



Emerging cellular senescence-centric understanding of immunological aging and its potential modulation through dietary bioactive components

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Abstract Immunological aging is strongly associated with the observable deleterious effects of human aging. Our understanding of the causes, effects, and therapeutics of aging immune cells has long been considered within the sole purview of immunosenescence. However, it is being progressively realized that immunosenescence may not be the only determinant of immunological aging. The cellular senescence-centric theory of aging proposes a more fundamental and specific role of immune cells in regulating senescent cell (SC) burden in aging tissues that has augmented the notion of senescence immunotherapy. Now, in addition, several emerging studies are suggesting that cellular senescence itself may be prevalent in aging immune cells, and that senescent immune cells exhibiting characteristic markers of cellular senescence, similar to non-leucocyte cells, could be among the

key drivers of various facets of physiological aging. The present review integrates the current knowledge related to immunosenescence and cellular senescence in immune cells per se, and aims at providing a cohesive overview of these two phenomena and their significance in immunity and aging. We present evidence and rationalize that understanding the extent and impact of cellular senescence in immune cells vis-à-vis immunosenescence is necessary for truly comprehending the notion of an ‘aged immune cell’. In addition, we also discuss the emerging significance of dietary factors such as phytochemicals, probiotic bacteria, fatty acids, and micronutrients as possible modulators of immunosenescence and cellular senescence. Evidence and opportunities related to nutritional bioactive components and immunological aging have been deliberated to augment potential nutrition-oriented immunotherapy during aging.

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Introduction

The mammalian immune system has evolved not only as a central instrument to protect against the invading pathogens, but is also essential for tissue repair and regeneration (Ding et al. 2019), as well as identification and removal of damaged host cells (Rock et al. 2011). The diverse cells of the immune system along

with its allied components such as the complement proteins, are present throughout the body and are critical to preserving the parenchymal tissue homeostasis. The immune system is also one of the major regulatory systems to be affected by the deleterious process of aging, and age-related immune dysfunctions are often associated with increased risk of diseases and weakened vaccine response in the elderly (Allen et al. 2020; Pereira et al. 2019). Understanding the development and progression of immunological aging is thus central to our mitigatory strategies against a variety of age-dependent disorders and infectious diseases as also aptly highlighted by the ongoing COVID-19 pandemic (Bartleson et al. 2021). Immunosenescence is an umbrella term that refers to a myriad of age-dependent qualitative and quantitative changes in the immune system such as shrinkage in the thymus gland output, decreased cell-mediated and humoral immune responses, development of chronic systemic inflammation (inflamm-aging), changes in T cell subset population, and loss of T cell differentiation which are together accounted for increased risk of morbidity and mortality in the elderly (Barnes 2015; Fulop et al. 2018; Goronzy and Weyand 2017; Sadighi Akha 2018; Xu et al. 2020). Considering these multifaceted deleterious effects, an immune system-oriented theory of aging was initially formulated which postulated that aging in organisms is pathologically linked to the impaired immune functions (immunosenescence), and that the loss of self and non-self recognition in immune cells due to immunogenetic diversification leads to the development of age-dependent auto-immune disorders and inflammation (Walford 1964). The original immunosenescence theory was then further integrated with perturbed age-associated cellular oxidative and inflammatory homeostasis, and an updated oxi-inflamm-aging theory of aging was proposed (De la Fuente and Miquel 2009). Recent advances in our understanding of the molecular basis of aging are now revealing even novel role(s) of the immune system in impacting aging. This is specifically aligned with the process of ‘cellular senescence’ that is rapidly emerging as the central and arguably the fundamental process governing both aging and age-related diseases (Borghesan et al. 2020; Gil 2019; McHugh and Gil 2018). The critical significance of the immune system in regulating senescent cells (SC) survival and accumulation has gained a particular attention, and cellular senescence-associated

immunotherapy is emerging as a desirable approach for targeting aging (Burton and Stolzing 2018; Kale et al. 2020).

The different facets of the immune system including its development, maturation, and activation are tightly regulated. However, dietary nutritional components including bioactive phytochemicals and probiotic microorganisms can strongly influence multiple aspects of the immune system. Studies have demonstrated that modulation of the immune functions by dietary factors can favorably influence the proliferation, activation, and efficacy of the immune system (Barrea et al. 2021; Childs et al. 2019; Tourkochristou et al. 2021). In particular, the role of food components in modulating the immune response for the mitigation of infectious agents including COVID-19 (Mriyunjaya et al. 2020; Tomas et al. 2022), food-borne contaminants (Pan et al. 2020), inflammatory disorders (Sung et al. 2018), and cancer immunotherapy (Soldati et al. 2018; Spencer et al. 2021) have been documented. Considering this and given the fact that immunological aging essentially involves impaired effector immune functions; the application of dietary factors in alleviating at least some of these deleterious aspects seems plausible. This is also reasonable since nutrition and exercise are currently at the forefront of developing anti-aging therapies and in fact, a novel discipline called ‘nutrigerontology’ was emphasized for achieving successful ageing and longevity (Aiello et al. 2016; Verburgh 2015). Therefore, in the present paper, we first discuss the emerging advances in our understanding of immunological aging in terms of immunosenescence and cellular senescence, and then deliberate the available evidence of nutritional and bioactive dietary factors-mediated modulation of immunity and aging. Future research directions and lacunae have been discussed aimed to truly understand immunological aging as well as the potential of diet in impacting immunity, aging, and diseases.

Immunosenescence and immunological aging

Immunosenescence refers to widespread age-dependent changes in the immune system including the lymphoid organs that ultimately manifest as impaired immune responses in the elderly. Despite its name, immunosenescence does not explicitly imply decreased or attenuated immune functions, but is rather best defined as immune-remodeling wherein

certain cellular functions may decline while others may be exaggerated (Xu et al. 2020). Moreover, the one-dimensional detrimental consideration of immunosenescence has recently been challenged, and it is argued that immunosenescence actually represents a continuum of adaptation and maladaptation to lifelong aggressions and insults which ultimately defines the course of organismal aging and health (Fulop et al. 2020). This also provides a rationale as to why healthy centenarians (≥ 100 years age) are able to preserve essential immune functions and are less prone to chronic age-related pathologies (Santoro et al. 2021). Regardless, modulation of the different aspects of immunosenescence has traditionally been considered a viable strategy for improving the quality of life in elderly (Borgoni et al. 2021; Stahl and Brown 2015; Weyand and Goronzy 2016). Although the exact underlying causes of immunosenescence are still not completely understood, the concept of immunosenescence has vastly contributed to our present knowledge of aging in both innate and adaptive immune functions, and are briefly discussed below (Table 1).

Innate immune system

Neutrophils are amongst the first innate immune cells to respond to growing infectious agents and inflammation. These short-lived cells are produced in vast numbers by the bone marrow, and studies have shown that circulatory neutrophil numbers in the blood or bone marrow precursors do not decline with age suggesting minimal quantitative impact on hemopoiesis

(Butcher et al. 2000; Chatta et al. 1993). However, deterioration of several functional aspects of neutrophils has been documented. We and others have reported that neutrophils exhibit impaired chemotaxis, reduced respiratory oxidative burst, and phagocytic potential with age in both experimental animals and humans (Brubaker et al. 2013; Mege et al. 1988; Perskin and Cronstein 1992; Sapey et al. 2014; Sharma et al. 2014b; Wenisch et al. 2000). Changes in neutrophil receptors and intracellular signaling have also been observed which may explain some of the apparent age-associated functional defects in neutrophils (Fülöp et al. 1984, 1985; Gasparoto et al. 2021; Sapey et al. 2014). Monocytes/macrophages are another critical component of the innate immune response. Several age-related changes have been documented in macrophages. It has been demonstrated that macrophages show reduced expression of toll-like receptors (TLRs) (Boehmer et al. 2005; Renshaw et al. 2002; Sharma et al. 2014b), decreased phagocytosis and respiratory burst (Linehan et al. 2014; Wong et al. 2017), altered cytokine production (Gomez et al. 2010; Roubenoff et al. 1998), diminished response to pathogen identification (Boehmer et al. 2004; Ding et al. 1994), impaired antigenic presentation (Větvicka et al. 1985), skewed M1/M2 macrophage polarization (Becker et al. 2018; Cui et al. 2019), and delayed resolution of inflammation and injury (Zhang et al. 2020a) suggesting multifaceted deleterious effects of age on macrophage functions.

