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Understanding the role of host metabolites in the induction of immune senescence: Future strategies for keeping the ageing population healthy

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Advancing age is accompanied by significant remodelling of the immune system, termed immune senescence, and increased systemic inflammation, termed inflammageing, both of which contribute towards an increased risk of developing chronic diseases in old age. Age-associated alterations in metabolic homeostasis have been linked with changes in a range of physiological functions, but their effects on immune senescence remains poorly understood. In this article, we review the recent literature to formulate hypotheses as to how an age-associated dysfunctional metabolism, driven by an accumulation of key host metabolites (saturated fatty acids, cholesterol, ceramides and lactate) and loss of other metabolites (glutamine, tryptophan and short-chain fatty acids), might play a role in driving immune senescence and inflammageing, ultimately leading to diseases of old age. We also highlight the potential use of metabolic immunotherapeutic strategies targeting these processes in counteracting immune senescence and restoring immune homeostasis in older adults.

KEYWORDS

immunesenescence, inflammaging, lactate, saturated fatty acids, short chain fatty acids

1 | INTRODUCTION

One of the most important triumphs of modern medicine and public health policy over the last 200 years is the dramatic extension of human lifespan. However, although we are living longer, we are spending more years in ill health, as healthy life expectancy has not kept pace with the expansion in lifespan (House of Lords Report, 2021). From 2016 to 2018, life expectancy in the United Kingdom increased by 0.8 and 0.6 years for males and females, respectively.

In contrast, healthy life expectancy for males increased by 0.4 years and females by only 0.2 years in the same period (Office for National Statistics, 2016 to 2018). Advancing age is accompanied by an increased risk of bacterial and viral infections (Yosikawa, 2000), autoimmune conditions (Goronzy & Weyand, 2003), cancer incidence (Falci et al., 2013), atherosclerosis (Dai et al., 2018), metabolic diseases and impaired vaccine responses (Giudice et al., 2017), all contributing towards ill health in older adults, making aged individuals a vulnerable population. These data emphasise the

Abbreviations: AhR, aryl hydrocarbon receptor; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; CRP, C-reactive protein; DHA, docosahexaenoic acid; EMRA, effector memory cells expressing CD45RA; EPA, eicosapentaenoic acid; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; IBD, inflammatory bowel disease; IDO, indoleamine 2,3-dioxygenase; KP, kynurenine pathway; NKCC, NK cell cytotoxicity; NLRP3, NOD-like receptor 3; PUFAs, polyunsaturated fatty acids; RA, rheumatoid arthritis; ROR γ , RAR-related orphan receptor γ ; SARS, severe acute respiratory syndrome; SASP, senescence-associated secretory phenotype; SCFA, short-chain fatty acid; SPMs, specialised proresolving mediators; SPT, serine palmitoyltransferase; TCA, tricarboxylic acid; TCR, T-cell receptor; TDO, tryptophan 2,3-dioxygenase; TLR, toll-like receptor.

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importance of developing a deeper understanding of the biology of ageing as targeting these processes holds the promise of maintaining health for longer, as we age.

Ageing is a complex process accompanied by alterations in the functional capacity of a wide range of body systems, including the immune system. Indeed, a recent study in mice has suggested that an aged immune system is sufficient to drive the development of many age-related diseases (Yousefzadeh et al., 2021). Additionally, metabolic alterations, such as increased visceral adiposity, altered circulating lipid composition and accumulation of lipids in primary lymphoid organs, have been observed in older adults. It is becoming increasingly clear that the immune and metabolic systems are closely interconnected and play a critical role in the maintenance of immune homeostasis, linking to several aspects of the ageing process and associated chronic inflammatory conditions (Gerriets & Rathmell, 2012). Immune cells sense and respond to exogenous metabolic signals (Ganeshan & Chawla, 2014), including fatty acids, free cholesterol, sphingosine-linked fatty acids, products of lipid metabolism, amino acids and microbial-derived metabolites. However, our understanding of the effects of the micro-environment on the immune system and how this changes as we age is far from complete. Thus, there is an increasing need to investigate this interrelationship,

as the prospect of resetting bioavailability of host metabolites and reversing immune senescence is now being realised and is readily testable. In this review article, we will discuss the recent evidence in the field to determine, beyond the association studies, what potential role the aged micro-environment plays in immune ageing and the related mechanisms leading to age-related chronic diseases.

2 | THE AGEING IMMUNE SYSTEM AND INFLAMMAGING

Advancing age is accompanied by profound remodelling of the innate and adaptive arms of the immune system, resulting in a state of immune dysregulation and a decline in the ability to mount a robust immune response, termed 'immune senescence' (Duggal, 2018). The underlying mechanisms driving immune senescence include many of the core biological ageing processes, the so-called hallmarks of ageing (Lopez-Otin et al., 2013), which include accumulation of DNA damage, telomere shortening (Akbar & Fletcher, 2005), reduced mitochondrial function (Callender et al., 2020), reduced autophagy (Alsaleh et al., 2020), chronic inflammation (Jose et al., 2017) and epigenetic changes (Goronzy et al., 2018) (Figure 1).

