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The role of T cells in age-related diseases

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Abstract | Age-related T cell dysfunction can lead to failure of immune tolerance mechanisms, resulting in aberrant T cell-driven cytokine and cytotoxic responses that ultimately cause tissue damage. In this Review, we discuss the role of T cells in the onset and progression of age-associated conditions, focusing on cardiovascular disorders, metabolic dysfunction, neuroinflammation and defective tissue repair and regeneration. We present different mechanisms by which T cells contribute to inflammageing and might act as modulators of age-associated diseases, including through enhanced pro-inflammatory and cytotoxic activity, defective clearance of senescent cells or regulation of the gut microbiota. Finally, we propose that 'resetting' immune system tolerance or targeting pathogenic T cells could open up new therapeutic opportunities to boost resilience to age-related diseases.

Age-related diseases are often characterized by the presence of sustained inflammatory processes that ultimately contribute to the breakdown of tissue homeostasis[1]. As immune cells are essential for both mounting and successfully resolving inflammatory responses, age-associated diseases are beginning to be understood through the prism of a causal contribution of the immune system. Although the contribution of the innate immune system to several age-related pathologies has long been acknowledged, more recent studies are also disclosing an active participation of the adaptive immune system, highlighting a central role for T cells.

In this Review, we discuss recent evidence supporting the idea that T cells contribute to the onset and progression of various age-related conditions. We focus on cardiovascular conditions — including hypertension, atherosclerosis and myocardial infarction — and on metabolic disorders such as obesity-associated insulin resistance. Despite their scarce presence in the central nervous system, roles for T cells in age-associated neurological disorders are also becoming evident and this area is currently a major research focus. Thus, we also discuss the roles of T cells in neurodegenerative disorders such as Alzheimer disease or Parkinson disease and in ischaemic stroke. Although other diseases that are classically categorized as autoimmune disorders — such as rheumatoid arthritis, multiple sclerosis, type I diabetes or myocarditis — can also be associated with ageing, we have excluded them from this Review because the involvement of T cells in these pathologies is unquestionable and has been discussed elsewhere[2]. Finally, in the context of ageing, the roles of T cells in tissue renewal, homeostasis and repair could be particularly important for the maintenance of barrier tissue integrity, especially in the gut. In line with this, Elie Metchnikoff proposed more than a century ago that age-related dysfunction could result from increased chronic systemic inflammation owing to enhanced colon permeability[3]. We have revisited this concept in light of recent advances that suggest a crucial role for T cells in regulating barrier tissue maintenance and the gut microbiota.

T cells in ageing and inflammageing

The most striking variations seen with age in the total T cell pool are the shrinking of the naive T cell compartment and the increase of the memory T cell pool, leading to a reduction in the size of the available T cell receptor (TCR) repertoire. These changes are caused, in part, by thymic involution, by impaired homeostatic proliferation of naive T cells and by the exposure of T cells to antigens throughout life[4]. Memory T cells in older people acquire extremely differentiated phenotypes, and lose the expression of co-stimulatory molecules such as CD28 and CD27, becoming senescent or exhausted[5,6]. Both senescent and exhausted T cells display certain molecular hallmarks of ageing, such as mitochondrial dysfunction[7,8] and epigenetic remodelling[4,9]. In addition, senescent T cells display signs of DNA damage and short telomeres and activate senescence-associated signalling pathways[10–12]. Besides low expression of co-stimulatory molecules, expression of natural killer cell-associated markers (KLRG1, NKG2A, NKG2C and NKG2D) allows the identification of senescent T cells in humans and mice[13]. In humans, senescent

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T effector memory CD45RA$^+$ (TEMRA) cells
A subset of human memory T cells. TEMRA cells re-express the naive T cell-associated marker CD45RA and display multiple characteristics associated with senescence.

Inflammageing
Low-grade chronic inflammation in the absence of infection that appears in association with ageing.

Senescence-associated secretory phenotype
(SASP). Cellular response associated with the irreversible arrest of cell proliferation and consisting of the release of cytokines, chemokines, proteases and growth factors that affect nearby cells in a paracrine manner.

Senescence surveillance
Immune-mediated clearance of senescent cells.