Similarly, studies have shown a decrease in circulatory numbers of dendritic cells (DC), as well as functional deterioration in all DC subsets with age

Table 1 Major immunosenescence markers in the innate and adaptive immune cells

S. no.	Innate immune cells	Adaptive immune cells
1	Decreased identification and stimulation in response to pathogens (Boehmer et al. 2005; Loyer et al. 2022)	Reduced stimulatory response and effector functions (Haynes and Eaton 2005; Nikolich-Zugich 2014)
2	Changes in circulatory numbers (Jing et al. 2009; Gounder et al. 2018)	Decreased synaptic activity with APCs (Marko et al. 2007)
3	Impaired chemotaxis (Brubaker et al. 2013)	Characteristic changes in the expression of cell surface markers (Rodriguez et al. 2021; Zhang et al. 2021)
4	Attenuated antigenic presentation (Wong and Goldstein 2013)	Increased memory T cells pool and reduced diversity (Saule et al. 2006)
5	Impaired effector functions (Gomez et al. 2010; Sharma et al. 2014b; Zacca et al. 2015)	Reduced activation of B cells and conversion to plasma cells (Pritz et al. 2015)
6	Impaired resolution of inflammation (Zhang et al. 2020a)	Decreased antigen-specific antibodies production output (Maue and Haynes 2009)

(Della Bella et al. 2007; Gardner et al. 2017; Jing et al. 2009). There is strong evidence that DC lose their potency to accurately process and present antigens which may result in failure of the activation of immune cells and inadequate effector functions (Grolleau-Julius et al. 2008; Guo et al. 2014; Wong and Goldstein 2013; Zacca et al. 2015). Further, DCs have been shown to exhibit impaired cytokine production (Della Bella et al. 2007; Grolleau-Julius et al. 2006), decreased expression of co-stimulatory molecules such as CD86 and CD40 (Varas et al. 2003), and altered intracellular signaling in response to activation signals (Agrawal et al. 2007) which ultimately results in poor response to infections and vaccines in elderly. Contrary to other immune cells, studies have consistently demonstrated that peripheral NK cell numbers increase with age (Gounder et al. 2018; Le Garff-Tavernier et al. 2010). However, a parallel decline in the proliferative and cytolytic capacity of NK cells as well as a decrease in cytokine production and NK cell migration has also been reported which is often associated with increased incidences of viral infection in the elderly (Almeida-Oliveira et al. 2011; Fang et al. 2010; Gounder et al. 2018; Hazeldine et al. 2012; Mariani et al. 2002).

Unlike neutrophils, the role of remaining granulocytes, i.e., eosinophils and basophils during aging is less understood. It has been reported that eosinophil deregulation response to IL5 stimulation and superoxide production decreases with age in human subjects (Mathur et al. 2008). A recent study has shown that eosinophils are critical for maintaining the adipose tissue functions and inflammatory homeostasis during aging (Brigger et al. 2020). Regarding basophils, some studies have demonstrated that absolute basophil numbers decrease with age (Song et al. 1999; Valiathan et al. 2016), and there is also evidence that basophils accumulate with age in tissues (van Beek et al. 2018). Age-associated impaired Th2 response of basophils has also been reported which can predispose elderly to parasitic infections (Nel et al. 2011; Smith et al. 2001). It is interesting to note that in addition to adaptive immunity, innate immune cells are now also emerging to be associated with immunological memory (Bulut et al. 2021). This phenomenon has been dubbed as ‘trained immunity’ or ‘innate immune memory’ that can augment host innate immune response to secondary microbial infections mediated by the activation of pathogen recognition

receptors and epigenetic changes in the cells of the innate immune system (Netea et al. 2016; Sherwood et al. 2022). However, the impact of aging on innate immune memory as well as the role of innate immune memory in influencing recurring infections and vaccine response in the elderly is yet to be explored. Nonetheless, a recent clinical trial has reported that trained immunity can be effectively induced in the elderly on account of BCG vaccination which suggests novel methods and mechanisms of vaccine effects (Giamarellos-Bourboulis et al. 2020).

Adaptive immune system

Most of our knowledge regarding immunosenescence and aging is attributed to studies in the adaptive immune cells such as T and B cells and is covered in detail elsewhere (Goronzy and Weyand 2005; Minato et al. 2020; Zhang et al. 2021). Although the numbers of T cells generally remain constant over the lifespan, several characteristic compositional changes in T cell subsets with age have been documented. Typically, the proportion, activation, and differentiation of naïve T cells decline with age presumably due to thymus involution and loss of thymic output that strongly affects the peripheral T cell homeostasis. (Appay and Sauce 2014; Čičin-Šain et al. 2007; Goronzy and Weyand 2005; Lazuardi et al. 2005). However, it is important to consider that the effects of thymic involution are species-specific and are much more pronounced in experimental animals as compared to humans. This is likely attributed to homeostatic proliferation potential of peripheral T cells in humans that results in their self-renewal thereby compensating for loss of naïve T cells population due to gradual thymic involution (Goronzy and Weyand 2019; Thome et al. 2016). Memory T cells subsets remain constant through the adulthood but show a decline in numbers as well as functions with advancing age (Salam et al. 2013; Zhou and McElhaney 2011). Further, an age-dependent shift of naïve T cell subsets towards central memory T cells and effector memory T cells has also been observed (Saule et al. 2006). The cytolytic CD8 T cells show a clear age-associated numerical decline as well as compromised effector functions with age (Čičin-Šain et al. 2007; Nikolich-Žugich 2014), while the CD4 helper T cells also develop progressive changes in functions such as reduced stimulatory response (Haynes and Eaton

2005), impaired immunological synaptic activity with APCs (Marko et al. 2007), and attenuated B cell antibody response which decreases downstream antigen specific responses (Maue and Haynes 2009). In addition, aged T cells exhibit a distinct phenotype of cell surface markers often characterized by decreased expression of genes such as CD28 and CD154 while an increase in the expression of certain receptors such as CD57 and CD95 are also reported which are often considered hallmarks of immunosenescence in T cells (Rodriguez et al. 2021; Zhang et al. 2021). It is pertinent to note here that age-dependent changes in CD8 T cells effector functions can be compensated by the acquisition of innate like immune phenotype in these cells that express markers of both TCR and NK cell lineage (Pereira and Akbar 2016). These innate-like $\alpha\beta$ CD8+T cells likely represent a beneficial adaptation to gradual age-dependent loss of CD8 T cell numbers and activity, and therefore are significantly considered for understanding the 'restructuring' nature of immunosenescence.

Naturally occurring Tregs (CD4+CD25+Tregs+) appear to increase with age in humans (Bryl and Witkowski 2004; Gregg et al. 2005), and studies in mice revealed increased suppressive functions of Tregs during aging (Garg et al. 2014) with possible implications in age-dependent diseases (Deng et al. 2021). Similar to T cells, naïve B cells output has been shown to decline presumably due to age-related changes in the bone marrow (Colonna-Romano et al. 2009; Lin et al. 2016), and B cell diversity is also reported to decrease with age with a direct impact on health status (Gibson et al. 2009). Aged B cells exhibit compromised immune functions such as differentiation to plasma cells on antigenic challenge as well as a general decline in antigen-specific antibody production with age (Howard et al. 2006; Pritz et al. 2015). Collectively, these changes in B cells populations and their functional capacity result in diminished antibody production and poor vaccine response in the elderly which is also implicated in the COVID-19 pandemic (Collier et al. 2021).

Inflamm-aging

Although the acute inflammatory response against pathogens decreases with age, surprisingly, elderly also report higher levels of circulatory pro-inflammatory cytokines such as TNF- α and IL-6 (Myśliwska

