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REVIEW ARTICLE

Perspectives on the dynamic implications of cellular senescence and immunosenescence on macrophage aging biology

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Abstract An intricate relationship between impaired immune functions and the age-related accumulation of tissue senescent cells is rapidly emerging. The immune system is unique as it undergoes mutually inclusive and deleterious processes of immunosenescence and cellular senescence with advancing age. While factors inducing immunosenescence and cellular senescence may be shared, however, both these processes are fundamentally different which holistically influence the aging immune system. Our understanding of the biological impact of immunosenescence is relatively well-understood, but such knowledge regarding cellular senescence in immune cells, especially in the innate immune cells such as macrophages, is only beginning to be elucidated. Tissue-resident macrophages are long-lived, and while functioning in tissue-specific and niche-specific microenvironments, senescence in macrophages can be directly influenced by senescent host cells which may impact organismal aging. In addition, evidence of age-associated immunometabolic changes as drivers of altered macrophage phenotype and functions such as inflamm-aging is also emerging. The present review describes the emerging impact of cellular senescence vis-à-vis immunosenescence in aging macrophages, its biological relevance with other senescent non-immune cells, and known immunometabolic regulators. Gaps in our present knowledge, as well as strategies aimed at understanding cellular senescence and its therapeutics in the context of macrophages, have been reviewed.

Keywords Macrophages · Senescence · Immunosenescence · Immunometabolism · Aging

Abbreviations

SC	Senescent cells
SASP	Senescence-associated secretory phenotype
SA-β-gal	Senescence-associated β-galactosidase
mTOR	Mammalian target of rapamycin
ROS	Reactive oxygen species
NAD^+	Nicotinamide adenine dinucleotide
MDSC	Myeloid-derived suppressor cells

Introduction

The last decade has seen rapid progress in our understanding of the molecular etiology and pathological effects of aging. There is increasing evidence that the stochastic phenomenon of aging is essentially a culmination of cellular and molecular damage over

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time that gradually manifests as the visible macrophenotype of aging (Bhatia-Dey et al. 2016; Chandrasekaran et al. 2017). Several different theories were formulated to explain the causes and mechanisms of aging, but gerontologists are now showing considerable interest in the cellular senescence centric interpretation of aging which is beginning to uncover an integrative and tangible understanding of the known effects of aging (Dodig et al. 2019; Borghesan et al. 2020). Aging itself is not a disease, but it rather predisposes the elderly to several age-associated disorders including the characteristic hallmark diseases of the twenty first century, i.e., cancer and diabetes (Huo et al. 2018; DeSantis et al. 2019). In fact, a view is now emerging that the various age-related diseases should be studied in the purview of cellular senescence and that targeting cellular senescence itself could be a novel approach in preventing frailty and the aggravation of several age-associated disorders (Wijshake and van Deursen 2016; Borghesan et al. 2020). This is supported by multiple studies which have demonstrated that accumulation of senescent cells (SC) shorten healthspan and lifespan (Baker et al. 2016), and that delaying the development of cellular senescence (Sharma et al. 2021) or lifelong removal of SC can enhance longevity (Baker et al. 2011), improve tissue regeneration (Krishnamurthy et al. 2006), and prevent the development of chronic age-associated disorders (Lewis-McDougall et al. 2019; Palmer et al. 2019; Cai et al. 2020; Ogrodnik et al. 2021). In fact, the targeted removal of SC using senolytics is an emerging area of research, and active preclinical search, as well as clinical assessment of putative senolytics is presently underway (Xu et al. 2018; Hickson et al. 2019; Wissler Gerdes et al. 2020).

The immune system is a complex, yet coordinated and highly plastic network of cells that has been traditionally recognized to protect the integrity of the organism from invading pathogens. However, it is now understood that the pattern recognition receptors of immune cells not only recognize the pathogen-associated molecular patterns but also respond to cell-intrinsic damage-associated molecular patterns or DAMPs suggesting their broader and more significant physiological role (Mogensen 2009). The innate and adaptive branches of the immune system communicate either directly or through a variety of signaling molecules, while the integrated neuroendocrine-immune system governs the interactions between immune cells and other regulatory systems. As observed with different physiological responses, the immune system also undergoes characteristic functional and phenotypical deterioration with age resulting in feeble response to pathogens and vaccination, and the development of chronic age-associated inflamm-aging (Aw et al. 2007; Del Giudice et al. 2017; Aiello et al. 2019; Xu et al. 2020). These changes have been loosely described as 'immunosenescence', although the exact biomarkers of immunosenescence and that whether this process is the cause or a consequence of aging itself is still debatable (Pawelec et al. 2020). Regardless, aging in immune cells has traditionally been considered within the purview of immunosenescence; however, similar to other mammalian cells, immune cells are also liable to be affected by the different facets of cellular senescence which can have a potentially deleterious impact on immune functions (Vicente et al. 2016). Although the triggers of immunosenescence and cellular senescence may overlap, both these processes show fundamentally distinct characteristics and yet have the potential to impair immune functions with age (Burton and Stolzing 2018) (Table 1). However, unlike immunosenescence, our understanding of the role, and particularly the biological impact of cellular senescence in immune cells is only emerging. This is especially relevant for innate immune cells such as macrophages which form the basis of parenchymal homeostasis, integrity, and perform unique tissue-specific functions as resident immune cells. This review describes our current understanding and relevance of cellular senescence in immune cells *per se*, with an emphasis on macrophages. The lacunae in our present knowledge, as well as the potential for further research are discussed to ultimately understand how cellular senescence contributes to the macrophage aging process.

