker, 2019). While randomized controlled trials aimed at reducing IL-1β levels using the monoclonal antibody canakinumab have shown promising results (Ridker et al., 2017), contrasting evidence was reported from studies aimed at reducing IL-6 levels, both with anti-IL-6 agents, such as tocilizumab, or as a secondary outcome of anti-IL-1β treatments (Ridker et al., 2020).

Importantly, IL-6 plays catabolic effects on muscle proteins (Krabbe et al., 2004). As a myokine, IL-6 levels increase for several hours following exercise, whereas chronically active persons have lower IL-6 levels (Elosua et al., 2005). Interestingly, a recent study demonstrated that a higher predictive IL-6 cut-off level should be determined for aging sarcopenia in men than in women (Miko et al., 2018). This meta-analysis revealed significantly higher circulating IL-6 levels in men, despite better muscle condition, than in similarly elderly women, with weaker muscle conditions (Miko et al., 2018). These findings may contribute to explaining, almost in part, the absence of an IL-6 circulating consensus cut-off point for the prediction of adverse physical and functional outcomes.

Sexual dimorphism was observed also in IL-10, the most relevant anti-inflammatory cytokine, analyzing blood leukocytes *ex vivo* (Islam et al., 2022). IL-10-mediated inhibition of TNF-α production was more pronounced in males, and this sex-based difference was not explained by differences in circulating plasma IL-10 concentrations, basal IL-10 receptor expression in unstimulated CD14 + and CD4 + cells, nor the basal expression of IL-10 signaling proteins in unstimulated peripheral blood mononuclear cells (Islam et al., 2022).

Important differences in comorbidities and clinical characteristics exist between women and men with cardiovascular disease. Women tend to exhibit higher levels of natriuretic peptides (NT-proBNP), and lower levels of cardiac troponins (hs-cTn) and the cardiac stress marker soluble suppression of tumorigenesis-2 (sST2) compared to men (Cediel et al., 2020; Sabbatinelli et al., 2022a) so that lower sST2 and hs-cTnT and higher NT-proBNP cut-offs were proposed for risk stratification in women (Vergaro et al., 2022). Notably, sST2 is a biomarker related to inflammation, since it is the soluble receptor of IL-33, an anti-inflammatory cytokine belonging to the IL-1superfamily (Homsak and Gruson, 2020). Indeed, in contrast to IL-1, IL-33 acts as an alarmin against injury-induced stress, pathogens, or cell death by activating local immune cells (Homsak and Gruson, 2020). In this framework, sST2 acts as a decoy receptor for IL-33, thus preventing the positive effects of the IL-33/ST2 axis, especially at the cardiac level (Vianello et al., 2019).

When some relevant biomarkers of DNA methylation status were assessed in older subjects living in two Mediterranean Blue Zones, sex differences were found, suggesting that men display positive epigenetic age acceleration (EAA) compared to women according to both Horvath and Hannum clocks (Engelbrecht et al., 2022).

Regarding leukocyte telomere length (LTL), another well-established biomarker of inflammaging, the extensive literature on LTL showed considerable variability among individuals, with females having, on average, longer telomeres than males (Lansdorp, 2022). Sex differences in average telomere length are already present at birth and could affect average life expectancy between the sexes (Jelenkovic et al., 2018). Sex hormones can provide a possible explanation for the sex differences in telomere length, through the modulation of telomerase expression (Calado et al., 2009). Higher telomerase activity in female embryo cells could result in longer telomeres in females compared with male embryos prior to embryo implantation (Lansdorp, 2022). This phenomenon could explain why leukocytes from females at birth and throughout life have longer telomeres, and this feature could contribute to delaying the accumulation of senescent cells during female aging. We recently suggested that the release into the cytoplasm and the extracellular vesicle-mediated intercellular exchange of telomeric TTAGGG repeats could exert anti-inflammatory activity by preventing the activation of the misplaced nucleic acid-sensing pathway (Bonafè et al., 2020b). In this framework, we can argue that females with longer telomeres compared to males, could exploit the anti-inflammatory activity of telomeric sequences over an extended time span, eventually delaying the development and progression of age-related diseases.