et al. 1998, 1997), indicating the presence of a chronic, sterile, and low-grade systemic inflammation referred to as inflamm-aging (Ferrucci et al. 2005; Franceschi et al. 2000; Franceschi and Campisi 2014; Fulop et al. 2021). The increased levels of cytokines and chemotactic proteins during inflamm-aging are often associated with predisposition of the elderly to increased risk of inflammatory disorders such as arthritis and diabetes (Franceschi and Campisi 2014). In addition, inflamm-aging can have adverse effects on the immune response itself. For instance, increased serum TNF- α levels with age are negatively correlated with T cell functions (Parish et al. 2009), while age-related increase in IL-6 levels can suppress macrophage functions (Gomez et al. 2010). Thus, inflamm-aging impairs the acute phase response to pathogens while the chronic presence of inflammatory proteins augments systemic damage. The precise factors augmenting inflamm-aging are yet unclear, but are likely to be multifactorial and could be attributed to lifelong exposure to antigens (including latent viruses such as CMV), accumulation of SC and their inflammatory secretome, increased macromolecular damage and release of damage-associated molecular patterns (DAMPs) that chronically activate the innate immune cells (Garb-aging), pro-inflammatory micro-RNAs, age-related gut dysbiosis and leaky gut, as well as certain disorders such as adiposity (Santoro et al. 2021). Specifically, the double-stranded DNA (ds DNA) sensor cyclic-GMP-AMP synthase (cGAS) and the downstream stimulator of interferon genes (STING) pathways (cGAS/STING) is emerging as an important regulator and therapeutic target of sterile inflammation and its unwarranted effects (Decout et al. 2021; Huang et al. 2020). Cytosolic dsDNA is recognized as a universal DAMP that acts as a ligand to activate cGAS/STING pathway, and the stress-induced cytosolic leakage of mitochondrial DNA (mt DNA), including in immune cells such as macrophages, has been implicated in augmented inflamm-aging that contributes to immunosenescence (Atayik and Çakatay 2022b; Conte et al. 2020; Lv et al. 2022; Zhong et al. 2022). Accumulating evidence suggests that inflamm-aging is essentially an age-dependent remodeling of the immune response due to an imbalance between anti-inflammatory and pro-inflammatory networks. This adaptation of the immune system to proinflammatory environment due to a weakening of anti-inflammatory state is considered a driving

force of age-dependent morbidity (Fulop et al. 2016, 2017; Santoro et al. 2021). Thus, strategies decreasing the proinflammatory stimulus as well as those enhancing the anti-inflammatory cellular attributes are desirable for negating inflamm-aging and thus promoting healthy aging. As a result, characterization of inflamm-aging is an important parameter of potential anti-aging therapies and understanding disease pathology during aging. It is prudent to consider here that the significance of compromised functions of the immune system during aging in augmenting organismal risk of infections and delayed immune response appears contentious. On one hand, there is mounting evidence that age-dependent functional and phenotypic changes in immune cells can contribute to reduced vaccine response and increased risk of infections during aging (He et al. 2021; Loyer et al. 2022; Sabbatinelli et al. 2022; Simmons et al. 2022); on the other hand, there are also reports indicating that aspects of immunosenescence, such as inflamm-aging, could be positively correlated with increased vaccine immunogenicity in older adults (Picard et al. 2022). These conflicting observations corroborate the recent efforts of Pawelec et al. that highlighted the limitations and lacunae of the prevailing one-dimensional view of immunosenescence (Pawelec et al. 2020).

Cellular senescence and immunological aging

Unlike other aspects of organismal growth and development, aging is not considered to be programmed but is rather argued as a quasi-programmed phenomenon (Blagosklonny 2013) that also appears to be a classic case of antagonistic pleiotropy (Austad and Hoffman 2018). Organismal aging begins in cells themselves (biological aging) and represents a culmination of progressive increase in cellular and molecular damage owing to several intrinsic and extrinsic cellular stressors (DiLoreto and Murphy 2015; Gil del Valle 2011; Liguori et al. 2018). Hayflick and Moorhead reported the phenomenon of ‘cellular senescence’ which indicated that primary human cells are not immortal as previously thought, but rather have a finite replicative lifespan in vitro (Hayflick and Moorhead 1961). Identification of replicative senescence was a seminal discovery as it provided a hint of a direct correlation between cells and organismal aging. The recent decade has seen tremendous

improvements in our understanding of cellular senescence and its relevance to the causes and effects of aging (Di Micco et al. 2021). SC are characterized by increased expression of cell cycle inhibitors (p53/p16^{Ink4a}/p21^{WAF1}), activation of senescence-associated β -galactosidase activity (SA- β -gal), enlarged and heterogenous morphology, persistent stress, DNA damage, telomere attrition, chromatin remodeling, apoptotic resistance, and altered metabolic and energetic homeostasis (Ovadya and Krizhanovsky 2018; van Deursen 2014). Although SC develop naturally and their presence is considered essential for certain processes such as wound healing and even embryonic development; the role of *accumulating* tissue SC in augmenting the aging phenotype across vertebrate species is also becoming evident (Childs et al. 2015; Mylonas and O’Loghlen 2022). An increased SC burden in several aging tissues has been reported (Idda et al. 2020; Yousefzadeh et al. 2020) and further landmark studies also identified their causative role in promoting age and age-related pathologies (Aguayo-Mazzucato et al. 2019; Baker et al. 2016). SC accumulation in tissues is particularly deleterious due to the chronic presence of the senescence-associated secretory phenotype (SASP) which is a milieu of characteristic cytokines and growth factors that augments proinflammatory and pro-tumorigenic environment in healthy cells surrounding SC through paracrine effects (Birch and Gil 2020). As a result, cellular senescence appears to be a common denominator for a variety of human inflammatory diseases and it is argued that pathophysiologically distinct but age-dependent disorders should be considered within the purview of cellular senescence itself (Prašnikar et al. 2021). As the cellular senescence-centric view of aging is being rapidly acknowledged; novel therapies aimed at mitigating or selectively removing SC (through senolytics) are of considerable interest for lifespan extension despite their potential pitfalls and apprehensions (Dolgin 2020; Owens et al. 2021; Pils et al. 2021; Sharma 2021a; Thirumurugan 2022).

Although most of our understanding regarding immunity and aging is often associated with immunosenescence, yet, immunosenescence has often been criticized for the lack of universal biomarkers, its causal relationship with organismal aging, and its association with inflamm-aging (Pawelec et al. 2020; Xu et al. 2020). The past decade has seen rapid transformation in our understanding of

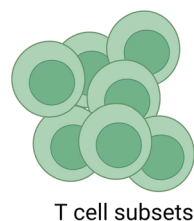
immunological aging, and as a result, previously unknown or less emphasized functions and phenomenon of the immune system that may impact aging have been discovered. In this regard, the role of immune system in the development and progression of cellular senescence in non-leucocyte cells as well as its impact on immune cells themselves is being greatly recognized (Budamagunta et al. 2021; Burton and Stolzing 2018; Sharma 2021b). It is becoming evident that immunosenescence may not be the only player in regulating immunological aging, and that cellular senescence in immune cells per se could be sufficient to drive organismal aging including immunosenescence (Yousefzadeh et al. 2021). Therefore, a mutual interrelationship between immunosenescence and cellular senescence can be envisaged and elucidating this association is critical for understanding immunological as well as organismal aging. At this point, it is also prudent to consider that although certain effects of cellular senescence and immunosenescence in immune cells may appear to overlap, yet the etiology of both these processes is fundamentally distinct (Burton and Stolzing 2018). Subsequent to the initial identification of cellular senescence in fibroblasts by Hayflick and Moorhead (Hayflick and Moorhead 1961), several other cell types were also reported to undergo cellular senescence in vitro. However, scientific interest in identifying cellular senescence in immune cells remained subdued until rather recently primarily due to the fact that T cells were initially observed to propagate indefinitely following an exposure to T cell growth factor (Gillis and Smith 1977). It was later discovered that similar to other cell types, replicative senescence in T cells can be induced by multiple rounds of antigenic stimulation which can also impair T cell effector functions

(Callender et al. 2018; Dunne et al. 2005; Spaulding et al. 1999). However, the extent and significance of cellular senescence in different immune cells as well as the role of senescent immune cells in promoting cellular senescence and accumulation of non-leucocyte SC is only beginning to be understood. Emerging studies are suggesting a more intricate, bidirectional, and dynamic role of cellular senescence in governing aging in both immune as well as in non-leucocyte cells. As a result, an emphasis on understanding the relationship between immunosenescence and cellular senescence, and its impact and relevance in the context of organismal aging, has been recently advocated (Budamagunta et al. 2021; Burton and Stolzing 2018).