Cellular senescence, immunity, and aging: emerging concepts

The fact that mitotic mammalian cells fail to divide after a certain finite number of cell divisions in vitro (replicative senescence) was a seminal discovery in biogerontology (Hayflick and Moorhead 1961; Rattan 2016). The so-called 'Hayflick limit' seemingly

Table 1 Major known markers of immunosenescence and cellular senescence characterizing macrophage aging

S. no.	Immunosenescence	Cellular senescence
1	Decreased activation response to LPS/IFN-γ (Mahbub et al. 2012)	Cell cycle arrest; persistent p53/p21 and/or p16 expression (Nyunoya et al. 2003; Yousefzadeh et al. 2021)
2	Reduced TLR expression (Renshaw et al. 2002)	DNA damage (Iglesias-Ara et al. 2010)
3	Impaired chemotaxis (Solana et al. 2012)	Telomere attrition (Sebastián et al. 2009)
4	Decreased cytokine response (Chelvarajan et al. 2006)	Presence of SASP (Wang et al. 2020)
5	Impaired wound healing (Swift et al. 2001)	Hypertrophy (Kumar et al. 2020)
6	M1/M2 polarization (Cui et al. 2019; Mahbub et al. 2012)	Reduced cell proliferation (Holt and Grainger 2012)
7	Impaired antigen presentation (Větvicka et al. 1985)	Increased SA-β-gal activity (Kumar et al. 2020)
8	ROS burden* (Sebastián et al. 2009)	ROS burden* (Yousefzadeh et al. 2021)
9	Metabolic alterations* (van Beek et al. 2019)	Metabolic alterations* (Lee et al. 2021)

*Overlapping parameters

provided a link between cell division and organismal aging, but this phenomenon remained controversial and was initially dismissed as a mere in vitro artifact (Hayflick 1998; de Magalhães 2004). However, multiple studies have now confirmed that SC play a causal role in governing organismal aging and age-dependent disorders (Campisi and Robert 2014; Childs et al. 2015; Katzir et al. 2021), and in fact, cellular senescence is established as one of the well-studied hallmarks of aging (López-Otín et al. 2013). In general, cellular senescence is characterized by cellular hypertrophy, permanent cell cycle arrest by the activation of cell cycle inhibitory pathways such as p53/p21^{WAF1} and/or p16^{Ink4a}/pRb, chromatin remodeling, resistance to apoptosis by deregulation of Bax/Bcl-2 signaling, telomere attrition, development of a senescence-associated secretory phenotype or SASP, and altered metabolic longevity pathways such as SIRT and mTOR (Carroll and Korolchuk 2018; Hernandez-Segura et al. 2018; Kumari and Jat 2021; Maduro et al. 2021). The induction of cellular senescence is intimately linked to external and intrinsic cell stressors. A decline in cellular stress response capacity results in impaired redox balance, augmentation of genotoxic stress, and DNA damage that ultimately aids in cell cycle arrest and the development of cellular senescence (Nacarelli et al. 2016; Zhang et al. 2017; Robinson et al. 2018; Chen et al. 2020). Moreover, there is evidence that the characteristic telomere attrition, as observed during replicative senescence, could also be accelerated by oxidative damage (von Zglinicki 2002; Ludlow et al. 2014). However, it is important to consider that SC are naturally occurring cells and their presence *per se* does not reflect on the pathological state of the organism, since SC are essential mediators of processes such as wound healing and repair (Demaria et al. 2014). In younger organisms, SC are constantly replaced, but as we age, SC turnover decreases, and tissue SC burden rapidly increases which contributes to age-related pathologies (Karin et al. 2019). More significantly, the accumulation of SC result in the chronic presence of SASP which has pro-tumorigenic and pro-inflammatory paracrine effects on nearby healthier cells (Coppé et al. 2010). Due to this, the SASP is being considered as a potent source of 'inflamm-aging'-which is a chronic and heightened state of inflammatory stimulus that augments inflammatory disorders in aging

population (Fulop et al. 2016; Olivieri et al. 2018). Thus, cellular senescence appears to be an antagonistic hallmark of aging and a candidate example of the antagonistic pleiotropy theory of aging.

The exact causes of SC accumulation with age are yet to be completely understood. In this regard, the role of immune cells in maintaining SC cell homeostasis in tissues is being increasingly recognized (Prata et al. 2018; Kale et al. 2020). The SASP components of SC serve to chemotactically attract various immune cells such as macrophages, NK cells, and cytotoxic T cells which subsequently recognize the upregulated immunogenic ligands on SC (such as MICA and ULBP2) resulting in their efficient removal (Coppé et al. 2010; Hall et al. 2016; Sagiv et al. 2016) (Fig. 1). That SC accumulate in aging organisms, could at least in part be ascribed to deficient immune functions/immunosurveillance associated with immunosenescence and/or cellular senescence (Fig. 1). Indeed, a recent work demonstrated that mice deficient in the cytotoxic potential of immune cells exhibited both higher SC tissue burden and chronic inflammation suggesting that weakened immunosurveillance could be a critical aspect regulating SC accumulation in vivo (Ovadya et al. 2018). Another study showed that impaired immunosurveillance in CD4+ T cells results in the development of murine hepatocellular carcinomas, thus suggesting that senescence surveillance is important for tumor suppression in vivo (Kang et al. 2011). Similarly, it was reported that NK cells play a critical role in eliminating senescence-activated stellate hepatic cells both in vitro and in vivo (Krizhanovsky et al. 2008). The role of macrophages in the removal of SC has long been speculated (Kay 1975; Mevorach et al. 2010). Using a co-culture system, a recent study showed that