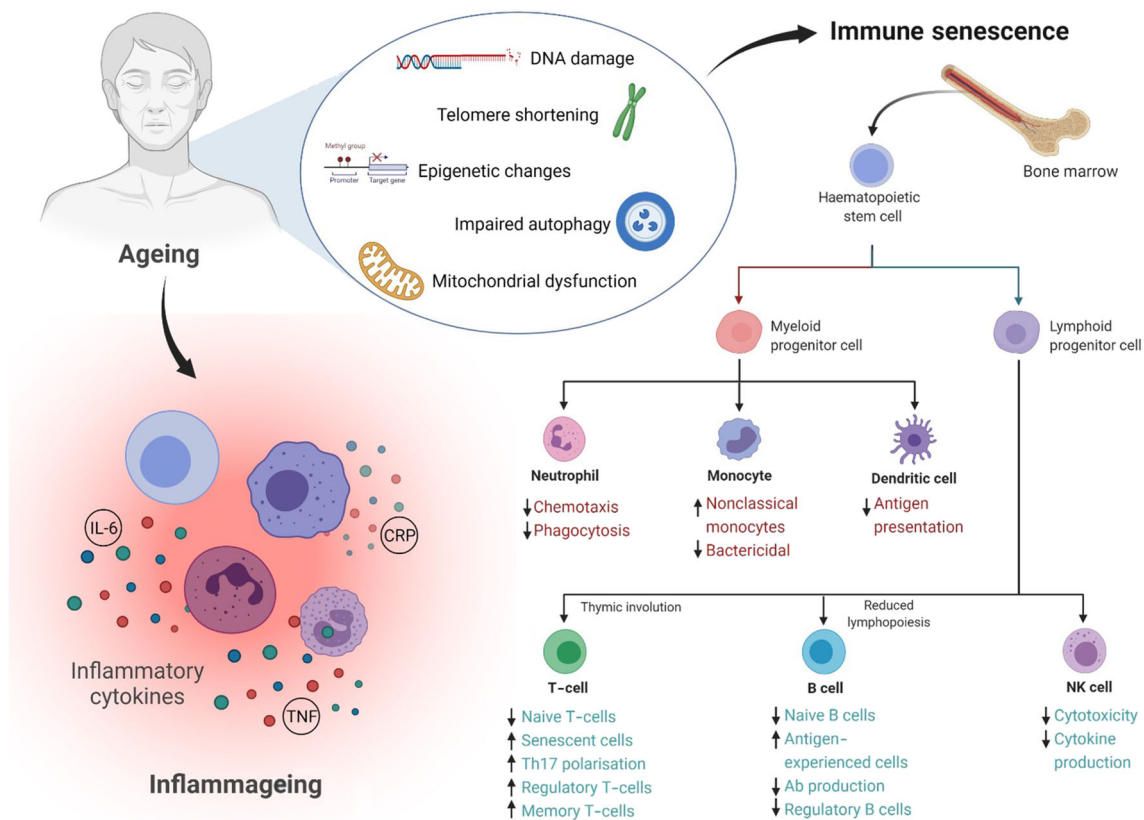


FIGURE 1 The ageing immune system and inflammaging. Many biological processes are involved in age-induced remodelling of the immunological system, known as immune senescence, which is characterised by dysregulation of both the innate and adaptive immune systems. Immune senescence, together with other age-related factors, leads to a chronic, low-grade inflammatory process known as inflammaging, which involves altered levels of pro-inflammatory cytokines. CRP, C-reactive protein

2.1 | Innate immunity

Neutrophils are key innate immune cells that provide immediate protection against bacterial and fungal infections, and their function is compromised with age. Key features of neutrophil ageing include reduced chemotaxis (Sapey et al., 2014), impaired phagocytosis (Butcher et al., 2001) and reduced ability to extrude neutrophil extracellular traps to entrap and eliminate bacteria (Hazeldine et al., 2014). An age-dependent redistribution of monocyte subsets with an increase in non-classical ($CD14^{+ve}CD16^{++ve}$) monocytes that exhibit a pro-inflammatory senescence-associated secretory phenotype (SASP) (Ong et al., 2018) is also a hallmark of immune senescence. Furthermore, age-associated alterations in cytokine production by monocytes in response to challenge, decline in bactericidal properties and delayed clearance of apoptotic cells have also been observed (Albright et al., 2016). Additionally, impaired antigen presentation by dendritic cells (Chougnnet et al., 2015) and a reduced NK cell cytotoxicity have been reported in older adults (Hazeldine et al., 2012) (Figure 1). Taken together, these factors increase the vulnerability of older adults to bacterial and viral infections, as shown very clearly during the severe acute respiratory syndrome (SARS)-CoV-2 pandemic (Cunha et al., 2020), and are likely to contribute to the increase in systemic inflammation with age, so-called “inflammageing”.

2.2 | Adaptive immunity

Within the adaptive immune system, ageing is accompanied by thymic involution, involving a reduction in naïve T-cell output that contributes towards an increased risk of novel pathogens (Cunha et al., 2020) and a reduced response to vaccinations (Crooke et al., 2019) in older adults. The driving factors for thymic involution include increased thymic adiposity, reduced stromal and thymocyte cellularity and an altered thymic micro-environment driven by reduced levels of thymostimulatory cytokines (**IL-7**) and up-regulation of thymo-suppressive cytokines (**IL-6** and **TNF- α**) (Ventevogel & Sempowski, 2013). Additional hallmarks of T-cell immune senescence include accumulation of highly differentiated memory EMRA T-cells and senescent T-cells that secrete a range of extracellular modulators including pro-inflammatory cytokines, chemokines, growth factors and bioactive lipids (SASP phenotype) (Callender et al., 2018; Di Mitri et al., 2011). Ageing is also accompanied by a skewing of T-cell responses towards the Th17 cell subset (Ouyang et al., 2011), which has been associated with an increased risk of chronic inflammatory conditions and autoimmune disorders. Furthermore, B-cell haematopoiesis is compromised in older adults, resulting in an increase in ‘antigen-experienced’ B cells (Riley, 2014), impaired antibody production and loss of B-cell diversity, contributing to poor vaccination efficacy (Arsenović-Ranin et al., 2019). Lastly, ageing is accompanied by an expansion of regulatory T-cells, T_{regs} (Jagger et al., 2014), a potential compensatory mechanism to restore immune homeostasis that has been perturbed due to excessive immune activation and pro-inflammatory immune responses. However, on the other hand, we have reported an age-

associated numerical deficit and reduced anti-inflammatory cytokine (**IL-10**) production for a subset of immunoregulatory $CD24^{hi}CD38^{hi}$ B cells (Duggal et al., 2013), which could contribute to reduced immune tolerance with age (Figure 1).

Another universal feature of ageing is chronic, elevated levels of pro-inflammatory cytokines (IL-6, TNF- α) and C-reactive protein (CRP) with reduced IL-10 levels, and is a characteristic of inflammageing (Franceschi & Campisi, 2014). There is mounting evidence suggesting a role for inflammageing in a wide range of age-related diseases, including dementia, cardiovascular disease, sarcopenia and cancer, and it is a powerful predictor of mortality in older adults (Singh & Newman, 2011). Inflammageing is a complex multifactorial process driven by immune senescence, lifelong antigenic load, microbial dysbiosis-inducing gut permeability, increased adiposity, accumulation of senescent cells and physical inactivity (Fulop et al., 2018).

3 | HOST METABOLITES AS INDUCERS OF IMMUNE SENESCENCE

The immune system is a tightly regulated network, which provides defence against foreign antigens and tolerance towards self-antigens. Our understanding of immune senescence is largely based on studies focussed on individual immune cells investigating age-associated phenotypic and functional alterations and intrinsic changes. However, it is crucial to keep in mind the extensive crosstalk between the complex network of immune cells and soluble factors in the micro-environment. Host metabolites present in the micro-environment have immune-modifying potential, which can skew the balance between inflammation and immune tolerance (Figure 2). In this review, we discuss the potential effects of immune senescence-inducing metabolites.