Cellular senescence in immune cells: characteristics and impact

Although often overlooked, but similar to other cells, immune cells are also liable to undergo cellular senescence. This is especially relevant since we now understand that cellular senescence is not simply a feature of proliferative cells, but even post-mitotic tissues have prevalent senescence program (von Zglinicki et al. 2021). Although replicative senescence was earlier established in T cells, characterization of cellular senescence in various immune cells has largely remained in obscurity and incompletely understood. However, given the emerging significance of cellular senescence, recent studies have demonstrated that cellular senescence could indeed be more prevalent and significant in immune cells, especially in T cells (Fig. 1). For instance, it was reported that similar to other somatic cells, peripheral blood mononuclear cells (PBMCs) in humans strongly display classical

Fig. 1 Identified markers of replicative senescence in T cells



Known markers of cellular senescence in T cells

increased SA- β -gal activity
 enhanced p16 expression
 telomere attrition
 reduced telomerase levels
 development of SASP
 reduced proliferative response
 increased DNA damage response
 activated p38MAPK

markers of cellular senescence such as high SA- β -gal activity, p16^{Ink4a} overexpression, telomere dysfunction, and impaired proliferative response (Martínez-Zamudio et al. 2021). Interestingly, the authors noted that the senescent CD8+T cells population (including TEM and TEMRA subsets) developed unique SASP-associated gene expression profile as compared to senescent fibroblasts, and such T cells reached average levels of 64% in aging subjects thereby suggesting that T cell senescence substantially overlaps with replicative senescence in non-leucocyte cells and that such senescent T cells could be far more abundant in circulation than previously thought (Martínez-Zamudio et al. 2021). Another recent work demonstrated that the development of p16^{Ink4a} mediated cellular senescence and suppressed proliferative response is a characteristic of aging human T cells which could be a potential therapeutic target (Janelle et al. 2021). Similarly, a high percentage of CD4+ and CD8+T cells expressing SA- β -gal activity, increased transcripts of p21, p16^{Ink4a}, and inflammatory cytokines, as well as DNA damage were observed in aged human PBMCs as compared to the cells isolated from younger subjects (Dewald et al. 2020). Using a murine model of spontaneous genotoxic damage as well as natural aging, senescent peripheral blood lymphocytes were identified that were characterized by over 15 folds increase in p16^{Ink4a} and p21^{Cip1} mRNA expression suggesting prevalent cellular senescence (Yousefzadeh et al. 2020). Further, senescent CD8+T cells exhibited p38MAPK-dependent SASP-like features characterized by the secretion of proteases and cytokines similar to non-leucocyte senescent cells (Callender et al. 2018; Henson et al. 2014). Similarly, p16^{Ink4a} expression increased exponentially with chronological age in human peripheral blood T-lymphocytes suggesting the systemic presence of senescent T cells (Liu et al. 2009; Shen et al. 2020). Similar to other senescent cells, expression of telomerase reverse transcriptase gene declines in aging T cells which directly contributes to shortened telomeres and development of senescence features (Matthe et al. 2022; Röth et al. 2003). Flow cytometry analyses of T cell subsets in elderly population have revealed that among CD8+T-lymphocytes, CD28+CD57+T cells represented a subset with strong senescent features such as increased expression of p16^{Ink4a}, p21, Bcl-2, CD95, CD45RO, CCR5 and PD-1 (Onyema et al. 2015).

A positive relationship between increased circulatory senescent CD8+T cells and the development of Behçet's disease was also reported (Yang et al. 2018). Moreover, induction of T cell senescence has been observed to be a key mechanism governing the pathophysiology of human infectious agents including COVID-19 (Covre et al. 2018; De Biasi et al. 2020; Witkowski et al. 2022).

On the other hand, studies identifying senescent innate immune cells *in vivo* are limited. Few reports have assessed tissue-associated macrophages for the presence of cellular senescence but with controversial findings. It was observed that characteristic markers of cellular senescence such as increased p16^{Ink4a} expression, SA- β -gal activity, and activation of SASP are prevalent in aging macrophages (Hall et al. 2016; Kumar et al. 2020b; Liu et al. 2019; Praticchizzo et al. 2018; Wang et al. 2021). A recent study further reported that irradiated macrophages exhibited several features of senescence, including increased expression of p16^{Ink4a} and p21, SA- β -gal activity, SASP, and impaired efferocytosis *in vitro*, and when transferred to mice, they exacerbated inflammation *in vivo* (Sadhu et al. 2021). However, curiously, it was also revealed that the apparent senescent phenotype in macrophages might be a reversible phenomenon in response to physiological stimuli (Hall et al. 2017), while another study observed distinct differences between *in vitro* and *in vivo* aged microglia cells (Stojiljkovic et al. 2019). In addition to macrophages, NK cells have also been reported to show increased markers of age-dependent cellular senescence although such studies are limited (Dewald et al. 2020). It is also interesting to note that in addition to endogenous factors, immune cells, especially tissue resident cells such as macrophages and memory T cells, which persist in the microenvironment of non-leucocyte tissue cells, can be chronically exposed to the SASP of tissue SC that may undermine their functional activities and potentially contribute to premature immunosenescence and increased accumulation of SC (Fig. 2). For instance, it was observed that acute exposure to the SASP of senescent fibroblasts impaired the phagocytic ability of macrophages and ultimately accelerated the accumulation of SC in the dermis (Ogata et al. 2021). Similarly, peritoneal macrophages isolated from old mice exhibited significant characteristics of cellular senescence which were aggravated by *ex vivo* exposure to the SASP of

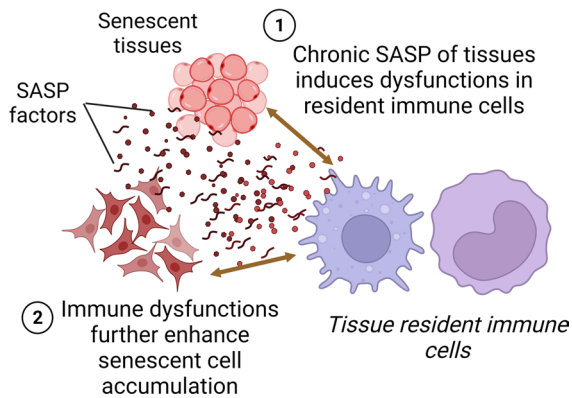


Fig. 2 Overview of interactions between tissue resident immune cells and senescent non-leucocyte cells with implications in immunological and systemic aging. (1) Chronic exposure to the SASP of nearby senescent cells can induce immunological dysfunctions in resident immune cells and (2) these changes can impair immune cells' ability of immunosurveillance and efferocytosis that may ultimately result in inefficient removal of senescent cells and thus augmentation of senescent cell burden

senescent preadipocyte cells (Kumar et al. 2020b). In vitro exposure to the SASP of hepatocytes induced migration of inflammatory macrophages (but not of non-inflammatory macrophages) that could contribute to a proinflammatory microenvironment (Irvine et al. 2014).

The immune system and tissue senescent cell burden

The relationship between immunity and cellular senescence appears to be bidirectional. While aging may augment levels of senescent immune cells, accumulation of various non-leucocyte SC in the body seems to be strongly regulated by immune cell functions. Several independent studies have demonstrated that SC secrete certain chemokines and cytokines that attract immune cells such as macrophages, NK cells, and CD8+T cells which then identify SC through upregulated SC-specific ligands such as MICA/B, ULBP1-6, and lysophosphatidylcholines (Antonangeli et al. 2016; Narzt et al. 2021) resulting in their targeted cytotoxicity. Thus, it is perceived that immune cells can identify and remove SC from the body thereby indicating their pivotal role in regulating tissue SC turnover with age. The exact causes for the apparent increase in SC numbers in the aging tissues is yet incompletely understood but it could

be attributed to either the increased development of SC in vivo or due to their decreased removal probably due to impaired immune functions with age. In a breakthrough study, it was demonstrated that if immune cells have defective cytotoxic properties, it results in higher SC burden in tissues, chronic inflammation, multiple age-related disorders, and ultimately decreased lifespan in experimental mice (Ovadya et al. 2018). This clearly indicated that defective immunosurveillance and effector immune functions (as observed during immunological aging) could be key mechanisms governing increased SC burden with age. In another significant study, it was demonstrated that mouse hematopoietic cells defective in DNA damage repair response resulted in induction of premature immunosenescence and cellular senescence in not only immune cells, but also in non-lymphoid cells thereby strongly indicating that senescence in immune cells is sufficient to drive systemic senescence (Yousefzadeh et al. 2021). Interestingly, transplantation of young immune cells significantly reduced systemic senescence suggesting that an aging immune system can be critical augmentor of SC development and accumulation (Yousefzadeh et al. 2021). Similarly, dysfunctional mitochondria in T cells were causatively related to premature systemic senescence and multimorbidity characterized by neurological, metabolic, muscular, and cardiovascular impairments, as well as inflamm-aging in mice (Desdin-Micó et al. 2020). Another emerging and interesting aspect of SC accumulation and immune cells is related to their immune evasive attributes. It was observed that senescent dermal fibroblasts exhibit heightened expression of non-classical MHC molecule HLA-E which inhibit immune responses against SC (Pereira et al. 2019). This study thus showed that similar to tumor cells, SC may develop strategies to circumvent the immune system thereby indicating that the relationship between immune cells and SC could be even more intricate. Further, whether and how the immune evasive attributes of SC could be facilitated by the presence of immunosenescence or cellular senescence in immune cells remains to be deciphered. Taken, together, these observations suggest that cellular senescence may be prevalent in immune cells (especially in adaptive immune cells), and although its significance is yet to be completely delineated, however, when coupled with immunosenescence, it can be envisaged that age-dependent

deregulation of the immune system could be a significant contributor to the systemic increase in tissue SC population (Fig. 3).