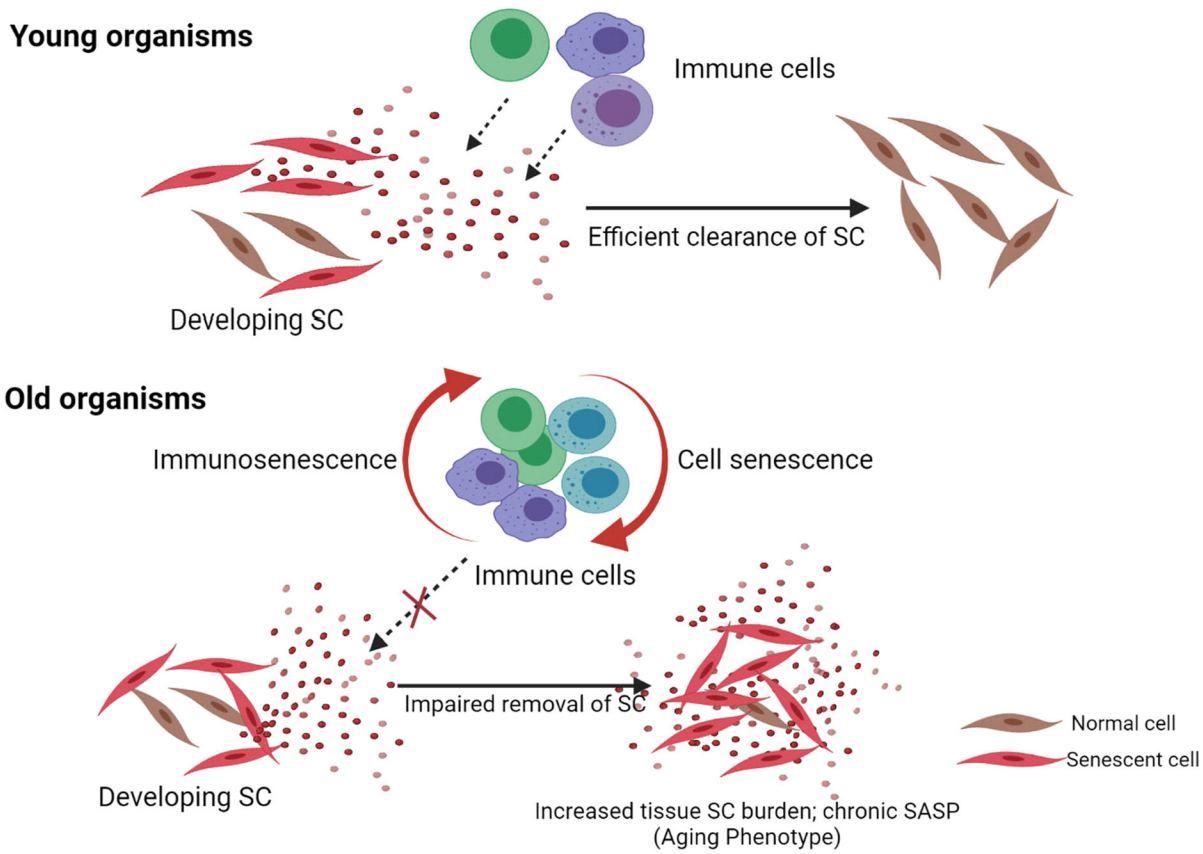

Fig. 1 Immune cells mediated removal of SC is affected by cellular senescence and immunosenescence. In young organisms, SC secrete SASP factors which attract innate and adaptive immune cells resulting in the removal of SC. During aging, immunosenescence and cellular senescence collectively impair several immune functions which may together contribute to the inefficient clearance of SC and their gradual accumulation

macrophages can induce TNF-α mediated apoptosis in senescent fibroblasts followed by their phagocytic clearance (Ogata et al. 2021). Macrophages are also involved in the elimination of SC in the uterine stroma surrounding the embryo implantation site following parturition in mice (Egashira et al. 2017). In addition, the SASP of senescent hepatic cells not only attracts macrophages (Irvine et al. 2014) but also influences the M1/M2 polarization state of macrophages (Lujambio et al. 2013). It is also interesting to note that SC themselves can also develop features of immune evasion. It was demonstrated that SC can escape the immune system by upregulating the expression of non-classical MHC molecule HLA-E, which inhibits NK cells and CD8+ T cells mediated immune responses against SC, thereby aiding in inefficient removal and accumulation of SC (Pereira et al. 2019). This potentially suggests autonomous functioning of SC, much in line with tumorous cells, and requires further exploration.

Macrophage senescence: a culmination of immunosenescence and cellular senescence?