3.1 | Saturated fatty acids and cholesterol

Fatty acids are carboxylic acids derived from foods and stored as triacylglycerols in adipose tissue. They play a diverse range of physiological roles, such as energy provision, signal transduction, cell membrane constituents and synthesis of immunomodulatory lipids (Pike, 2013). Fatty acids can be separated into three main groups: saturated, monounsaturated and polyunsaturated fatty acids (PUFAs). Saturated fatty acids derived from animal fats and tropical oils (palm oil and coconut oil) are pro-inflammatory with elevated circulating levels and a state of hypercholesterolaemia, frequently observed with advancing age (Houtkooper et al., 2011). Elevated levels of saturated fatty acids and free **cholesterol** have also been associated with insulin resistance (Lee et al., 2006), sarcopenia (Welch et al., 2014), coronary heart disease (Liu et al., 2019) and Alzheimer's disease (Gustafson et al., 2020).

Saturated fatty acids, particularly **palmitic acid**, have been shown to induce a pro-inflammatory phenotype in immune cells, such as increased pro-inflammatory cytokine (**IL-1 β** , **IL-8 (CXCL8)** and TNF- α)

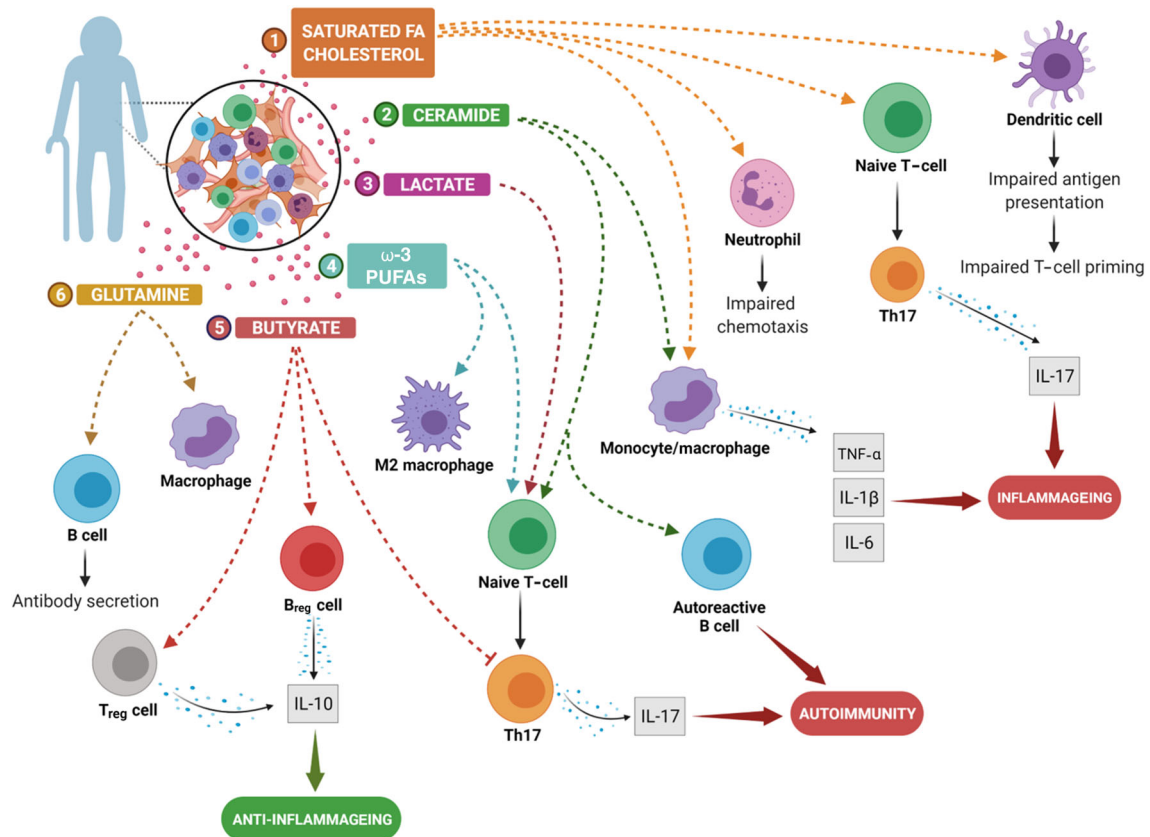


FIGURE 2 The effects of host metabolites on immune senescence and inflammaging. Host metabolites present in the micro-environment have immune-modifying potential, skewing the balance between inflammation and immune tolerance. The figure summarises the potential effects of immune senescence-inducing and immunomodulatory metabolites on different types of immune cells. Breg, regulatory B cell; FA, fatty acid; M2, M2 polarised macrophages; PUFA, polyunsaturated fatty acid; Treg, regulatory T-cell

secretion by monocytes/macrophages, via **toll-like receptor (TLR)**-mediated inflammasome activation (Samblas et al., 2019; Snodgrass et al., 2013). Thus, raised levels of these fatty acids are thus potential contributors to inflammaging. However, according to these studies, DNA methylation modifications are not involved in saturated fatty acid-mediated regulation of inflammatory genes and the mechanism of action remains to be elucidated. Additionally, palmitic acid been identified as a **TLR4** ligand to induce IL-1 β secretion by dendritic cells (Nicholas et al., 2017) and most importantly impair DC antigen presentation and ability to prime naïve T-cells and regulate T-cell differentiation (Shaikh et al., 2008), contributing towards impaired T-cell priming in older adults. Furthermore, CD4 T-cell exposure to saturated fatty acids induces T-cell differentiation into pro-inflammatory effector memory-like T-cells, via **PI3K/Akt** activation (Mauro et al., 2017), skewing towards Th17 polarisation and reduced Th2 differentiation (Hammer et al., 2017), which have all been identified as hallmarks of T-cell ageing.