Dietary bioactive factors and immunological aging

In addition to essential functions for growth and development, dietary constituents can dynamically influence the immune system including its maturation and effector immune responses (Ponton et al. 2011; Saeed et al. 2016). The human immune system undergoes characteristic changes and maturation with different phases of life. For example, pregnancy is characterized by downregulation of cell mediated immune responses, while post-birth, exposure to food (including milk antigens), benign environmental factors, as well as colonization of commensal bacteria in the gut induces tolerance in the immune system resulting in overall immunological maturation and management of inflammation (Calder et al. 2006; Gil and Rueda 2002). Thus, nutritional exposure in early life is considered critical for immunological competence in later life against pathogens and the development

of immunological disorders. Similarly, modulation of the aging immune system through various dietary factors has also been observed that may have implications for improving the deleterious effects of immunological aging (Fig. 4).

Phytochemicals

Food-based phytochemicals are a major source of immunomodulators including immunostimulators and immunosuppressants (Behl et al. 2021). Phytochemicals describe a collection of various categories of plant metabolites such as polyphenols, alkaloids, carotenoids, carbohydrates, and lipids. These chemicals are abundant in fruits and vegetables, and in addition to immunomodulation, they have been recognized for various cell signaling modulatory and cytoprotective attributes (Pham et al. 2020). As such, the modulatory effects of phytochemicals on different aspects of organismal healthspan and lifespan have also been documented (Corrêa et al. 2018; Si and Liu 2014). In terms of immunological aging, several studies have shown that dietary polyphenols

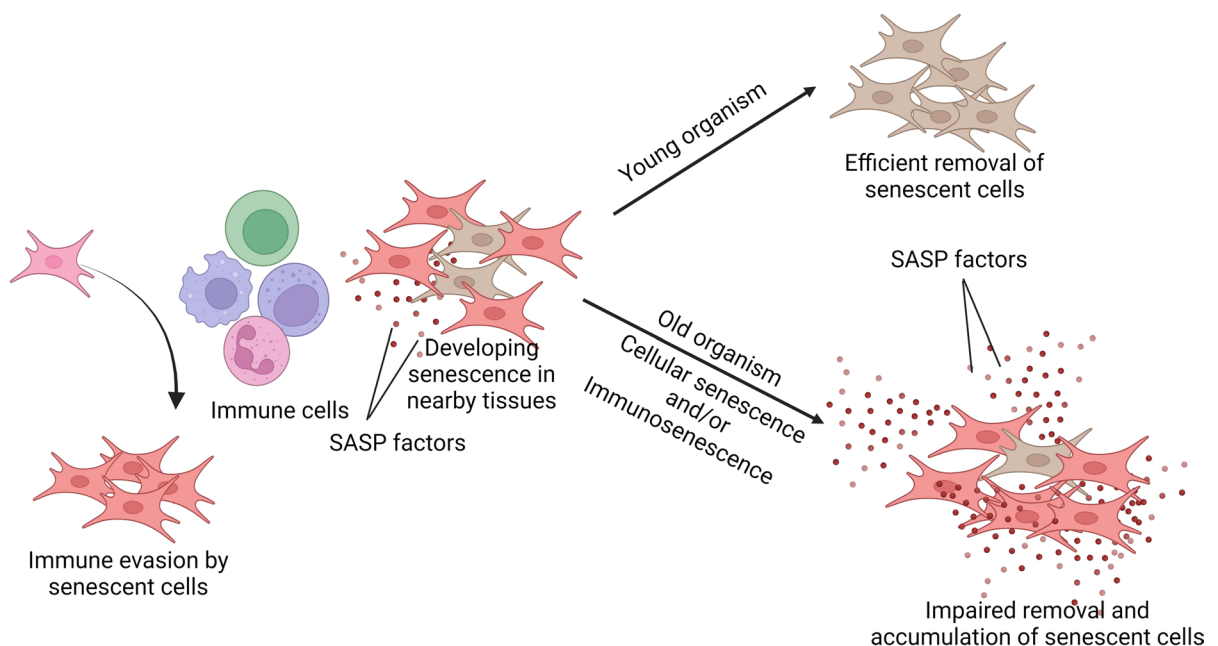
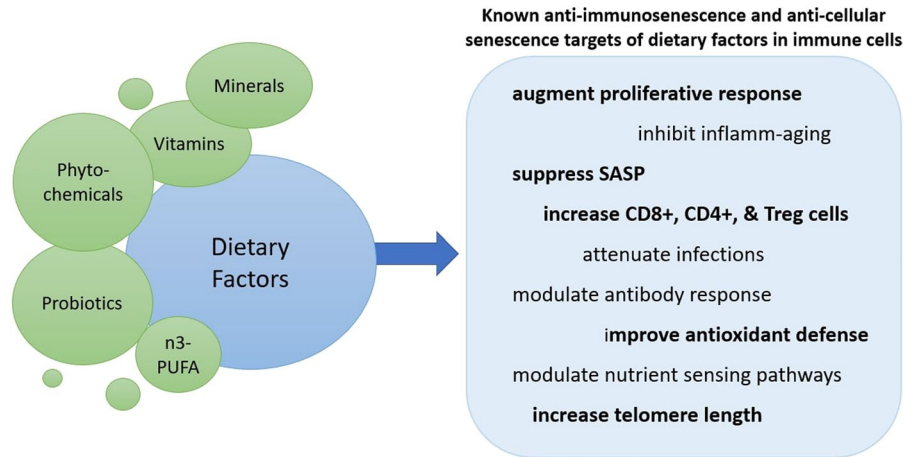


Fig. 3 Interrelationship between immune cells, cellular senescence, and aging. (1) In young organisms, SASP mediated activation of immune cells such as macrophages and NK cells identify and clear senescent cells efficiently. (2) However, in old organisms, due to cumulative effects of both cellular senescence and immunosenescence, immune cells lose the potency to manage senescent cell turnover that gradually decreases with age. (3) Inherent immune evasive attributes of senescent cells are also indicated that further highlight the complex interplay between immunity and senescent cells

cence and immunosenescence, immune cells lose the potency to manage senescent cell turnover that gradually decreases with age. (3) Inherent immune evasive attributes of senescent cells are also indicated that further highlight the complex interplay between immunity and senescent cells

Fig. 4 An overview of identified anti-cellular senescence and anti-immunosenescence effects of various dietary factors specific to immunological aging



can influence multiple facets of immunosenescence although their impact on cellular senescence in immune cells is little understood. For instance, we previously observed that ex vivo exposure to green tea catechin EGCG reversed SASP-induced markers of cellular senescence in murine macrophages including SA- β -gal activity, expression of cell cycle inhibitory genes, and oxi-inflammatory stress (Kumar et al. 2020b). In a further study, chronic consumption of green tea catechin EGCG influenced multiple markers of cellular senescence and immunosenescence in experimental mice (Sharma et al. 2022). Similarly, long term consumption of the phytochemical resveratrol in Sprague–Dawley rats improved neurocognitive performance through the downregulation of inflammatory and oxidative stress pathways in the innate immune system (Garrigue et al. 2021). Resveratrol consumption also attenuated surgery-induced cognitive impairment and hippocampal neuroinflammation in aged rats through the downregulation of hippocampal microglial activity (Locatelli et al. 2018). Dietary supplementation with polyphenol-rich plant extract enhanced the median lifespan of obese mice by improved lipid metabolism and restriction in activation and infiltration of tissue macrophages in the adipose tissue (Aires et al. 2019). Consumption of the polyphenol syringaresinol to middle-aged mice delayed markers of immunosenescence by enhancing the numbers of total CD3+ T cells and naïve T cells, enhanced humoral immunity against influenza vaccination to the level of young control mice, and also attenuated inflamm-aging (Cho et al. 2016). An increase in the number of cytotoxic T-lymphocyte