The immune system reacts to exogenous and endogenous threats by initiating an inflammatory response. Macrophages are involved both during the onset of inflammation as well as its successful resolution. The recognition of a foreign particle prompts proinflammatory behavior in macrophages (also called classical activation or M1) characterized by increased production of inflammatory cytokines, respiratory burst, and phagocytosis (Orecchioni et al. 2019). To resolve the latent inflammation and debris, macrophages switch to an anti-inflammatory M2 phenotype by initiating reconstruction of damaged tissue and by prompting synthesis of extracellular matrix and cell growth (Rőszer 2015). As antigen-presenting cells, macrophages are involved in the regulation and differentiation of adaptive immune responses, while scavenger receptors on macrophages recognize and remove oxidized proteins/lipoproteins expressing damaged or apoptotic cells (Krieger and Herz 1994; Schliehe et al. 2011). These diverse functions of macrophages are severely hampered with age and are often attributed to the characteristic process of immunosenescence. For instance, it is known that M1/M2 polarization of macrophages is affected during aging, although the nature of this skewness is debatable. Age-dependent M1 to M2 polarization of macrophages has been observed in aging skeletal muscles (Cui et al. 2019) and during macular degeneration (Zandi et al. 2015), while we previously observed an anti-inflammatory phenotype in aged animals (Sharma et al. 2014). On the other hand, an age-dependent shift towards M1 pro-inflammatory state was also observed in aged mice which were ascribed to the degeneration of the enteric nervous system (Becker et al. 2018). These observed differences could be attributed to the heterogeneity and plasticity of macrophages, but regardless, any perturbations in the normal M1/M2 balance in macrophages may dysregulate the development of the host response, making the elderly more susceptible to inflammatory and infectious diseases (Mahbub et al. 2012; Wynn et al. 2013). Studies in experimental animals have also shown that macrophage phagocytic ability and respiratory burst (Linehan et al. 2014; Wong et al. 2017), TLR expression (Renshaw et al. 2002), response to antigenic stimulation (Ding et al. 1994), and LPS-induced cytokine production decline with age (Chelvarajan et al. 2006). Importantly, it was identified that an age-related decrease in phagocytic ability was not observed in bone marrow-derived macrophages and monocytes suggesting that age-associated changes in macrophage functions might not be cell-intrinsic, but could be related to external environmental factors (Linehan et al. 2014). Aging also results in a decreased antigen-presenting capacity of macrophages which may compromise the swiftness and the potency of the adaptive immune response. It has been observed that old mice exhibit impaired stimulation as well as expression of MHC class II molecules compared to macrophages isolated from young mice after stimulation with IFN-γ (Davila et al. 1990; Herrero et al. 2001). Aging has also been shown to reduce macrophage-mediated tissue repair and regeneration both in mice and humans. Danon et al. (1989) reported that local injection of peritoneal macrophages isolated from young mice could accelerate would healing in older animals. Age-related shifts in macrophage infiltration into wounds, alterations in chemokine content, and a concurrent decline in macrophage phagocytic function was also documented which may contribute to the delayed injury repair response during aging (Swift et al. 2001). A recent study showed that injured

arteries in aging rats develop thicker neointimas, which were significantly correlated with a higher number of tissue macrophages and increased vascular IL-18 (Rodriguez-Menocal et al. 2014). Further, in vivo depletion of macrophages by clodronate liposomes ameliorated the vascular accumulation of IL-18 and the development of thicker neointimas (Rodriguez-Menocal et al. 2014).

Unlike immunosenescence, conclusive evidence of cellular senescence in macrophages is only beginning to be elucidated. Prior studies in T cells have shown that immune cells *do* exhibit the features of cellular senescence both in vitro and in vivo, while such work on macrophages remained scanty (Vallejo et al. 1999; Effros 2004; Chou and Effros 2013; Pawelec and Barnett 2016; Covre et al. 2020). However, using mice deficient in DNA repair protein *Ercc1*, a recent report has demonstrated that various immune cell populations, including the myeloid cells lineage, undergo characteristic features of cellular senescence such as increased expression of $p16^{Inka4a}$, $p21^{CIP1}$, and SASP which ultimately contribute to enhanced accumulation of SC in various murine tissues (Yousefzadeh et al. 2021). Previously, in vitro studies have shown that on exposure to external stressors, macrophages can develop senescence-like features including p21/p53 mediated cell cycle arrest (Fong et al. 2007; Nyunoya et al. 2003), altered morphology, and the development of SA-β-gal activity (Kim et al. 2015). Recently, we observed that peritoneal macrophages isolated from old mice exhibit heterogenous and elongated morphology, enhanced expression of cell cycle inhibitors $p53/p21^{WAF1}/p16^{Ink4a}$, and SA-β-gal activity as compared to macrophages isolated from younger animals (Kumar et al. 2020). In another study, an age-related increase in the characteristic marker of senescence $p16^{Ink4a}$ inhibited the normal phenotype of adipose tissue macrophages and contributed to type II diabetes risk (Fuentes et al. 2011). A negative correlation between Ki67 proliferation marker and cellular senescence marker SA-β-gal expression was observed in cultured macrophages suggesting that SA-β-gal activity labels macrophages with decreasing proliferation tendency (Holt and Grainger 2012). Another report noted that the majority of $p16^{Ink4a}$ and SA-β-gal positive cells in the tissues of aging mice were, in fact, macrophages, indicating a significant role of senescent macrophages which previously had been attributed to non-immune SC only (Hall et al. 2016). However, in their follow-up work, the same authors argued that $p16^{Ink4a}$ and SA-β-gal expression in macrophages could be unrelated to senescence, and may only be a part of a reversible response of macrophages to their physiological stimuli (Hall et al. 2017). These observations suggest an unexpected role of $p16^{Ink4a}$ expression in macrophages which warrants deeper characterization vis-à-vis other markers of cellular senescence. Notwithstanding this, another hallmark indicator of cellular senescence, i.e., telomere attrition, has also been observed in macrophages both during aging and disease. Analyses of bone marrow-derived macrophages showed strong age-dependent shortening of telomere length in aged (19–24-months-old) mice as compared to young (6-week-old) mice (Sebastián et al. 2009). Murine peritoneal macrophages isolated from first-generation telomerase reverse transcriptase-deficient mice significantly upregulated SA-β-gal activity and the expression of genes regulating cell cycle arrest such as p16, p21, and the retinoblastoma protein (Gizard et al. 2011). Mean telomere length in peripheral blood leukocytes was significantly shorter in sickle cell disease patients which directly correlated with the disease genotype and inflammation markers (Colella et al. 2017). Some studies have suggested that a characteristic SASP is also prevalent in senescent macrophages. A recent report has shown that LPS treated THP-1 macrophages develop features of cellular senescence and SASP as evident by expression of p53/p21/p16 cell cycle inhibitors and various SASP components (Wang et al. 2020). Using a diabetic mice model, it was observed that macrophages in diabetic kidneys showed archetypal features of cellular senescence as evident from increased mRNA expression pertaining to cell cycle arrest (p16/p21) and SASP (IL-6, TGF-β, PAI-1, MCP-1) suggesting that senescent macrophages are prevalent in vivo and could be a potential source of SASP in disease condition (Prattichizzo et al. 2018). Taken together, it is reasonable to envisage that both cellular senescence and immunosenescence can impact the different aspects of macrophage aging. However, either a conclusive correlation or a causative linkage between cellular senescence and immunosenescence in macrophages or other immune cells has not been established yet. Nonetheless, studies on telomere shortening have highlighted multiple negative effects on immune functions which could be related to some aspects of immunosenescence. For