Age-associated hypercholesterolaemia results in the accumulation of cholesterol crystals in macrophages, which induces lysosomal damage via activation of the **NOD-like receptor 3 (NLRP3)** inflammasome (Duell et al., 2010) and triggers TLR-mediated secretion of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8 and TNF- α)

(Køllgaard et al., 2017). Additionally, high cholesterol levels impair neutrophil chemotaxis, driven by attenuation of calcium flux in response to chemoattractants and a decreased neutrophil cytokine transcription in response to inflammatory stimuli due to desensitisation of signalling pathways (Palvinskaya et al., 2013). Cholesterol is known to be crucial for the maintenance of cell membrane raft integrity and is required for T-cell receptor (TCR) dimerisation. Therefore, increased plasma cholesterol concentrations perturb T-cell homeostasis and induce T-cell activation, predisposing to aggravated T-cell responses (Mailer et al., 2017). Moreover, preliminary evidence from animal studies has suggested a causal relationship between cellular cholesterol accumulation and development of autoimmunity. Intracellular cholesterol accumulation in antigen presenting cells results in the up-regulation of NF- κ B-dependent genes, such as those for **BAFF** and **APRIL**, both B-cell proliferation factors, driving dysregulated antigen presentation and the expansion of autoreactive B cells (Ito et al., 2016). On the other hand, an expansion of peripheral anti-inflammatory T_{regs} and up-regulation of transcription factor Foxp3 among thymocytes has been observed in mice fed with a high cholesterol-containing diet (Mailer et al., 2017), suggesting that hypercholesterolaemia affects thymic development of T_{regs}, which could possibly serve as a compensatory mechanism to stabilise the immunological balance.

3.2 | Ceramides

During lipid metabolism, palmitic acid can be converted into ceramides by the rate-limiting enzyme **serine palmitoyltransferase (SPT)** in the de novo synthesis pathway. Once generated, ceramides can be converted into a variety of metabolites such as ceramide-1 phosphate and **sphingosine**, which also possess immunoregulatory properties (Wigger et al., 2019). Sphingolipids, such as ceramides, act as signalling molecules in a wide range of cellular processes including cell growth, cell differentiation, apoptosis, cellular senescence, autophagy and inflammation (Chaurasia & Summers, 2020). An age-associated ceramide accumulation in plasma has been linked with an increased risk of cardiovascular diseases, neurodegeneration, insulin resistance, chronic inflammation and cancers. Interestingly, the disruption of ceramide production exerts pro-longevity effects (Johnson & Stolzing, 2019).

The immunomodulatory potential of ceramide accumulation includes skewing towards pro-inflammatory M1 macrophages and elevated expression and secretion of IL-6, TNF- α , IL-1 β and the chemokine **CCL2**, contributing towards inflammaging (Chaurasia et al., 2016; Hamada et al., 2014). Elevated ceramide levels have been reported in macrophages with advancing age, resulting in increased **caspase-1** activation and IL-1 β secretion in response to NLRP3 inflammasome activation (Vandanmagsar et al., 2011). This age-associated increase in ceramide production contributes towards increased **COX-2** expression and **PGE₂** synthesis in macrophages (Claycombe et al., 2002; Wu et al., 2007), both of which are associated with reduced macrophage phagocytic activity in older adults. Ceramides can further induce a shift towards a pro-inflammatory micro-environment, by serving as pro-apoptotic molecules and suppress the development and generation of iT_{regs} (Zhou et al., 2016). Furthermore, an age-associated accumulation of ceramides and lipids in the thymus is linked with an increase in by-products of fatty acids and lipid peroxidation that induce a shift towards a pro-inflammatory micro-environment, serving as a precursor of age-associated defects in thymic export of naïve T-cells (Dixit, 2012). The presence of ceramides and free cholesterol also triggers caspase-1 activation leading to thymic tissue damage and this is also a potential driver of age-associated thymic involution.

Together, these studies support the hypothesis that plasma lipid imbalance is a contributing factor towards age-associated immune dysfunction and inflammaging, suggesting that lipid removal could be beneficial in restoring immune homeostasis in older adults and could have therapeutic utility in reversing the age-associated increased risk of novel infections and autoimmunity.

3.3 | Lactate

Aged organisms display an altered metabolic homeostasis resulting in build-up of lactate at the expense of glucose in a range of peripheral tissues. Using proton magnetic resonance spectroscopy and HPLC, it has been shown that brain lactate levels are

increased twofold in both normally and prematurely aged mice. The molecular link between accumulation of lactate in the brain of mice and the ageing process has been found in an up-regulation of LDH and LDH-A gene, a down-regulation of LDH-B gene expression and consequent increased conversion of **pyruvate** to **lactate** (Ross et al., 2010). Lactate has long been considered a waste product that accumulates at sites of inflammation. However, recent evidence suggests that lactate is an active metabolite, a major carbon source for cellular metabolism that can play an important role in cell signalling. For instance, lactate represents an important source of carbon for the tricarboxylic acid (TCA) cycle in both normal and cancer tissues (Faubert et al., 2017; Hui et al., 2017). Lactate accumulates in inflamed tissues such as atherosclerotic plaques and joints in **rheumatoid arthritis (RA)** and regulates the function of local immune cells, by influencing intracellular metabolism (Fujii et al., 2015). Lactate accumulation contributes towards the up-regulation of the **lactate transporter SLC5A12** on human CD4 T-cells, resulting in reprogramming of cellular metabolism, which supports a pro-inflammatory response by CD4 T-cells. In particular, lactate has been shown to increase IL-17 production via **PKM2/STAT3** signalling (Pucino et al., 2019), and this switch towards Th17 differentiation has also been identified as a key feature of immune ageing (Ouyang et al., 2011). Furthermore, numerous age-related inflammatory conditions, such as rheumatoid and psoriatic arthritis, are associated with Th17 immune signatures (Stadhouders et al., 2018). Interestingly, the immunomodulatory properties of lactate extend to anti-inflammatory properties, including inhibition of **LPS**-triggered pro-inflammatory cytokine production by murine macrophages (Errea et al., 2016) and human monocytes (Ratter et al., 2018).

Through metabolomic analysis, senescent fibroblasts have been shown to shift towards glycolysis with increased glucose consumption and lactate production (James et al., 2015). A similar shift towards glycolysis also occurs in T_{EMRA} cells, a subset of T-cells that acquire a senescent phenotype (Callender et al., 2020). Furthermore, Th17 cells induce senescence in healthy fibroblasts and that senescent fibroblasts, in turn, can polarise naïve T-cells towards a Th17 phenotype (Faust et al., 2020). Advancing age is accompanied by an accumulation of senescent cells, leading to the hypothesis that elevated lactate production by senescent cells with advancing age can modulate the phenotype and function of neighbouring immune cells, promoting a sustained inflammatory response. These inflammatory cells may then induce or support the senescence process of the surrounding cells. For example, foamy macrophages expressing senescence markers (SA- β -gal) are present in the subendothelial space, contributing to the atherosclerotic process by enhancing the expression of pro-inflammatory cytokines, suggesting the involvement of macrophage ageing and senescence in the development of age-related diseases (Childs et al., 2016). As lactate is increased locally in atherosclerotic plaques, it is essential to investigate whether the release of lactate by senescent macrophages can contribute to inducing senescence in surrounding cells and how this may affect the age-associated elevated risk of cardiovascular disease. Further studies are required to

comprehensively determine whether high lactate concentrations in the aged micro-environment play a role in the age-associated increased risk of cancer and other diseases.