Several studies reported sex-specific associations of TL with the risk of mortality (Barrett and Richardson, 2011; Jemielity et al., 2007). Recent studies including a large number of participants, definitively demonstrated that shorter LTL was associated with an increased risk of overall mortality and this association was stronger for noncancer causes of death (Arbeev et al., 2020; Schneider et al., 2022).

Handgrip strength, which was extensively investigated as a functional biomarker associated with healthy aging, was recently independently associated with better learning ability for novel verbal information only in men, suggesting sex-related different performances also of functional biomarkers (Prokopidis et al., 2022).

Fig. 1 summarizes sex/gender differences in the most extensively investigated biomarkers of inflammaging.

6. Sex-dependent differences in inflammaging: possible implications for sex/gender gap in COVID-19 severe outcomes

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiological agent causing the respiratory and systemic sickness referred to as coronavirus disease 2019 (COVID-19) in humans (Wang et al., 2020). Globally, to date, more than two million people have died from the COVID-19 outbreak. The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic to severe respiratory failure (Lu et al., 2022). Many infectious diseases have been associated with gender differences in disease incidence, morbidity, and mortality (Bosch et al., 2018). Epidemiological differences between men and women have also been reported with regard to previous outbreaks of pathogenic coronaviruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) (Alghamdi et al., 2014; Karlberg et al., 2004). Overall, regarding coronavirus infections, men have an increased risk of worse outcomes compared to women (Karlberg et al., 2004; Lakbar