example, telomerase knockout mice developed exaggerated lung inflammation and increased mortality upon respiratory staphylococcal infection (Kang et al. 2018). Authors observed that telomere dysfunction caused macrophage mitochondrial abnormality, oxidative stress, and hyperactivation of the NLRP3 inflammasome, suggesting that loss of telomeres is sufficient to drive mitochondria-mediated redox imbalance, and thus contribute to macrophage functional incapacity which could be directly related to immunosenescence (Kang et al. 2018). Similarly, using telomerase knockout mice, it was observed that telomere loss is the cause for the enhanced oxidative stress, reduced Stat5a oxidation and phosphorylation, and, ultimately, for the impaired GM-CSF-dependent macrophage proliferation (Sebastián et al. 2009). It was also demonstrated that monocytes (but not lymphocytes) of aged type II diabetic patients had significantly lower mean telomere length and a significant inverse relationship between oxidative DNA damage and telomere length was observed in the diabetic group (Sampson et al. 2006). Another study showed a causative link between accumulating ROS and the development of senescent phenotype in macrophages (Singh et al. 2019). Thus, there appears to be a certain degree of causation between cellular senescence and immunosenescence, although, the data available are largely sporadic and preliminary in nature thereby necessitating further deeper and specific studies to completely understand the dichotomy of cellular senescence and immunosenescence in macrophage aging.

Interactions between macrophages and senescent cells

Macrophages are present throughout the body, wherein they reside as specialized tissue-resident cells and perform tissue-specific and niche-specific functions. As a result, different tissue-resident macrophages may be functionally distinct and respond differentially to effector functions (Minutti et al. 2017; Lacerda Mariano et al. 2020). Moreover, in terms of cellular senescence, recent studies have demonstrated that different aging tissues experience varying degrees of SC burden as the rate of cellular senescence is dependent on both the age as well as the type of tissue (Karin et al. 2019; Tuttle et al. 2020; Sharma et al. 2021). Thus, it is conceivable that dynamic interactions between specialized long-lived macrophages and different host tissues with varying degrees of cellular senescence, may differentially influence their functional capacity and/or the rate of cellular senescence (Fig. 2). Although these aspects are less explored, our previous *ex vivo* study showed that the secretory phenotype of senescent preadipocytes, but not proliferating preadipocytes, could induce a senescence-like phenotype in peritoneal macrophages isolated from young animals (but not from old animals) characterized by a strong SA-β-gal activity, cellular hypertrophy, increase in $p16^{Ink4a}$ expression and intracellular ROS production (Kumar et al. 2020). This implies that in a heterogeneous and dynamic in vivo system, the highly senescence-prone adipose tissue (Minamino et al. 2009; Sharma et al. 2021) could directly influence cellular senescence in adipose tissue macrophages. A recent study demonstrated that macrophages induced apoptosis in senescent fibroblasts and prevented their accumulation, however, chronic presence of fibroblast SASP factors downregulated macrophage-mediated apoptosis and phagocytosis thereby potentially suggesting that senescent tissues can directly affect macrophage functions which can contribute to increased tissue SC burden (Ogata et al. 2021). Similarly, another report identified that lysophosphatidylcholines expression is elevated in the phospholipids of senescent dermal fibroblasts which interfere with the toll-like receptor 2 and 6/CD36 signaling and subsequent phagocytic capacity in macrophages (Narzt et al. 2021). Exposure of macrophages to the secretome of senescent hepatocytes induced an M2 phenotype, while an M1 phenotype was observed in macrophages exposed to secretory factors of non-senescent hepatocytes (Sen et al. 2021). Similarly, exposure of macrophages to the conditioned media of senescent thyrocytes induced an anti-inflammatory M2 phenotype in macrophages showing high CD206 and low MHC II markers and upregulated CCL17 secretion which ultimately promoted tumor progression (Mazzoni et al. 2019).

In addition, a tantalizing interrelationship between myeloid-derived suppressor cells (MDSC), macrophage functions, and cellular senescence is also emerging in aging and disease (Ostrand-Rosenberg et al. 2012; Fulop et al. 2016; Salminen et al. 2018a, b).