associated protein 4-positive cells and in the gene expression levels of CTLA-4, FoxP3, IL-10 and TGF- β was recorded after dietary supplementation with arachidin-1 and resveratrol in aged mice suggesting their role in successful aging of regulatory immune cells (Weng et al. 2016). Further, age-dependent stimulatory effects on T cell cytokine production were observed after in vitro exposure to the polyphenol-Oenothain B (Ramstead et al. 2015). Administration of Brazilian green propolis induced positive effects on innate and adaptive immune functions in aged mice characterized by enhanced phagocytosis and antibodies production (Gao et al. 2014). Consumption of Pu-erh tea extracts by senescence accelerated mice reversed elements of immunosenescence by significantly increasing the fractions of naïve T lymphocytes, CD8(+)/CD28(+) T lymphocytes and NK cells in the peripheral blood, and concomitant decrease in the levels of proinflammatory IL-6 (Zhang et al. 2012). We also observed that oral administration of green tea catechin EGCG enhanced immune functions in aging mice by suppressing inflamm-aging, enhancing CD8+ T cell population, and modulation of antibody response (Sharma et al. 2017). Resveratrol supplementation in aged mice significantly increased the T helper cells (CD4(+)) population and delayed-type hypersensitivity response, and promoted the production of IgG without disturbing immunological homeostasis and therefore leading to immune rejuvenation (Yuan et al. 2012). Consumption of polyphenols derived from *Cassia auriculata* flowers by aged rats increased T and B cells percentage accompanied by an elevation

of CD4+, CD8+, and CD4+CD25+ regulatory cells along with enhanced proliferation of splenocytes in both resting and LPS-stimulated cells (John et al. 2011). Supplementation with polyphenol-rich biscuits in aged mice conferred immunomodulatory effects on both the innate and adaptive immune functions as compared to the control (De la Fuente et al. 2011). In another study, ovariectomy accelerated the age-related impairment of immune functions in old mice as well as the oxidative and proinflammatory imbalance, which was reversed by the administration of soybean isoflavones and green tea (Baeza et al. 2010).

Not only polyphenols, consumption of other bioactive phytochemicals, such as carotenoids, has also demonstrated potential modulatory effects in D-galactose induced aging rats by attenuating cellular and humoral markers of immunosenescence (Chen et al. 2020). Similarly, administration of the lignan Anwulignan reversed the effects of D-galactose induced immunosenescence in aged mice by suppressing circulatory levels of inflammatory cytokines, enhancing immunoglobulins production, reducing oxidative stress in spleen, and augmenting antioxidant defenses (Li et al. 2020). Further, when aged animals were fed with a novel wheat–lentil bread, a significant decrease in inflamm-aging and an increase in CD8+ T cells was observed (Carcea et al. 2019). Consumption of *Chrysanthemum indicum* plant extracts ameliorated the effects of D-galactose induced senescence in mice through decreased oxidative stress, inflammation, and apoptosis in various animal tissues (Zhang et al. 2019). Oral administration of β -1,3-glucans to aged male mice modulated immunosenescence characterized by a significant increase in T helper cells, the delayed-type hypersensitivity response, and immunoglobulin production (Song et al. 2020). The plant melatonin, i.e., phyto-melatonin, is also emerging as a potential nutraceutical with pharmacological effects against cellular senescence and immunosenescence in experimental animals (Arnao and Hernández-Ruiz 2018; Atayik and Çakatay 2022a; Cruciani et al. 2022; Fernández-Ortiz et al. 2022; Srinivasan et al. 2005). The mechanisms governing the apparent cellular senescence and immunosenescence modulatory effects of phytochemicals are multifaceted but are linked to the longevity nutrient sensing pathways such as the Sirtuins and mTOR as well as transcription factors such as NRF-2 and NF- κ B (Mannick et al. 2014; Micó et al. 2017; Robledinos-Antón et al.

2019). As such, pharmacological natural modulators of these pathways are considered important intermediates to extend longevity including through immunomodulation (Sharma 2021a).

Although preclinical studies using mice and other animals have been greatly useful in biomedical research; however, their association and translation with respect to humans is not always linear due to the evolutionary distance between species. This is starkly evident from the failure of a large percentage (up to 85%) of clinical trials despite promising results in preclinical animal studies (Ledford 2011; Mak et al. 2014). While this could be attributed to multiple reasons including dosage, route, and concerned disease; however, the differences in the physiologies of experimental animals and humans cannot be overlooked. It has been reported that despite having the same genes, species-dependent differences in cellular functions exist that contribute to considerable heterogeneity in cellular responses (Hodge et al. 2019). In terms of the immune system too, several characteristic changes in the innate and adaptive immune system, even during immunosenescence, have been identified which warrant a cautious approach in using and interpreting studies, especially related to immune modulatory preclinical work, for human translation (Goronzy and Weyand 2013; High et al. 2012; Mestas and Hughes 2004). Nonetheless, similar to preclinical reports, few clinical trials in elderly have directly demonstrated the immunosenescence modulatory effects of phyto-molecules. For instance, a recent double-blind, randomized controlled pilot trial observed that consumption of non-digestible polysaccharide preparations significantly improved the humoral immune response of healthy seniors (50–79 years aged) against influenza vaccination (Laue et al. 2021). Similarly, administration of a fermented green banana-derived acidic glycoconjugate to 30 elderly bed-ridden patients for 8 weeks increased the antibody responses to influenza vaccination thereby countering the deleterious effects of immunosenescence (Horie et al. 2021). A randomized clinical trial on sixty-six old subjects (aged \geq 60 years) revealed that 8-week long consumption of a polyphenol-rich diet significantly attenuated systemic inflamm-aging by improving gut dysbiosis (Del Bo et al. 2021). A Japanese case study observed preventive effects of coffee consumption on the occurrence of pneumonia in the elderly (Kondo et al. 2021). Another clinical trial reported that diet

supplementation with combinations of resveratrol, pterostilbene, morin hydrate, quercetin, δ -tocotrienol, riboflavin, and nicotinic acid reduced cardiovascular risk factors and inflammation in healthy senior subjects (Qureshi et al. 2012).

Probiotics

The impact and relevance of commensal gut microbes in the development, maturation and regulation of immune response as well as maintenance of immune homeostasis is well recognized (Belkaid and Hand 2014; Zheng et al. 2020). The composition of the gut microbiota strongly influences the type of immune response, and the presence of dysbiotic gut microbiota is implicated in several inflammatory and immunological disorders including immunosenescence (Al-Rashidi 2022; DeJong et al. 2020; Shimizu et al. 2021; Toor et al. 2019). On the other hand, application of probiotics is considered useful for the maintenance of gut eubiosis and improved immunological response and homeostasis (Gagliardi et al. 2018; Maldonado Galdeano et al. 2019; Martin Manuel et al. 2017; Unno et al. 2015). Not only the gut, probiotics are known to influence several distal organs and functions through the generation of novel secretory metabolites that can enter circulation. Studies have also demonstrated that probiotics are particularly effective in altering different aspects of immunosenescence. For example, a recent study reported that consumption of probiotic *Lactobacillus casei* CRL 431 in aged mice not only improved the cellular and functional markers of immunosenescence but also restored the age-related loss in the thymus medulla (Balcells et al. 2022). Probiotic *Lactobacillus plantarum* JBC5 enhanced the lifespan of *Caenorhabditis elegans* through the modulation of multiple markers related to oxidative stress and innate immunity (Kumar et al. 2022). Application of a probiotic cocktail containing 5 *Lactobacillus* and 5 *Enterococcus* strains to old mice prevented the leaky gut by improving the expression of tight junction proteins that ultimately prevented unwarranted aggravation of intestinal immune cells and thus inflammation (Ahmadi et al. 2020). Supplementation of milk fermented with probiotic microbes improved the redox state and functions of peritoneal immune cells such as macrophages and NK cell in aged mice (Hunsche et al. 2019). Administration of *Lactobacillus acidophilus*

DDS-1 to aging mice attenuated the proinflammatory profile in serum and colonic explants as compared to age match controls (Vemuri et al. 2019). Feeding accelerated aging *Ercc1*^{- Δ 7} mice with probiotic *Akkermansia muciniphila* for 10 weeks modulated the colonic immune profile by inhibiting B-cell migration, expression of genes related to inflammation along with a reduction in peritoneal resident macrophages thereby suggesting its anti-inflammatory effects for healthy aging (van der Lugt et al. 2019). In our previous study, we also observed that consumption of a synbiotic formulation containing green tea EGCG and probiotic *Lactobacillus fermentum* alleviated various aspects of immunosenescence as evidenced by increased proliferation and activation of CD3+ T cells as well as improved Th1/Th2 cytokines ratio in splenic culture supernatants (Sharma et al. 2019). Further, oral consumption of milk fermented with probiotic *Lactobacillus rhamnosus* to aged mice attenuated age-related Th1/Th2 cytokine imbalance, inflamm-aging, IgG1/IgG2a antibodies ratio, and also improved the immune response against pathogenic *E. coli* (Sharma et al. 2014a). Similarly, administration of probiotic fermented *dahi* increased the phagocytic potential and oxidative burst capacity in aging mice (Kaushal and Kansal 2014). When supplemented with probiotic *Lactobacillus reuteri* BM36301, aged mice exhibited gender-specific effects wherein male mice experienced less weight gain and higher testosterone level while females maintained a lower serum TNF- α levels as well as healthy skin with active folliculogenesis and hair growth (Lee et al. 2016).