T cells include a fraction of the terminally differentiated T effector memory CD45RA$^+$ (TEMRA) cells that re-express CD45RA and have preferential homing capacity for peripheral tissues[12]. This is due to the expression of chemokine receptors, such as CX_3C-chemokine receptor 1 (CX_3CR1) and CC-chemokine receptor 5 (CCR5), that enable homing to peripheral sites of inflammation and the loss of lymphoid-homing receptors, such as CD62L and CCR7. Additionally, CD57 and FAS (also known as CD95) have also been used to identify senescent human T cells[14] and CD153 is commonly used to identify a minor population of senescent T cells in mice[15–17]. Functionally, senescent T cells acquire extremely differentiated phenotypes, harbouring features of T helper 1 (T_H1) cells, T_H17 cells, T_H9 cells, T follicular helper (T_{FH}) cells or activated regulatory T (T_{reg}) cells, and are characterized by increased secretion of pro-inflammatory, cytotoxic and anti-inflammatory cytokines[5,18]. On the other hand, exhausted T cells lose the capacity to secrete effector cytokines and are characterized by the expression of inhibitory molecules such as PD1, TIM3 and LAG3, and the transcription factors TOX and BLIMP1 (REF.[6]). Traditionally, owing to their inflammatory and cytotoxic signature, senescent T cells have been considered to harbour pathological potential[19]. However, a recent report showed that exhausted T cells secrete high amounts of granzyme K that can also exacerbate inflammation[18], supporting the idea that different subsets of age-associated T cells can promote tissue damage. The accumulation of these age-associated T cells can also be accelerated by external factors, such as chronic viral infections that occur over the human lifespan[19]. Of note, individuals less susceptible to age-associated accelerated immunosenescence upon cytomegalovirus infection are associated with families with extreme longevity[20].

Inflammageing is the chronic, low-grade inflammatory state that appears in association with ageing. It is characterized by increased circulating levels of certain cytokines, such as IL-6 and tumour necrosis factor (TNF)[21,22]. Although inflammageing was initially attributed to the accumulation of non-immune senescent cells, recent evidence has highlighted T cells as major drivers of this age-associated inflammation[18,23,24]. Our studies using a mouse model with T cell-specific deletion of the mitochondrial transcription factor A (TFAM) have shed light on the role of T cells in inflammageing. These mice mimic the age-related mitochondrial dysfunction and glycolytic reprogramming that occur in T cells from older mice. Indeed, TFAM-deficient T cells show several features of immunosenescence, such as impaired TCR-dependent proliferation, the acquisition of an extremely differentiated T_H1-type phenotype by effector CD4$^+$ T cells[25] and enhanced vulnerability to infections[23]. Remarkably, these mice present with premature inflammageing[23], accompanied by dramatic cardiovascular, metabolic and cognitive dysfunction, overall leading to a lifespan reduction of 50%. These observations establish a causal link between T cells, inflammageing and age-related disorders, turning this mouse model into an innovative platform to study the consequences of the age-related decline in T cells. The detrimental role of an age-associated upregulation of the expression of glycolytic genes in T cells has also been supported by an alternative experimental approach based on the changes in expression of certain microRNAs (miRNAs) that are important molecular regulators of T cell function during ageing. Both miR-146a and miR-155 are induced upon T cell activation, the first as a negative regulator and the latter as an enhancer of the immune response. Interestingly, the global deletion of miR-146a in a mouse model causes life-shortening chronic inflammation. The molecular mechanism mediating this dramatic phenotype in response to the ablation of miR-146a involves the skewing of T cell metabolism towards aerobic glycolysis, which is dependent on the T cell-specific expression of miR-155 (REF.[26]).

T cells may contribute to age-related diseases by several mechanisms (FIG. 1). First, the sustained production of cytokines, mainly interferon-γ (IFNγ) and TNF, by age-associated T cells directly contributes to inflammageing and can promote the activation of a senescence programme in neighbouring and distant cells[23]. In turn, the senescence-associated secretory phenotype (SASP) boosts inflammation and promotes T_H17 and T_H1 cell differentiation[27], fuelling a feedback loop that ultimately contributes to tissue damage (FIG. 1a). Moreover, the secretion of granzyme K by exhausted T cells aggravates the SASP of senescent cells[18]. Second, dysfunctional T cells could also be inefficient in senescence surveillance function, thus failing in the clearance of irreversibly damaged cells that become sensescent[28] (FIG. 1b). Third, a loss of self-tolerance is driven not only by the increased cytotoxicity of senescent CD8$^+$ T cells but also by the fact that senescent CD4$^+$ T cells acquire cytotoxic properties and become able to secrete cytotoxic granule contents that directly damage cells in the tissues[5,13,29] (FIG. 1c). Last, T cells can indirectly participate in age-associated disorders through the modulation of gut homeostasis[30,31] (FIG. 1d). Given the paramount role of immune cells in age-related diseases, the ageing process could directly result from a breakdown in immune tolerance mechanisms and/or from immune system hyperactivation. Below, we consider the specific roles of T cells in different age-related diseases (FIG. 2).