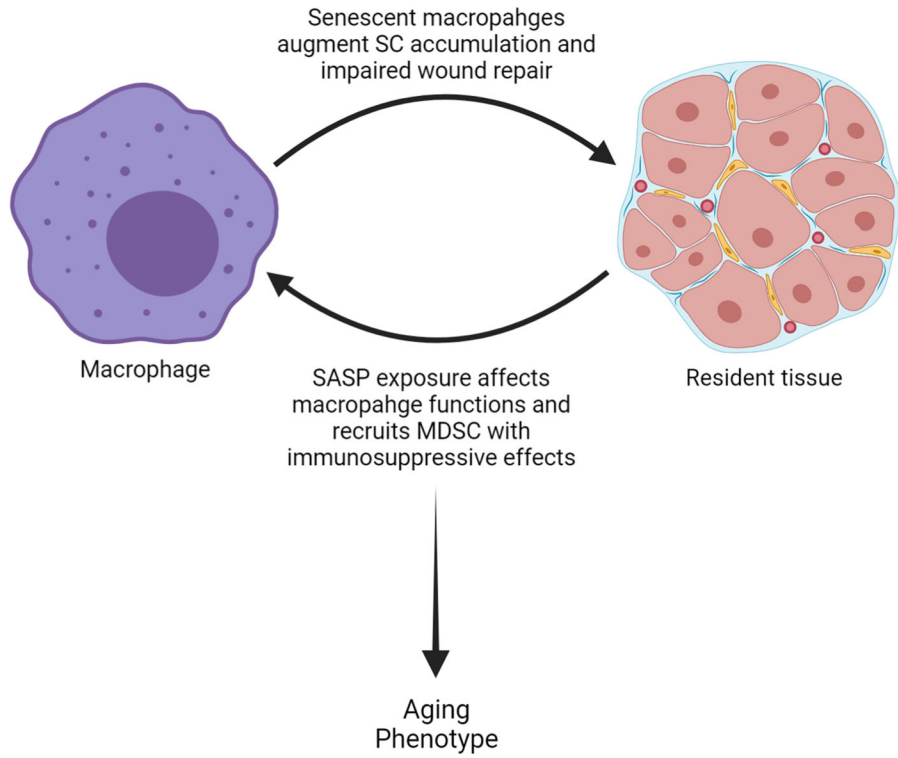

Fig. 2 Bidirectional relationship between resident macrophages and tissues. Dynamic interactions between senescent host tissues and long-lived tissue resident macrophages may impact senescence and aging. SASP of host tissues can augment the recruitment of MDSC, modulate macrophage functions and decrease their potency to remove damaged cells. In turn, senescent macrophages can directly augment SC accumulation owing to impaired immunosurveillance

MDSC are a heterogeneous group of myeloid cells that originate from hematopoietic stem cells and perform immunosuppressive functions in the resolution of inflammation (Veglia et al. 2018). These cells are highly plastic and can also differentiate into mature myeloid cells such as macrophages and dendritic cells (Veglia et al. 2018). Since MDSC respond to inflammation, the chronic presence of a systemic and sterile inflammatory stimulus during aging (inflamm-aging) as well in other pathological conditions such as obesity, and hepatic steatosis can enhance the recruitment and proliferation of MDSC to affected tissues wherein they exert immunosuppressive effects on the innate and adaptive immune systems (Salminen et al. 2018a). This state is harmful as the prolonged existence of MDSC in tissues can not only disturb tissue homeostasis by impairing macrophage-mediated clearance of cell debris and tissue repair during injury (Veglia et al. 2018; Duong et al. 2021), but can also augment suppressive activity in macrophages (Ostrand-Rosenberg et al. 2012). It has been demonstrated that the numbers of MDSC increase in aged animal and human tissues, presumably due to persistent inflamm-aging, which results in enhanced T-cell suppression and thus compromised immunological state during aging (Enioutina et al. 2011; Verschoor et al. 2013; Flores et al. 2017). Further, the role of SASP factors secreted by senescent tissues in recruiting and augmenting the proliferation and activation of MDSC has also been envisaged (Salminen et al. 2018a). It was demonstrated that senescent stromal cells alone are sufficient to drive the localized increase in numbers of MDSC as well as their CD8 T cell inhibitory activity which was ultimately attributed to the SASP secretome of SC (Ruhland et al. 2016). Together, it is reasonable to assert that mutual dynamic interactions between SC and resident myeloid cells (including both macrophages and MDSC) can significantly shape the functional and phenotypical aspects of aging in these cells.

Immunometabolism and macrophage senescence

Understanding the metabolic regulation of immune functions, especially during aging, is an emerging area of research (Lee et al. 2021). To precisely perform their diverse functions, immune cells like