3.4 | Amino acid metabolism dysregulation

Amino acids are important signalling molecules that play a crucial role in protein synthesis (Jackman et al., 2017), energy metabolism (Li et al., 2007), cell growth (Shao et al., 2018), the gut microbiome (Ren et al., 2014) and immune homeostasis. Findings from recent studies indicate that amino acids, such as **glutamine**, **arginine** and **tryptophan**, modulate immune responses by regulating the activation, proliferation and redox state of immune cells and the production of inflammatory mediators (Li et al., 2007). Ageing is associated with dysregulated amino acid metabolism (Houtkooper et al., 2011), which could possibly contribute towards immune senescence and inflammaging. Indeed, imbalances in glutamine, arginine and tryptophan levels have been linked with the development of several age-related diseases including frailty (Valdiglesias et al., 2018), **Type 2 diabetes** (Yu et al., 2012), cardiovascular disease (Tang et al., 2009) and **Alzheimer's disease** (Huang et al., 2017).

Glutamine is the most abundant amino acid in the circulation, and it is becoming increasingly clear that it is utilised by immune cells and possesses immunomodulatory properties. Glutamine availability is essential for proliferation, efficient phagocytosis, surface expression of HLA-DR and cytokine production by macrophages under basal and inflammatory conditions (Spittler et al., 1995). Recent research suggests that glutamine utilisation has been linked with the skewing of macrophages towards a pro-inflammatory M1 phenotype, associated with its effects on the TCA cycle (Jha et al., 2015). This enhanced the pro-inflammatory phenotype of brain-resident macrophages, increasing the risk of neuroinflammation and cognitive impairment in mice (Palmieri et al., 2017). In neutrophils, glutamine plays a vital role in the production of reactive oxygen and nitrogen species, by regulating the expression of components of **NADPH oxidase** (p22, gp91 and p47), and also plays a role in the maintenance of neutrophil viability (Pithon-Curi et al., 2002). Furthermore, glutamine can act as a respiratory fuel and enhances T-cell proliferation, via regulation of IL-2 production (Newsholme, 2001) and the differentiation of B cells into antibody-secreting cells (Crawford et al., 1995). Glutamine depletion has been shown to inhibit T-cell production of the cytokine **IFN- γ** (Carr et al., 2010) and impair Th1 polarisation (Nakaya et al., 2014). However, the underlying molecular mechanisms of interactions between glutamine and T-cells remain largely unknown.

Advancing age is accompanied by a decline in glutamine levels in endothelial cells and reduced cellular synthesis (Huang et al., 2017). Although no research so far has investigated the impact of the age-associated decline in glutamine levels on immune senescence, we speculate that lower glutamine levels might contribute towards the age-associated functional defects in immune cells. Furthermore, we propose that supplementation with glutamine could have a beneficial effect on immune cell function. In support of this, *in vitro* studies have

shown that glutamine augments neutrophil and monocyte superoxide generation (Furukawa et al., 2000) in animal (Yoo et al., 1997) and human studies (Ziegler, 2000). Glutamine supplementation enhanced neutrophil bactericidal killing by serving as an energy substrate and increasing cellular ATP, resulting in a reduction in mortality after infection.

Arginine, a crucial amino acid and substrate for **inducible NOS (iNOS)** and **arginase**, serves to modulate the cellular immune response, especially during infections. Adequate levels of arginine are necessary for NK cell proliferation and cytotoxicity, as well as T-cell proliferation and cytokine production (Choi et al., 2009; Tarasenko et al., 2015). The absence of arginine during T-cell priming is associated with reduced expression of activation markers (CD25 and CD62L) that result in functional alterations (Choi et al., 2009). Altered arginine metabolism is also known to occur with advancing age, with several studies reporting reduced levels in the plasma and brain of aged rodents and a decline in Bergin et al. (2018) and Moretto et al. (2017). Thus, arginine dysregulation could serve as a potential amplifier of age-associated immunosuppression, opening new avenues for clinical interventions.

Tryptophan, an essential amino acid that is metabolised mainly through the kynurenine pathway (KP), can be catabolised by **tryptophan 2,3-dioxygenase (TDO)** in the liver and by **indoleamine 2,3-dioxygenase (IDO)**. It plays a crucial role in the maintenance of immune homeostasis, and dysregulation of tryptophan metabolism has been linked with various inflammatory disorders, such as inflammatory bowel disease (IBD) and multiple sclerosis (Nikolaus et al., 2017; Roger & Licht, 2018). Ageing is associated with an increase in IDO-mediated tryptophan catabolism reflected by decreased tryptophan and elevated kynurenine levels in serum (Pertovaara et al., 2006; Ramos-Chávez et al., 2018). Tryptophan depletion leads to reduced proliferation and increased apoptosis of T-cells via **caspase-8** activation, associated with **Fas/FasL** interactions (Fallarino et al., 2002; Terness et al., 2002), which could contribute towards defects in adaptive immunity with ageing. In support of this, inhibition of IDO-induced tryptophan degradation resulted in an expansion of IFN- γ -expressing cells during viral infection and enhanced influenza vaccine efficacy in mice (Fox et al., 2013). Induction of IDO is driven by pro-inflammatory signals (Jürgens et al., 2009). The question arising here is whether IDO inhibitors could restore age-associated impaired vaccine responses in aged humans.

4 | POTENTIAL OF HOST METABOLITES IN COMBATING IMMUNE SENESCENCE

In the previous sections, we have summarised the evidence for some aspects of the aged micro-environment as drivers of immune ageing, and we will now discuss the potential of immunomodulatory metabolites such as ω -3 PUFAs and short-chain fatty acids (SCFAs) in restoring immune homeostasis and enhancing immune responses (Figure 2), especially in the context of advancing age.