T cells in cardiovascular disorders

Cardiovascular disorders (CVDs) are the major cause of death in the world. The incidence of these diseases, which include aortic aneurysm, heart failure, myocardial infarction and ischaemic stroke, dramatically increases with age. As part of their pathogenesis, numerous CVDs present with increased systemic and organ-specific immune activation. Indeed, during the formation of the atherosclerotic plaque, macrophages uptake low-density lipoprotein (LDL) particles, secrete pro-inflammatory molecules and eventually become foam cells, which are lipid-laden macrophages known to form the core of the plaque and to promote its instability[32]. This facilitates further recruitment of other immune cells, including T cells. Within the plaque, infiltrating T cells can tune macrophage polarization through the secretion of pro-inflammatory molecules, such as TNF or IFNγ, or via anti-inflammatory cytokines such as IL-10. Thus, T cells can either act as positive or negative modulators

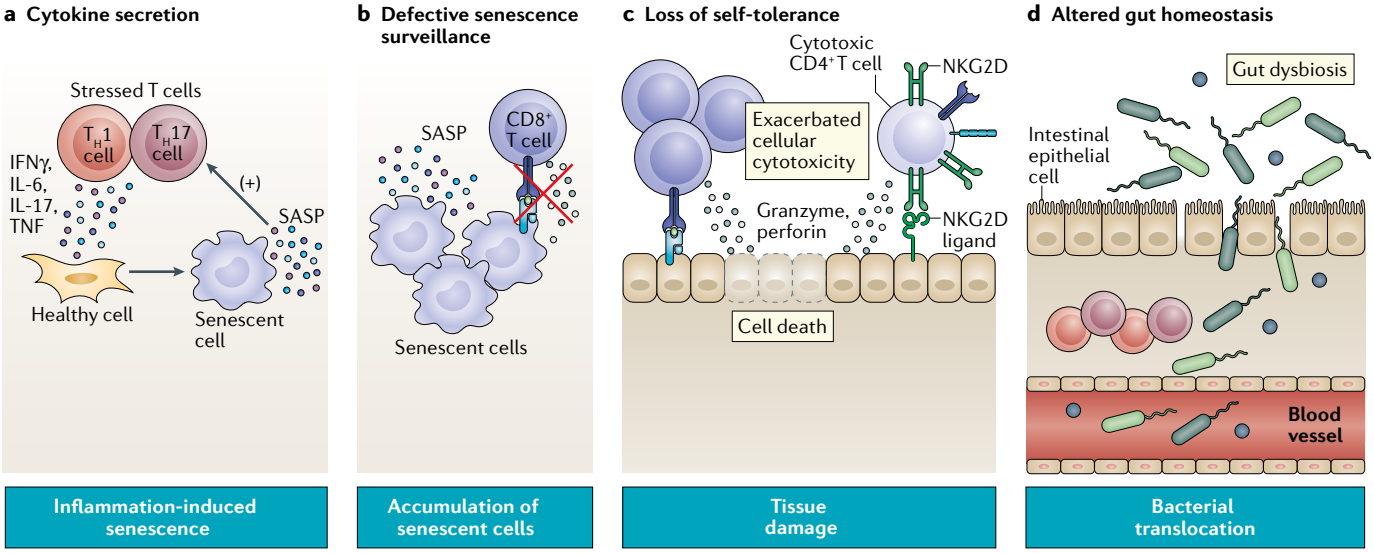

Fig. 1 | **Molecular basis of T cell contribution to inflammageing and age-related diseases.** Accumulating data highlight that dysregulated T cell responses contribute to inflammageing and unhealthy ageing through several mechanisms. **a** | Metabolic T cell dysfunction associated with ageing leads to acquisition of a pro-inflammatory T cell phenotype. The resulting T cell subsets secrete cytokines that promote the accumulation of senescent cells, which are characterized by the senescence-associated secretory phenotype (SASP). SASP-associated mediators fuel T helper 1 (T_H1) cell and T_H17 cell differentiation, exacerbating inflammation. **b** | Dysfunctional T cells lose their ability to effectively clear senescent cells from tissues. Accumulation of senescent cells contributes to inflammation and promotes tissue damage. **c** | Cytotoxic $CD8^+$ and $CD4^+$ senescent T cells indiscriminately recognize and destroy cells in tissues, highlighting the importance of immune tolerance mechanisms. **d** | Imbalanced T cell activity in the gut mucosa can compromise intestinal barrier integrity, allowing bacteria to translocate into the circulation and contributing to systemic inflammation. IFNγ, interferon-γ; TNF, tumour necrosis factor.

of atherosclerotic plaque formation and maintenance[33] (FIG. 2). Together with atherosclerosis, hypertension can be the starting point of many CVDs. In this regard, T cells have emerged as controllers of the blood pressure in mouse models of angiotensin II-induced hypertension[34].