macrophages need to quickly shift between various activation states which are subject to tight regulation by metabolic pathways and nutrient availability. For instance, upon activation, M1-like macrophages rapidly convert arginine to nitric oxide through inducible NO synthase activity, while M2 macrophages convert arginine to ornithine for effector functions (Galván-Peña and O'Neill 2014). Several studies suggest that nutrient signaling longevity pathways, such as mTOR, SIRT, and Insulin/IGF-1 are the key modulators and therapeutic targets of health and lifespan (Mazucanti et al. 2015). Aged macrophages generally show heightened inflammatory metabolic pathways, despite reduced phagocytic ability, antigen presentation, and mitochondrial dysfunction (van Beek et al. 2019; Lee et al. 2021). Using a mass spectrometry-based proteomic approach, age-dependent alterations in inflammatory signaling, mitochondrial function, and cellular metabolic pathways were observed in aged microglia cells, while a component of the mTORC2 complex was identified as a novel upstream regulator of several biological functions (Flowers et al. 2017). Rapamycin-induced inhibition of mTOR signaling accelerated diabetic encephalopathy in rats through the augmentation of macrophage autophagy (Wang et al. 2018). Knockdown of SIRT1 in the mouse macrophage RAW264.7 cell line and in intraperitoneal macrophages broadly activated the JNK and IKK inflammatory pathways, and increased LPS-stimulated TNFα secretion (Yoshizaki et al. 2010). On the other hand, overexpression of SIRT1 during bone marrow-derived macrophage differentiation increased their proliferative capacity and self-renewal (Imperatore et al. 2017). Sirtuin family of enzymes depend on the coenzyme NAD^+ for their activation and function. NAD^+ levels decline with age in different tissue types, including macrophages, which have been shown to increase inflammation and impair oxidative metabolism (Minhas et al. 2019). It is plausible that declining NAD^+ levels in aged macrophages could also compromise SIRT activity that may negatively impact inflammatory homeostasis during aging (He et al. 2020). Interestingly, senescent macrophages have recently been implicated in the immunometabolism of NAD^+ (Covarrubias et al. 2020). It was observed that NAD^+ consuming CD38 + M1 macrophages with upregulated markers of senescence (p16/p21) and inflammation accumulated in adipose tissue which was primarily responsible for decreased NAD^+ availability in tissues during aging, suggesting a causative relationship between CD38+ macrophages, NAD^+ consumption, Sirtuins and aging (Covarrubias et al. 2020). In addition, M2 phenotype macrophages were identified as novel sources of IGF1, and ablation of IGF1 receptors from myeloid cells reduced phagocytosis, increased macrophages in adipose tissue, elevated adiposity, lowered energy expenditure, and led to insulin resistance in mice fed a high-fat diet indicating that IGF1 signaling shapes the macrophage-activation phenotype (Spadaro et al. 2017). A recent study showed the regulatory role of IGF1 signaling in cellular senescence and macrophage polarization wherein mice deficient for IGF1 receptors showed attenuated premature senescence in pneumocytes, reduced M2 macrophage polarization, and lung fibrosis (Chung et al. 2020). Together, it is evident that understanding the metabolic control of cellular senescence mediated by nutrient-sensing pathways is essential for completely comprehending the etiology and effects of macrophage senescence.

Unanswered questions and niche research areas

There are several lacunae in our present understanding of the causes and biological effects of cellular senescence in macrophages. This is of particular importance since tissue-resident macrophages, similar to memory T cells, are considered to be long-lived (Bain et al. 2016), and are thus liable to accumulate cellular and biochemical insults over time leading to genotoxic stress and the development of cellular senescence (Sedelnikova et al. 2004). Some of the key aspects to be investigated are (Fig. 3).

- The extent and depth of in vivo cellular senescence in macrophages are unclear. This is especially significant since the presence and relevance of some of the established markers of cellular senescence, such as $p16^{Ink4a}$ expression and SA-β-gal activity, in macrophages, have been inconsistent and contentious. There is thus an urgent need to profile macrophages for age-dependent as well as tissue-dependent changes pertaining to the development of cellular senescence using the established markers of immune cell senescence (Zhou