4.1 | Polyunsaturated fatty acids

Optimal nutrition is a key determinant of healthy ageing, which is important for maintenance of physiological function and reducing the risk of disease in old age. Dietary intake and composition is altered, and nutrient absorption declines with advancing age, increasing the risk of malnutrition (i.e., lower intake of essential fatty acids, vitamins and minerals) in older adults (Elia & Russell, 2009). ω -3 PUFAs such as **eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)** derived from fish and fish oil, exhibit anti-inflammatory properties and are known for their beneficial effects on several inflammatory diseases associated with ageing (Jeffery et al., 2017).

The ω -3 PUFAs exert important immunomodulatory effects on innate and adaptive immune cells and promote an anti-inflammatory environment. In macrophages, EPA and DHA treatment decreases LPS-induced secretion of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α (Allam-Ndoul et al., 2017) and increases release of the anti-inflammatory cytokine IL-10 in vitro (Jin et al., 2018), potentially driven by a reduction in NF- κ B activation (Oliver et al., 2012). ω -3 PUFAs have also been reported to induce polarisation of macrophages towards an anti-inflammatory M2 phenotype through **PPAR γ** signalling (Chang et al., 2015; Kumar et al., 2016). Furthermore, ω -3 PUFAs induce an improvement in the phagocytic capacity of monocytes and neutrophils (Gorjão et al., 2006) and enhanced neutrophil recruitment during endotoxin-induced inflammation (Arnardottir et al., 2013). Animal studies have reported that supplementation with ω -3 PUFAs reduces Th17 polarisation (Monk et al., 2013) via dampening expression of **ROR γ** and STAT3 and decreasing responsiveness to Th17 polarising cytokines (Monk et al., 2013). Furthermore, EPA has been reported to dampen adipose inflammation via macrophage-mediated T_{reg} induction in mice (Onodera et al., 2017). Preclinical evidence in mice has reported the potential of DHA in enhancing IgM and anti-inflammatory cytokine (IL-10) production by B cells, driven by changes in B-cell membrane packaging of lipid microdomains (Teague et al., 2014).

The ω -3 PUFAs exert their immunomodulatory effects via a range of mechanisms; for example, they can be enzymically converted into specialised pro-resolving mediators (SPMs), which include lipoxins, resolvins, protectins and maresins. SPMs activate GPCRs on immune cells to promote the uptake and clearance of apoptotic cells and cellular debris, enhance bacterial killing, regulate leukocyte trafficking to inflammatory sites and suppress the production of pro-inflammatory mediators (IL-1 β and TNF- α) (Chiang et al., 2012; Cucchi et al., 2019; Dalli et al., 2015). Furthermore, ω -3 PUFAs have been reported to inhibit ceramide production by targeting de novo synthesis (Dong et al., 2017; Jin et al., 2018), increase fatty acid oxidation and decrease lipogenesis, reducing circulating triglyceride and cholesterol levels (Green et al., 2020). PUFAs possess multiple double bonds in their carbon chain and are also able to increase fluidity of cellular membranes, which can in turn affect their cellular signalling function (Hashimoto & Hossain, 2018).

4.2 | Short-chain fatty acids

Commensal gut bacteria produce metabolites, such as SCFAs (**butyrate**, **acetate** and **propionate**), which are end-products of bacterial fermentation of non-digestible dietary fibres. Additionally, amino acid fermentation and lactate metabolism also produce SCFAs (Bourriaud et al., 2005). These microbiota-metabolised fatty acids play a key role in the maintenance of health and serve as energy sources for gut epithelial cells, enhance epithelial barrier integrity, alter lipid metabolism, regulate appetite and body weight and possess anti-inflammatory and immunomodulatory properties (Morrison & Preston, 2016). Emerging evidence suggests that SCFAs exert multiple effects on a range of immune cells. For instance, butyrate enhances macrophage antimicrobial function, mediated through inhibition of **histone deacetylase 3 (HDAC3)** and a switch in glucose metabolism (Schulthess et al., 2019), and inhibits inflammatory cytokine production (Usami et al., 2008). SCFAs can act as chemoattractant for neutrophils and play a critical role in neutrophil chemotaxis, mediated by **FFA2 receptors (GPR43)**, during intestinal inflammation (Sina et al., 2009). Furthermore, SCFAs, in particular butyrate, promote differentiation of naïve T-cells to T_{reg} via HDAC inhibition at the *Foxp3* locus (Furusawa et al., 2013), activate **aryl hydrocarbon receptor (AhR)**-dependent gene transcription in B cell to promote regulatory B-cell differentiation (Rosser et al., 2020) and up-regulate anti-inflammatory IL-10 expression while suppressing Th17 polarisation (Singh et al., 2014; Zhang et al., 2016).

Along with the decline in immune function with age, there is a decline in gut commensal SCFA-producing bacteria, such as *Clostridium leptum* and *Eubacterium rectale* (Biagi et al., 2010), resulting in a decline in stool and circulating SCFA levels (Rampelli et al., 2013). Host-microbiota interactions drive inflammatory diseases beyond the intestine; for instance, there is mounting evidence for a pathogenic role in RA, with reduced levels of SCFA in stool samples of RA patients (Rosser et al., 2020). Thus, from this and the previously mentioned effects of SCFAs on the immune system, it is not unreasonable to suggest that this age-associated reduction in SCFAs may be involved in disrupted immune homeostasis and inflammaging (Conway et al., 2021).

5 | STRATEGIES FOR SLOWING IMMUNE SENESENCE AND EXTENDING HEALTHSPAN

In the previous sections, we discussed evidence suggesting a potential link between age-associated changes to the micro-environment, driven by changes in the bioavailability of key metabolites and inflammaging. Given that ageing is a malleable process, this section will explore the immune stimulatory, anti-inflammatory and healthspan extension effects of metabolite-based nutrient and pharmacological intervention strategies (Figure 3).