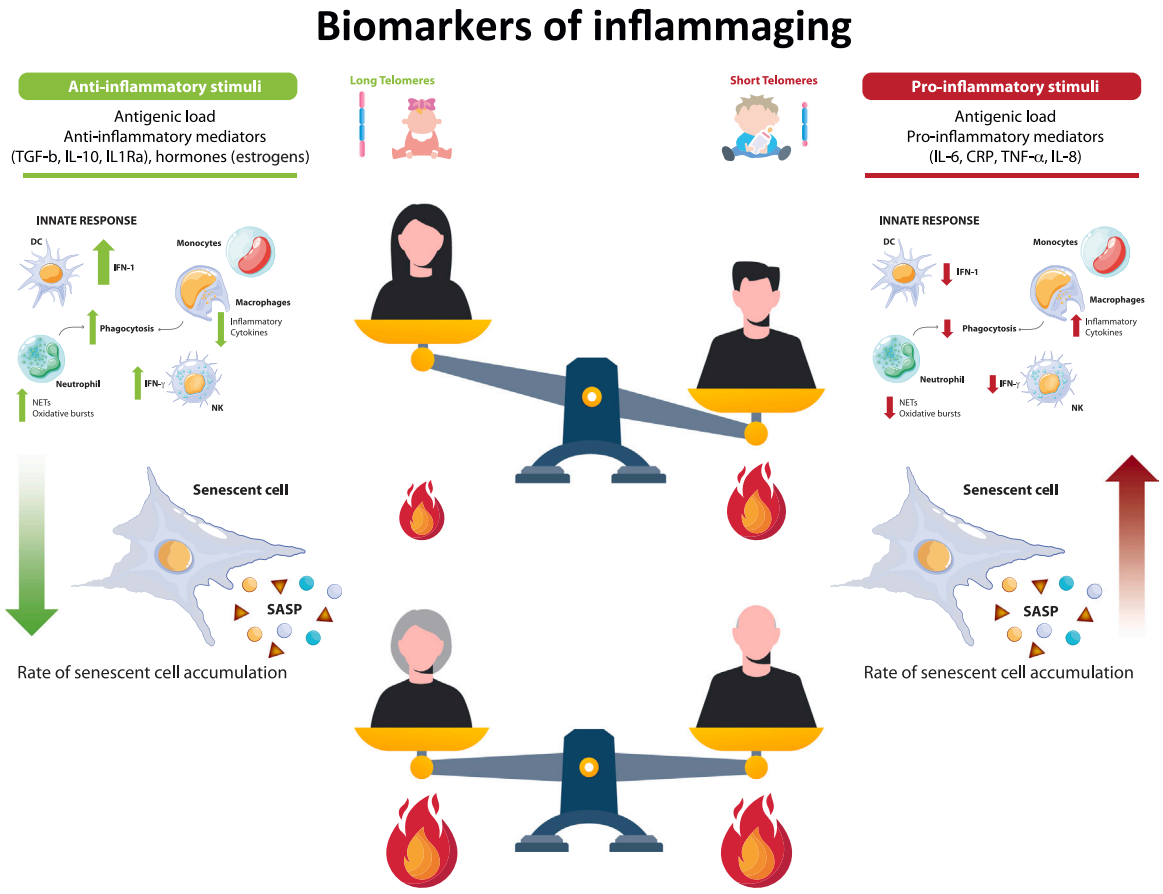

Fig. 1. Sex/gender differences in the most extensively investigated biomarkers of inflammaging. CRP, C-reactive protein; DC, dendritic cell; IL1Ra, interleukin-1 receptor agonist; NETs, neutrophil extracellular traps; NK, natural killer; SASP, senescence-associated secretory phenotype; TGF-b, transforming growth factor beta; TNF-α, tumor necrosis factor α.

et al., 2020). These clinical findings are consistent with mouse models suggesting that estrogen reduces the susceptibility and severity of SARS-CoV-2 infection (Channappanavar et al., 2017).

We can argue that "the gender medicine perspective" can be adequately highlighted by discussing COVID-19 severe outcomes. Overall, males are more likely to exhibit enhanced disease severity and mortality than females (Jin et al., 2020). The gender difference was observed worldwide; in China, the mortality rate was 2.8 for men versus 1.7 for women; a similar situation occurred in Europe, with older men affected by preexisting cardiological conditions showing an increased mortality (Gebhard et al., 2020). Several studies enrolling very large numbers of patients showed that males had a higher fatality rate, higher inflammation, and an impaired immune response during SARS-CoV-2 infection and recovery (Huang et al., 2021). However, limited data are currently available on COVID-19 gender differences in very old patients. It was recently reported that the mortality risk for men increased steadily to very old ages, and at the same time, men over the age of 90 become relatively more resilient than women of the same age (Marcon et al., 2020). Consistently, we recently showed no significant difference between males and females in the in-hospital mortality rate in the setting of geriatric patients (Cardelli et al., 2022; Olivieri et al., 2022). However, why COVID-19 tends to be more severe in males than in females is still under discussion. There are certainly many reasons that can partially explain this phenomenon, such as gender-specific behaviors, and genetic, hormonal, and immune factors, among others. We will focus our discussion on how immunological responses and the inflammaging rate could affect COVID-19 outcomes differently in men and women. When sex differences in plasma cytokines and blood-cell phenotyping were analyzed in patients with moderate COVID-19 who had not received immunomodulatory medications and uninfected healthcare workers (HCW), increased plasma levels of innate immune cytokines such as IL-8 and IL-18 along with more robust induction of non-classical monocytes were observed in COVID-19 patients compared to HCW, especially in men (Takahashi et al., 2020). The higher production of innate immunity cytokines, such as IL-6, IL-8, and MCP-1, in men with COVID-19 was confirmed also in intensive care patients, where the amplitude of the sex-specific bias appeared to be related to disease severity (Qi et al., 2021). By contrast, female patients had more robust T cell activation (Takahashi et al., 2020), and a significant elevation in B cell number (Qi et al., 2021), compared to male patients during COVID-19. Similarly, women seem to display an immunological advantage over men in mounting antibody responses against SARS-CoV-2, as suggested by the observation of increased numbers of circulating T follicular helper (Tfh) cells (Dimitrijevic et al., 2020), which regulate B cell proliferation and induce immunoglobulin class switching (Nurieva and Chung, 2010). In this regard, by limiting the systemic spreading of the virus, early antibody responses were associated with favorable COVID-19 outcomes (Bunders and Altfeld, 2020). Notably, the extent and dynamics of the antibody response against SARS-CoV-2 could also explain, at least in part, sex-related differences in the establishment of immunological memory after COVID-19 infection and vaccination (Vassallo et al., 2021), especially at advanced age. However, these data are not conclusive, and some researchers suggested considering this study as an exploratory study of possible associations between immunological variables and sex disparities in COVID-19 outcomes (Shattuck-Heidorn et al., 2021).