Human randomized controlled studies have also reported immunosenescence alleviating effects of probiotics. A recent study observed that consumption of combination of the probiotics *Lactocaseibacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. lactis BB-12 in elderly subjects for 12 months enhanced seasonal influenza vaccination response despite limited effects on other immune functions (Castro-Herrera et al. 2021). A randomized, double-blind, placebo-controlled trial was conducted with 98 elderly subjects (aged 84.6 ± 7.8 years), supplemented for 30 days with a biscuit containing a probiotic mixture of *Bifidobacterium longum* Bar33 and *Lactobacillus helveticus* Bar13 resulted in increased naive, activated memory, regulatory T cells, B cells, and NK cell activity compared with placebo suggesting strong influence on prevalent immunosenescence (Finamore

et al. 2019). Several other studies have reported that consumption of probiotic bacteria in elderly subjects can protect against incidences of acute upper respiratory tract infections and augment vaccine response (Boge et al. 2009; Davidson et al. 2011; Fonollá et al. 2019; Jespersen et al. 2015; Pu et al. 2017). Further, immune cell subpopulations also appeared to change in elderly subjects supplemented with heat-killed *Lactobacillus gasseri* wherein CD8(+) T cells not only significantly increased in PBMCs, but expression of the co-stimulatory molecule CD28 did not exhibit age-dependent decline in expression as observed for the placebo group (Miyazawa et al. 2015). Similarly, increased levels of CD4+ T cells and reduced markers of inflammation were observed after ingestion of *Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1, and *Bifidobacterium longum* MM-2 in older adults (Spaiser et al. 2015). Supplementation of a synbiotic composed of probiotic *Lactobacillus rhamnosus* GG and prebiotic corn fiber in healthy elderly enhanced NK cell response while decreasing systemic inflamm-aging (Costabile et al. 2017). In contrast, some studies have also observed limited or complete lack of immunomodulation by probiotic bacteria in elderly subjects which could be related to the efficacy of the particular type of probiotic strain used (Maruyama et al. 2016; Van Puyenbroeck et al. 2012). Studies assessing the role of probiotics in influencing cellular senescence and SASP are limited but emerging. It has been demonstrated that probiotic bacteria and their metabolites can directly suppress cellular senescence at least in vitro (Kumar et al. 2020a) while previous studies indicated that probiotic treatment can inhibit colonic senescence by downregulating the expression of cell cycle markers p53/p16 (Jeong et al. 2015a, b). However, to the best of our knowledge, there is no information whether probiotic treatment can also suppress cellular senescence in immune cells. Nonetheless, given the known immunosenescence modulatory as well as emerging anti-cellular senescence effects of probiotics, it seems prudent to assess their cellular senescence modulatory attributes in senescent immune cells.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs), especially n-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are important constituents

of a healthy diet and are implicated in a myriad of health beneficial effects including against cardiovascular diseases, chronic inflammation, diabetes, and age-related cognitive decline (Shahidi and Ambigaipalan 2018). Fish and sea food are particularly rich sources of PUFAs and studies have demonstrated that PUFAs can impact certain features of cellular senescence and immunosenescence in immune cells per se. For instance, clinical trials have shown that consumption of n-3 PUFAs is associated with increased telomere length of blood leucocytes in elderly that results in improved proliferative response and attenuation of several markers of immunosenescence (Ali et al. 2022). A study on Chinese population concluded that higher plasma n6:n3 PUFA ratio, and lower EPA and DHA n-3 PUFAs were associated with shorter leucocyte telomere length and increased coronary artery disease (Chang et al. 2020). Another study observed that age-related telomere shortening in leucocytes can be attenuated in elderly subjects with mild cognitive impairments by PUFA supplementation for 6 months (O'Callaghan et al. 2014). A double-blind 4-month trial on older adults revealed that supplementation with n-3 PUFA increased telomere length in leucocytes which correlated with decreasing n-6:n-3 ratios and decreased oxidative and inflammatory stress thereby indicating that n-3 PUFAs can impact immune cell aging (Kiecolt-Glaser et al. 2013). Supplementation with EPA and DHA (2.5 g/day) in elderly subjects for 8 weeks reduced the circulatory markers of inflamm-aging (Tan et al. 2018). Similarly, consumption of PUFA by middle aged older adults reduced systemic inflamm-aging as evident by a decrease in markers of pro-inflammatory cytokines (Kiecolt-Glaser et al. 2012). Another randomized clinical trial observed that even very low consumption of marine oil (600 mg/day) for 6 weeks by elderly subjects can significantly improve the immune response by enhancing the proliferative potential and antioxidant capacity of lymphocytes (Bechoua et al. 2003). Animal studies have also demonstrated that consumption of fish oil and other PUFAs can attenuate several markers of age-related immunosenescence, inflamm-aging, and Th1/Th2 cytokine imbalance (de Gomes et al. 2018; Gheorghe et al. 2017; Jolly and Karri 2009). Despite these compelling observations, few studies have also reported the lack of any significant effect of n-3 PUFA administration on frailty and infection rates in the elderly (Bischoff-Ferrari et al.

2020; Orkaby et al. 2022). However, taken together, there appears to be enough data to suggest that PUFA may be effective in modulating aging immune cell functions including both immunosenescence and cellular senescence, and thus could be useful sources of potential anti-aging foods although their further characterization in terms of anti-cellular senescence effects is desirable.

Vitamins and minerals

Micronutrients such as vitamins and minerals are essential for immunocompetence and their nutritional deficiency is associated with inadequate immunological response (Alpert 2017; Djukic et al. 2014). Micronutrients can influence multiple aspects of immune functions such as activation of phagocytes, regulation of inflammation, antigen presentation, as well as humoral antibody response (Gombart et al. 2020). Studies have also shown that supplementation with certain vitamins and minerals can counter immunosenescence and boost the immune response in elderly. For instance, oral application of vitamins C and E to elderly subjects improved blood neutrophils and lymphocytes functions which were maintained even after 6 months of treatment (De la Fuente et al. 2020). Ex vivo application of vitamins C and E to lymphocytes isolated from healthy elderly significantly enhanced the proliferative response and attenuated oxidative stress (Bouamama et al. 2017). Similarly, long-term high-dose intake of vitamin C (200 mg/kg/day) in senescence marker protein-30 knockout mice for 1 year significantly enhanced the circulatory leucocyte profile and splenic T cell differentiation while also suppressing thymic involution with age (Uchio et al. 2015). Vitamin C application to old mice prevented age-related depletion of memory T cells in bone marrow while also augmenting the activation of antigen presenting cells (Meryk et al. 2020). In addition to vitamins C and E, clinical trials of vitamin D have observed improved response to vaccines and enhanced ability to resist respiratory infections in old age adults (Ginde et al. 2017; Goncalves-Mendes et al. 2019; Sadarangani et al. 2016). Using vitamin A, it was observed that retinoic acid had no significant effect on the leukocyte subpopulations or on the functions of PBMCs but enhanced the spontaneous migration and adhesion of neutrophils in elderly subjects (Minet-Quinard et al. 2010). Similarly, vitamin

A levels were correlated with preserved neutrophil functions during aging in humans characterized by increased cellular migration and phagocytic activity (Farges et al. 2012).