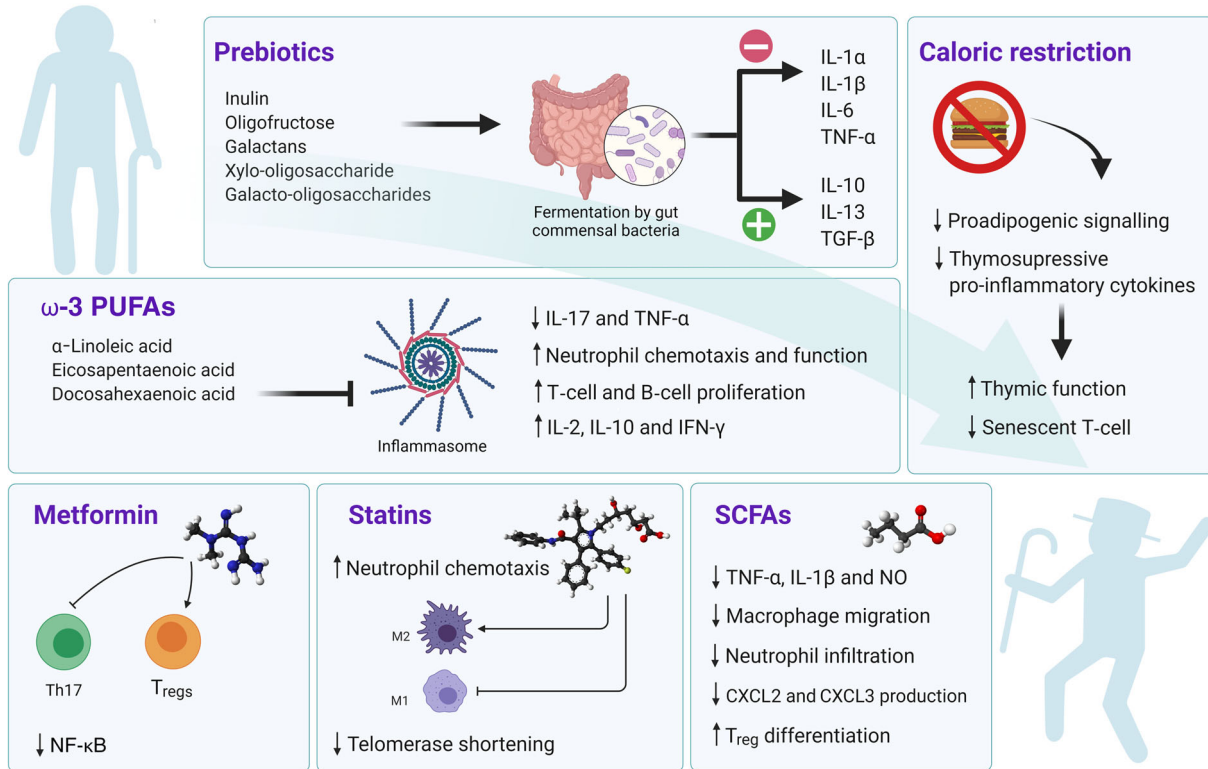


FIGURE 3 The reversal of immune senescence via dietary modifications and pharmacological interventions. The close link between diet, bioactive nutrients, supplements and immune function provides evidence of the crucial role of dietary strategies as regulators of the immune response and immune senescence. Together with caloric restriction, the intake of prebiotics and nutraceuticals can help restore normal immune system functions, leading to a reduction in the chronic inflammatory state. In addition, pharmacological approaches, that is, metformin and statins, are promising treatments for several age-related pathologies, including immune senescence. CXCL2, CXCL3, chemokines; M1, M1 polarised macrophages; M2, M2 polarised macrophages; PUFAs, polyunsaturated fatty acids; SCFAs, short-chain fatty acids; Treg, regulatory T-cells

5.1 | Prebiotics

These are non-digestible food ingredients, such as inulin and oligofructose, which are fermented by gut commensal bacteria to produce SCFAs, and have gained attention due to their potential for enhancing the health of the gut microbiome (Wong et al., 2006). Additional health benefits of prebiotics including improved mineral absorption, lipid metabolism and mucin production have been reported (Roy et al., 2006). The beneficial effects of prebiotics on the intestinal mucosa and disease resolution have been shown in patients with a variety of intestinal diseases, such as ulcerative colitis and irritable bowel syndrome (Hamer et al., 2010; Kles & Chang, 2006). Multiple studies have reported direct and indirect immunomodulatory effects of prebiotics via the induction of SCFA production. For example, the prebiotic composition of inulin and oligofructose decreases caecal inflammation (IL-1 β) in rats (Hoentjen et al., 2006). Human studies investigating the effects of supplementation with galactans (5.5 g·day⁻¹) for 10 weeks showed increases in the production of anti-inflammatory cytokine IL-10 and reduced production of pro-inflammatory cytokines (IL-1, IL-6 and TNF- α) by leukocytes in older adults (Vulevic et al., 2008). Moreover, anti-inflammatory effects of other prebiotics, such as inulin, xylo-oligosaccharide and galacto-oligosaccharides, have also been reported in young individuals

(Shokryazdan et al., 2017). Although manipulating the diet-gut microbiome-host metabolism axis represents a relatively simple and cost-effective prospect if targeted appropriately, these health-promoting benefits of prebiotics are short-lived, with the gut microbial profile returning to its pre-supplementation condition within weeks of supplement discontinuation. This presents a challenge in translating these initial promising findings into strategies that could improve immune health with advancing age.

5.2 | Polyunsaturated fatty acids

Intake of specific nutrients, particularly ω -3 PUFAs, has been reported to modify host lipid composition, improve cardiovascular health (Hu et al., 2019), increase muscle mass and function (Smith et al., 2015), improve cognitive health and reduce several morbidities (Buhr & Bales, 2009). As discussed above, the ω -3 PUFAs possess immunoregulatory properties, shown in clinical trials in obese individuals reporting that supplementation with ω -3 PUFAs reduced systemic inflammation, via inhibition of inflammasome activation (Haghiac et al., 2015; Lee et al., 2019). Other clinical trials have highlighted the ability of fish oil supplements rich in ω -3 PUFAs to enhance neutrophil chemotaxis (Gorjão et al., 2006), reduce peripheral IL-17 levels

(Farjadian et al., 2016) and enhance B-cell differentiation towards antibody-secreting cells (Ramon et al., 2012) in young individuals and children. To our knowledge, there are only two studies that have investigated the effects of supplementation with ω -3 PUFAs on immune cell function in older adults. Fish oil consumption by older women for 60 days improved neutrophil phagocytosis and ROS production, increased T-cell proliferation, decreased TNF- α production and increased IL-2, IL-10 and IFN- γ production by lymphocytes (Rodacki et al., 2015). However, in another study, fish oil supplementation for 12 weeks decreased NK cell cytotoxicity (NKCC) in healthy adults aged 55 and over (Thies et al., 2001). In conclusion, these studies suggest the need for further studies in older adults to determine the optimal dose and duration of supplementation and the potential of ω -3 PUFAs to reduce immune senescence.