Morbidity and mortality associated with COVID-19 are mediated by intense viral stimulated inflammation and increased levels of

inflammatory biomarkers and cytokines, commonly referred to as "cytokine storm". Notably, IL-6 and CRP, two well-established biomarkers of inflammaging, have been found to be particularly increased in COVID-19 patients at higher risk of fatality rate (Cardelli et al., 2022; Zeng et al., 2020).

When metabolic profiling was performed in COVID-19 patients at hospital admission, several plasma pro-inflammatory biomarkers showed a significant correlation with deregulated metabolites, especially with L-kynurenine and L-tryptophan, and a strong sex-related dysregulation of metabolites, cytokines, and chemokines between severe and moderate patients were observed (Ceballos et al., 2022).

The neutrophil-to-lymphocyte ratio (NLR) is a well-known marker of inflammation and appears to reflect the severity of COVID-19, particularly among patients older than 50 years of age (Olivieri et al., 2022). Since neutrophils can activate NETs, which consist of decondensed nuclear and mitochondrial chromatin, to counteract infectious agents (Euler and Hoffmann, 2019), extracellular DNA could play a role in modulating the systemic inflammation in patients affected by COVID19, and gender differences can be highlighted in this process (Storci et al., 2021).

Recently, other biomarkers of inflammaging were analyzed in COVID-19 patients, showing that leukocyte telomere shortening was associated with a higher risk of dying of COVID-19 in women (Vireseda-Berdices et al., 2022).

From a genetic point of view, type 1 IFN was highlighted among genes associated with severe forms of pneumonia in COVID-19 patients (Bonafè et al., 2020a; Zhang et al., 2020). In humans, the interferon-induced gene encodes for proteins involved in the activation of the "antiviral status" (Wickenhagen et al., 2021). An inefficient immune response in counteracting the SARS-Cov-2 infection could depend on an impaired capability to trigger type I IFNs responses (Blanco-Melo et al., 2020). Overall, it might be conceivable that females, owning genes for IFNs more active than males, could be more likely to counteract severe outcomes associated with SARS-Cov-2 infection (Mavragani et al., 2022). Since the sex-biased difference in COVID-19 hospitalization has been observed, as male patients tend to be more likely hospitalized than female patients, some studies analyzed sex-biased genetic variants showing a differential association between sexes and COVID-19 hospitalization (Luo et al., 2022). Twelve SNPs in 8 genes were suggested to show differential COVID-19 associations between sexes (GADD45G, TRIM29, PVRL1, KNDC1, STK32C, PGAP2, TRIM21 and CSMD1) (Luo et al., 2022). Interestingly, some of these genes are related to innate immune functions (Jones et al., 2021).

Some of the sex disparities in immune functions were associated with sex-related differences in estrogens (Fish, 2008). Even if present literature has greatly underlined data suggesting a beneficial effect of estrogens and a detrimental one for androgens in COVID-19 patients, the role of sex hormones in COVID-19 is likely to be far more complicated than "estrogens is the good and androgens the bad" (Stasi and Rastrelli, 2021). Estrogens, via the activation of the eNOS gene, could contribute to promoting the inhibition of viral replication (Mukherjee and Pahan, 2021). The diffuse inflammation associated with pulmonary blood vessel endothelial dysfunction leads to eNOS uncoupling, reduced NO production, pulmonary physiological alterations, and systemic coagulopathy. On the other hand, macrophagic iNOS activity is increased during infection, but the overproduction of NO may be deleterious, fueling inflammatory conditions (Guimaraes et al., 2021).