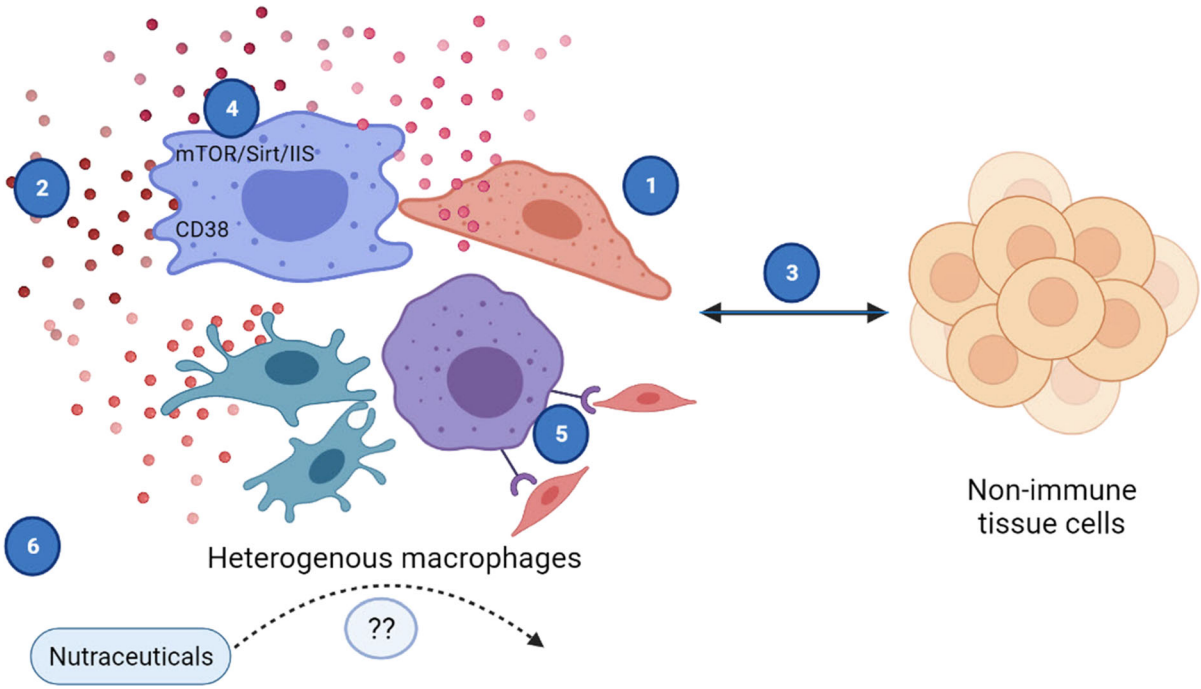

Fig. 3 Schematic illustration of outstanding questions and experimental opportunities in understanding the causes and effects of cellular senescence in macrophages. 1 Characterization and profiling of in vivo cellular senescence in different types of tissue resident macrophages is lacking. 2 Whether the SASP of senescent macrophages is different or similar to the SASP of non-immune cells is not known. 3 The extent and effect of interactions between macrophages and host tissues with age is unclear. 4 Immunometabolism in the context of longevity pathways in senescent macrophages is least explored. 5 Mechanism(s) and age-related changes in macrophage immunosurveillance are incompletely understood. 6 Whether and how nutraceuticals affect cellular senescence in macrophages in vivo is not known

et al. 2021). Given the high heterogeneity amongst macrophages, using multi-omics approach at single-cell resolution would be a prudent approach.

- Macrophage secretory phenotype changes with age, but whether it is related to the SASP of non-immune cells, or if senescent macrophage secretome contributes to inflamm-aging remains to be fully understood. In this context, whether senescent macrophages play any direct role in driving age-related inflammatory disorders such as type II diabetes or osteoarthritis is also unknown.
- More information is required to understand the interrelationship between tissue-resident macrophages and SC. How SC or their secretome influence immunosenescence and/or cellular senescence in macrophages in vivo, and whether senescent macrophages can also impact the development of senescence in non-immune cells remains to be explored.
- Immunometabolism of senescent macrophages is also poorly studied. Whether the longevity pathways play a similar role in macrophage senescence, and if these pathways could be therapeutic targets regulating macrophage functions during aging and disease remains to be elucidated.
- Much information about the mechanisms and ligands of macrophage-mediated immunosurveillance is not known. It needs to be determined whether senescent macrophages preserve their capacity of immunosurveillance which can directly impact tissue SC accumulation.
- Finally, nutraceuticals such as probiotics and polyphenols, as well as micronutrients are known to affect immunosenescence (Sharma et al. 2013; Wu et al. 2019) (Fig. 4), but whether the underlying mechanisms are relatable to cellular senescence is little understood (Sharma and Padwad 2020). In this regard, our previous work showed that green tea catechin EGCG can strongly

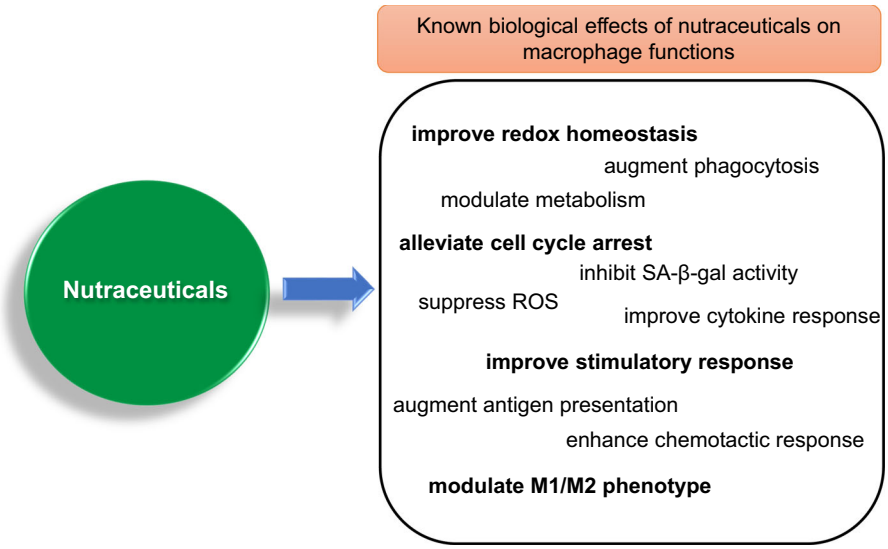

Fig. 4 Multifaceted effects of nutraceuticals in modulating different aspects of cellular senescence and immunosenescence

attenuate the development of senescence-like features such as expression of p53/p21^{WAF1}/p16^{Ink4a}, and SA-β-gal activity in macrophages exposed to conditioned media of senescent preadipocytes (Kumar et al. 2020). This suggests that nutraceuticals can impact senescence induction in macrophages, although further elaborative studies are warranted.

Concluding remarks

Aging, cellular senescence, and immunosenescence appear to be intimately linked (Sharma and Padwad 2020). As most diverse and plastic immune cells, delineating the dichotomy of cellular senescence and immunosenescence in macrophages is necessary for comprehending the relationship between aging and immune functions. Evidence that cellular senescence is an active force driving the aging of macrophages and which may contribute to age-related pathologies is already emerging. In addition, it is very much plausible that senescent non-immune cells can significantly impair macrophage immune functions through paracrine effects, recruitment of MDSC, and augmentation of SC burden. This suggests an intricate relationship between host tissues and macrophages vis-à-vis cellular senescence which promises exciting research opportunities. In short, future studies must consider macrophages in the purview of cellular senescence which may ultimately provide an integrative and deeper understanding of organismal aging and the pathology of age-dependent diseases.

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