5.3 | Short-chain fatty acids

The increased antibiotic consumption by older adults results in butyrate depletion, exerting a dampening effect on immunity. In recent years, there has been an expansion in the number of research studies reporting the therapeutic potential of SCFAs in treating inflammatory conditions and colon cancer. Whether restoring butyrate levels can reduce immune senescence is less clear, and the majority of studies focus on inflammation. Animal studies have reported anti-inflammatory effects of oral administration of sodium butyrate, including reduced concentrations of TNF- α , IL-1 β and NO in bronchoalveolar lavage fluid, reduced infiltration of neutrophils and lung injury caused by sepsis and improved survival rate (Ni et al., 2010; Zhang et al., 2007). Additionally, a butyrate-supplemented chow diet for 10 weeks suppressed macrophage migration and inflammation and increased collagen deposition in lesions and plaque stability in apolipoprotein (apoE) knockout mice, resulting in a 50% decline in atherosclerosis in the aorta (Aguilar et al., 2014). These findings highlight the potential of SCFAs as a therapeutic strategy for atherosclerosis. A study in human IBD patients has reported that butyrate enema, alone or as a cocktail of SCFAs, was successful in ameliorating colonic inflammation in these patients (Scheppach et al., 1992). A pilot study in 12 older adults undergoing upper abdominal surgery confirmed the feasibility of pharmacological butyrate administration via enema in increasing butyrate concentrations in portal vein blood (Van der Beek et al., 2015). Whether butyrate supplementation enhances immune responses in older adults receiving antibiotics is an important question that should be addressed in future studies. This research will enable us to exploit the multifaceted roles of SCFAs in protecting the body against deteriorating metabolic control and increased inflammatory status with advancing age.

5.4 | Caloric restriction

The modulation of metabolic pathways via caloric restriction, the practice of reducing ad libitum calorie intake by 20–40% while

maintaining intake of vitamins and minerals, has been reported to extend lifespan, delay the onset of age-related diseases and reduce visceral body fat accumulation (Mattison et al., 2017). Thus, it is not surprising that caloric restriction has anti-inflammatory effects in animals (Willette et al., 2010) and humans (Das et al., 2017). Age-associated lipid accumulation in the thymic space contributes towards thymic involution. A mouse model of caloric restriction reported maintenance of thymic function and T-cell output driven by a reduction on proadipogenic signalling (Yang et al., 2009). Another potential driver of increased thymic output in calorie-restricted animals is reduced levels of thymosuppressive pro-inflammatory cytokines such as TNF- α . Furthermore, studies in calorie-restricted aged mice have reported decreased senescent T-cell frequency, altered cytokine (IFN- γ and TNF- α) secretion profile by T-cells (Messaoudi et al., 2006) and improved memory T-cell responses (Collins, 2020). Whether these findings can be replicated in humans remains to be established. Furthermore, it is crucial to determine the period of caloric restriction that is sufficient for inducing an anti-immune senescence effect and whether aged individuals will be willing to adopt a calorie-restricted diet for a prolonged period of time.

5.5 | Pharmacological alternatives

Although improving health in old age via dietary-based interventions discussed above remains attractive, they are unlikely to be adopted at a population level. Thus, pharmacological drugs with anti-immune senescence properties are gaining attention (Figure 3). One such agent is metformin, a diabetic drug that mimics some of the benefits of caloric restriction, including healthspan extension and reduction in cholesterol levels (Martin-Montalvo et al., 2013). Recent clinical studies have reported an anti-inflammatory effect of metformin (Saisho, 2015), driven by inhibition of the age-associated increase in NF- κ B (Sultuybek et al., 2019). An attenuation of Th17 differentiation and up-regulation of T_{regs} has also been reported in mouse models of arthritis (Son et al., 2014). Interestingly, the potential of metformin in reducing mortality in patients hospitalised with COVID-19 infection has been observed, possibly due to its anti-inflammatory effects (Bramante et al., 2020).

Statins, inhibitors of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, are known inhibitors of cholesterol synthesis that exert a cardioprotective effect (Ludman et al., 2009). However, they also result in reduced GTPase signalling due to reduced generation of geranylgeranyl moieties required for G-protein prenylation and function, giving them much wider, pleiotropic, effects. Additional health benefits of statins include extension of lifespan and healthspan in *Drosophila* (Spindler et al., 2012), adipose tissue remodelling, and prevention of insulin resistance and diabetes in obese mice (Holland et al., 2007). Statins also possess anti-inflammatory properties in healthy older individuals (Mora et al., 2010). Our own data have reported a beneficial effect of statins in restoring the age-associated decline in neutrophil chemotaxis (Sapey et al., 2017). The clinical relevance of these findings is supported by data showing that patients admitted to hospital with

pneumonia who are already on statin medication have reduced mortality compared with those not taking statins (Grudzinska et al., 2017) and that giving statins to older patients with pneumonia significantly reduces mortality (Sapey et al., 2018). Additional immunomodulatory properties of statins include elevated macrophage polarisation towards anti-inflammatory M2 phenotype (Chaurasia et al., 2016), antimicrobial effects (Hennessy et al., 2016) and slowing of telomerase shortening (Boccardi et al., 2013). Considering the widespread use of statins globally, further studies to investigate their immune-enhancing potential, optimal dosage and treatment duration are crucial for statins to be considered as an anti-immune senescence drug.

6 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Ageing is a highly complex process, accompanied by remodelling of the immune system (Figure 1), resulting in an age-associated increased risk of infections, chronic diseases and autoimmunity. Our understanding of the effects of metabolites in the micro-environment on immune responses has expanded in recent years, but numerous questions remain unanswered. There is an increasing need to develop a better understanding of the signals in the micro-environment that affect the phenotype and function of immune cells.

An age-associated elevation in the levels of saturated fatty acids, cholesterol, ceramides and lactate, decline in SCFAs and loss of glutamine and tryptophan are potential contributors towards age-associated inflammageing and several features of immune senescence (Figure 2). The prospect of restoring bioavailability of host metabolites and reversing immune senescence is a possibility. Moreover, we have discussed the immune-enhancing effects of dietary modifications and pharmacological interventions (Figure 3) and proposed additional areas of promising gerotherapeutic agents that target these metabolites, such as glutamine supplementation and IDO inhibitors, to improve immune function in older adults. Therefore, there is a need for well-designed studies that mechanistically link metabolites to immune senescence and inflammageing beyond association, and reduce the age-associated increased risk of chronic diseases, thus extending healthspan in older adults.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (<http://www.guidetopharmacology.org>) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Cidlowski et al., 2019; Alexander, Fabbro et al., 2019a, 2019b; Alexander, Kelly et al., 2019a, 2019b)

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest connected to this paper.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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