Among minerals, the role of zinc is recognized as of particular significance in countering immunological aging (Baarz and Rink 2022). That elderly are often deficient in zinc suggesting a direct correlation between chronic inflammation, immunosenescence, and increased susceptibility to infections (Cabrera 2015). Studies have demonstrated that dietary supplementation with zinc can reverse several facets of immunosenescence as evident by increased naïve T-cell subset (Wong et al. 2020, 2021), improved immune cell functions (Barnett et al. 2016; Varin et al. 2008), increased thymopoiesis (Wong et al. 2009), attenuated inflamm-aging (Wong et al. 2013), and modulated Th1/Th2 immune homeostasis (Uciechowski et al. 2008) during aging. In addition to zinc, copper (Giacconi et al. 2017; Malavolta et al. 2015) and iron (Handono et al. 2021; Macciò and Madeddu 2012) deficiency is also correlated with aging and health, including immunosenescence. Further, there is sporadic evidence indicating that impaired metabolism of specific minerals in senescent non-leucocyte cells could be a prevalent phenomenon (Killilea and Ames 2008; La Fata et al. 2015; Masaldan et al. 2018a, b), and that supplementation with certain vitamins can delay cellular senescence (Chen et al. 2019; Jeong et al. 2017; La Fata et al. 2015; Ricciarelli et al. 2020). However, such information in immune cells is completely lacking and needs to be pursued. Further, it is important to consider that although elderly often have dietary deficiency of minerals such as zinc, copper, selenium, and iodine (Vural et al. 2020) as well as vitamins including vitamins D, K, and B (Fabian et al. 2012; Wei et al. 2019); indiscriminate supplementation of vitamins and minerals in individuals with no clinical deficiency is considered controversial, especially related to non-communicable diseases (Zhang et al. 2020b), and could even be harmful (Hamishehkar et al. 2016). Moreover, supplementation with multivitamins and minerals is not always sufficient to alter immune status in the elderly population as evidenced recently (Fantacone et al. 2020), and thus a cautious approach in this regard is warranted. Table 2 summarizes selected studies demonstrating nutritional modulators of immunological aging.

Table 2 Representative examples of modulation of immunological aging through major dietary bioactive factors

S. no.	Dietary factors	Reported effects	Experimental model	References
1	EGCG	Anti-SASP and anti-cellular senescence effects ex vivo	Murine macrophages	Kumar et al. (2020b)
2	Resveratrol	Suppression of inflamm-aging and oxidative stress in immune cells in vivo	Sprague-Dawley rats	Garrigue et al. (2021)
3	Lignan	Anti-immunosenescence effects in vivo	ICR mice	Li et al. (2020)
4	Carotenoids	Improved immunoglobulins profile during aging in vivo	Rats	Chen et al. (2020)
5	Polysaccharide preparations	Improved humoral immune response against influenza vaccine during aging	Clinical trial	Laue et al. (2021)
6	Polyphenol-rich diet	Anti-inflammaging effects and gut eubiosis during aging	Clinical trial	Del Bo et al. (2021)
7	<i>Lactobacillus casei</i> CRL 431	Anti-immunosenescence effects including on thymus	Aged mice	Balcells et al. (2022)
8	Probiotic <i>Akkermansia muciniphila</i>	Modulation of colonic B cell migration and inflammation	Aging Ercc1 ^{-Δ7} mice	van der Lugt et al. (2019)
9	Synbiotic preparation	Increased proliferation and activation of CD3+ T cells	Aged mice	Sharma et al. (2019)
10	n-3 PUFAs	Increased telomere length of blood leucocytes	Clinical trial	Ali et al. (2022)
11	EPA and DHA	Anti-inflamm-aging	Clinical trial	Tan et al. (2018)
12	Vitamins C&E	Improved neutrophils and lymphocyte functional markers	Clinical trial	De la Fuente et al. (2020)
13	Zinc	Increased naïve T-cell subset	Aged mice	Wong et al. (2020)

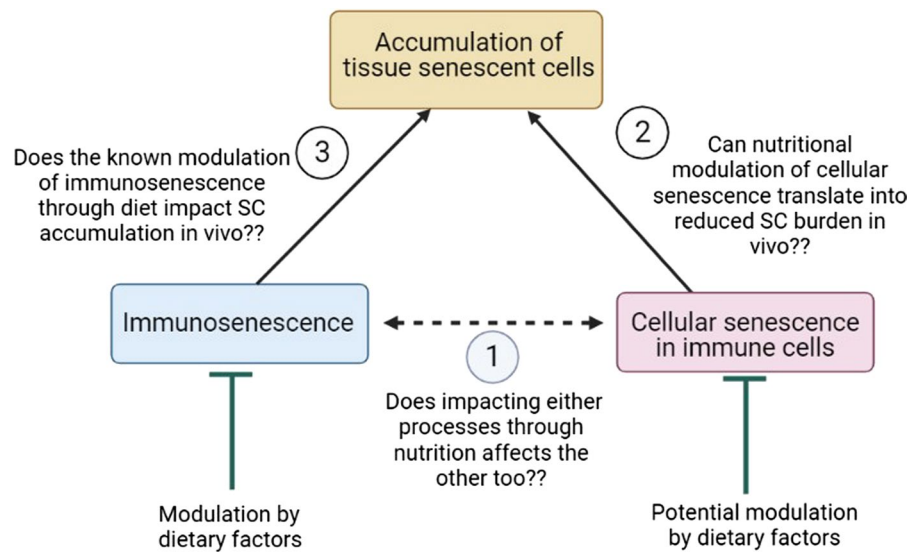
Conclusions and future prospects

How to define an aged immune cell? The answer to this deceptively simple question is challenging since, as discussed in this manuscript, the immune cells are unique to undergo two different and mutually inclusive age-dependent processes, i.e., cellular senescence and immunosenescence. Besides, understanding aging in immune cells has always remained ambiguous due to the limitations and contradictions associated with immunosenescence (Pawelec et al. 2020), and the emerging significance of cellular senescence in immune cells only adds to this conundrum. The relevance of the emerging immunoadaptation view of immunosenescence in cellular senescence in immune cells is also not known. However, in this regard, it is interesting to note that unlike non-leucocyte cells, contradictions among characteristic effects of cellular senescence in immune cells such as macrophages have already been reported (Hall et al. 2017; Stojiljkovic et al. 2019), which perhaps suggest a similar

plasticity akin to immunosenescence that, however, needs further exploration. Nonetheless, the emerging cellular senescence-based perspective in understanding of the aging immune system as well as developing mitigative nutritional therapies has prompted more questions than answers. There are several niche research areas that need immediate attention:

- The extent and depth of cellular senescence in immune cells is not fully understood, particularly in innate immune cells including macrophages and DCs, which is important considering their heterogeneity and tissue-specific niches. Although such attempts have been made recently, but elucidation of cellular senescence in immune cells is still much limited as compared to immunosenescence. Moreover, several available reports are contradictory which possibly indicate an unexpected role of cellular senescence in these cells.
- More significantly, the impact and biological relevance of cellular senescence in immune cells

Fig. 5 Dietary factors can influence different aspects of aging by impacting both cellular senescence (both in immune and non-leucocyte cells) and immunosenescence (to a relatively larger extent). However, whether their known anti-immunosenesence or anti-cellular senescence effects can also translate into enhanced removal of tissue senescent cells in vivo and thus systemic improvements in organismal senescent cell burden remains to be elucidated



in vivo is little understood and lacks conclusive evidence in natural aging settings. Besides, since immune cells constantly interact with tissue SC (and SASP thereof), how tissue SC can impact aging in resident immune cells (such as macrophages) is only beginning to be understood.

- Delineating the dichotomy of cellular senescence and immunosenescence in aging immune cells should be the ultimate goal. Studies focused on the molecular etiology of these processes are thus highly desirable for specifying the functional features of cellular senescence and immunosenescence.
- The relationship between accumulation of SC in tissues and the aging immune system is still developing and unclear. There seems to be causative association, but is yet to be verified in vivo during natural aging. The effects of adaptive immune system aging and increased SC turnover with age is even less understood.
- Functional foods and especially curated diets, such as the Mediterranean diet or plant-based diets, have shown the potential to suppress inflammaging as well as cellular senescence (Canudas et al. 2020; Crous-Bou et al. 2019; García-Calzón et al. 2015; Sharma and Diwan 2022). However, studies identifying nutritional targets of cellular senescence in immune cells per se are severely limited and thus efforts should be made to assess the immune modulating potential of natural bio-

active compounds and/or healthy diets within the purview of cellular senescence (Fig. 5).

- Similarly, whether the apparent immunosenescence modulatory effects of dietary factors also result in improved immune functions with regard to clearance of natural SC in vivo is not known (Fig. 5). This is of significance as it could unravel a direct correlation between improved immune functions and senescence immunotherapy. It is therefore desirable that future investigations study the immune rejuvenation potential of putative nutraceuticals within the purview of cellular senescence for a more meaningful and integrative understanding.

In conclusion, cellular senescence is emerging as an impactful phenomenon in immune cell aging which should be considered not only for truly comprehending the aging physiology in the immune system but also for implementing nutritional strategies aimed at potentially rejuvenating the aging immune system.

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Authors' contributions RS conceived the idea, wrote the initial draft, and edited the manuscript. BD curated data and prepared figures. AS and JW edited and reviewed the manuscript. All authors read and approved the final manuscript.

Data availability The manuscript has no associated data.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

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