Overall, we can speculate that SARS-CoV-2 infection could promote a beneficial pro-resolutive inflammation in young subjects, especially in young females characterized by reduced inflammaging rate and in which sex hormones, estrogen/or progesterone, may have a protective role against SARS-CoV-2 by acting as an immune booster and by providing protection from lung and myocardial injury. On the contrary, in elderly people with a high inflammaging rate, SARS-Cov-2 infection could trigger a cytokine storm with deleterious effects on tissues and organs, especially in older and comorbid men (Bonafe and Olivieri, 2022; Bonafè et al., 2020a; Sabbatinelli et al., 2022b).

The post-menopausal period is associated with imbalanced immune cell activation/function and increased rate of immunosenescence in females compared to males of the same age, so that older men are more prone to develop a cytokine storm than older women. We can conclude that the disadvantage in terms of reduced immune system activation in older women has become an advantage during SARS-CoV-2 infection, triggering an excessive and detrimental inflammatory response in older men.

7. Conclusion

We reviewed and critically discussed sex-dependent differences in the two key cellular mechanisms that foster inflammaging, such as immunosenescence and the accumulation of senescent proinflammatory cells during aging in human tissues. These two phenomena can be modulated by hormonal behavior. The reduction in estrogen production in the post-menopausal period can be associated with imbalanced immune cell function and an increased rate of immunosenescence in females compared to males of the same age. As a consequence, the advantage in terms of immune system efficiency that women experience in the reproductive period is lost in the post-reproductive period, and in turn, women live longer than men, but in worse health conditions later in life. Within an evolutionary framework, aging and reproduction are intrinsically linked. Reproductive senescence, concluding in menopause, is a feature of female mammals including women that experience exceptionally long post-reproductive lifespans. Hormonal and genetic/epigenetic differences seem to impinge upon sex-related differences in lifespan and health span. This consideration is not in contrast with the hypothesis of social/gender distinction, since the interaction between environmental factors and genetic make-up, referred to as epigenetic mechanisms, can act differently in men and women, and in women in the pre- and post-reproductive period. The potential crosstalk between hormonal and genetic sex-related factors and the socio-economic sex-related factors could contribute to better explaining the sex differences in health span. Our hypothesis is that sex-related differences in inflammaging could be at the crossroad between these multiple factors and could help to identify and better characterize sex-specific biomarkers of aging trajectories. This issue could have clinical relevance, highlighting the need for sex-specific inflammatory biomarkers as diagnostic, prognostic, and pharmacological response-predicting biomarkers, especially in the setting of geriatric patients.

An additional consideration concerns the hypothesis of sex-related different responses to anti-aging treatment. In *Drosophila melanogaster* males and females have different sensitivities to anti-aging interventions, depending probably ondifferent genetic backgrounds, mating, dose, and exposure duration (Lushchak et al., 2023). Of note, no evidence exists that in humans males and females respond differently to therapeutic intervention against aging, but the identification of mechanisms that underlie sex-related differences in inflammaging could be of relevance for age- and sex-tailored anti-aging intervention strategies (Aiello et al., 2019).

Regarding the sex disparity of COVID-19–related morbidity and mortality, it is a very complex phenomenon, likely explained by biological sex differences, including differences in chromosomes, reproductive organs, and related sex steroids, but also by other gender-specific factors, such as differential behaviors and activities by social and cultural/traditional roles. We highlighted the potential influence of sex differences in inflammaging rate, in sex disparity of COVID-19–related morbidity and mortality. In the context of COVID-19 research, descriptive biomarker levels are currently reported by sex, but data on the effect of patient sex on the relationship between biomarkers and COVID-19 disease severity/outcomes need to be more extensively discussed. The higher COVID-19 case fatality rate and increased severity of disease in males compared with females underlies biological sex differences, but it is likely due to a combination of risk

factors, including biological aging and behavioral/lifestyle factors.

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Declaration of Interests

None.

Data availability

No data was used for the research described in the article.

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