Different $CD4^+$ T cell subpopulations accumulate in human atherosclerotic plaques[35]. Depending on the subset, they can either exert a protective role or become pathogenic through the acquisition of a T_H1 cell phenotype and contribute to the progression of the disease[33,36,37] (FIG. 2). A T_H1-type cytokine profile was identified by histological techniques in human atherosclerosis samples[36] and the direct causative role of T_H1 cells was established in T-bet-deficient atherosclerotic mice, in which a switch from a T_H1-type towards a T_H2-type response leads to reduced atherosclerosis[37]. Moreover, as binding of oxidized LDL to CD69 is known to maintain human and mouse T cells in an anti-inflammatory state, a decrease in T cell CD69 levels correlates with increased pro-inflammatory cytokine production and with the presence of subclinical atherosclerosis in humans[38]. In addition, $CD4^+$ T cells expressing the TNF-related apoptosis-inducing ligand (TRAIL) promote plaque instability by inducing apoptosis of vascular smooth muscle cells that express the death receptor 5 (TRAIL receptor 2)[39]. The pathogenic role of pro-inflammatory $CD4^+$ T cells is not restricted to atherosclerosis. In fact, in older mice, $CD4^+IFN\gamma^+$ T cells accumulate in the heart and in the heart-draining lymph nodes and contribute to myocardial impairment by promoting inflammation[40].

Although the pro-atherogenic role of $CD4^+$ T_H1 cells has been established, the role of $CD8^+$ T cells remains controversial. A particular subtype of peripheral $CD8^+$ T cells that display enhanced proliferation and express naive markers, despite expressing CD95 and secreting pro-inflammatory cytokines, has been associated with increased CVD severity in humans and promotes atherosclerosis when transferred into mice[41]. In APOE-deficient mice fed a high-fat diet (HFD), $CD8^+$ T cells contribute to the progression of atherosclerosis by inducing apoptosis in endothelial cells and vascular smooth muscle cells via perforin and granzyme B release, and antibody-mediated depletion of $CD8^+$ T cells ameliorates the disease[42]. Strikingly, the presence of $CD8^+$ T cells confers protection against lesion instability by inducing FAS/FASL-mediated apoptosis of macrophages and T_H1 cells in advanced atherosclerotic plaques from *Ldlr*$^{-/-}$ mice, suggesting that these cells could play a dual role depending on the stage of the disease[43]. Similarly, IFNγ-producing $CD8^+CD43^+$ T cells promote the development of abdominal aortic aneurysm lesions in an elastase-induced murine model[44].

Dysfunctional T_{FH} cells are beginning to be recognized as contributors to CVDs. ATF3-dependent expression of PDL1 in marginal zone B cells supresses T_{FH} cell function, decreasing the size of aortic plaques in a mouse model of a high-cholesterol diet[45]. Reinforcing this idea, the conversion of a fraction of T_{reg} cells into T_{FH} cells has been shown to promote atherogenesis, involving the increased expression of IL-6Rα and the downregulation of IL-2Rα and phosphorylated STAT5 (REF.[46]).

Reduced numbers of circulating T_{reg} cells are associated with the development of acute coronary events, but not stroke, in humans[47]. In addition, a decline in T_{reg} cell function occurs in many CVDs, such as atherosclerosis,

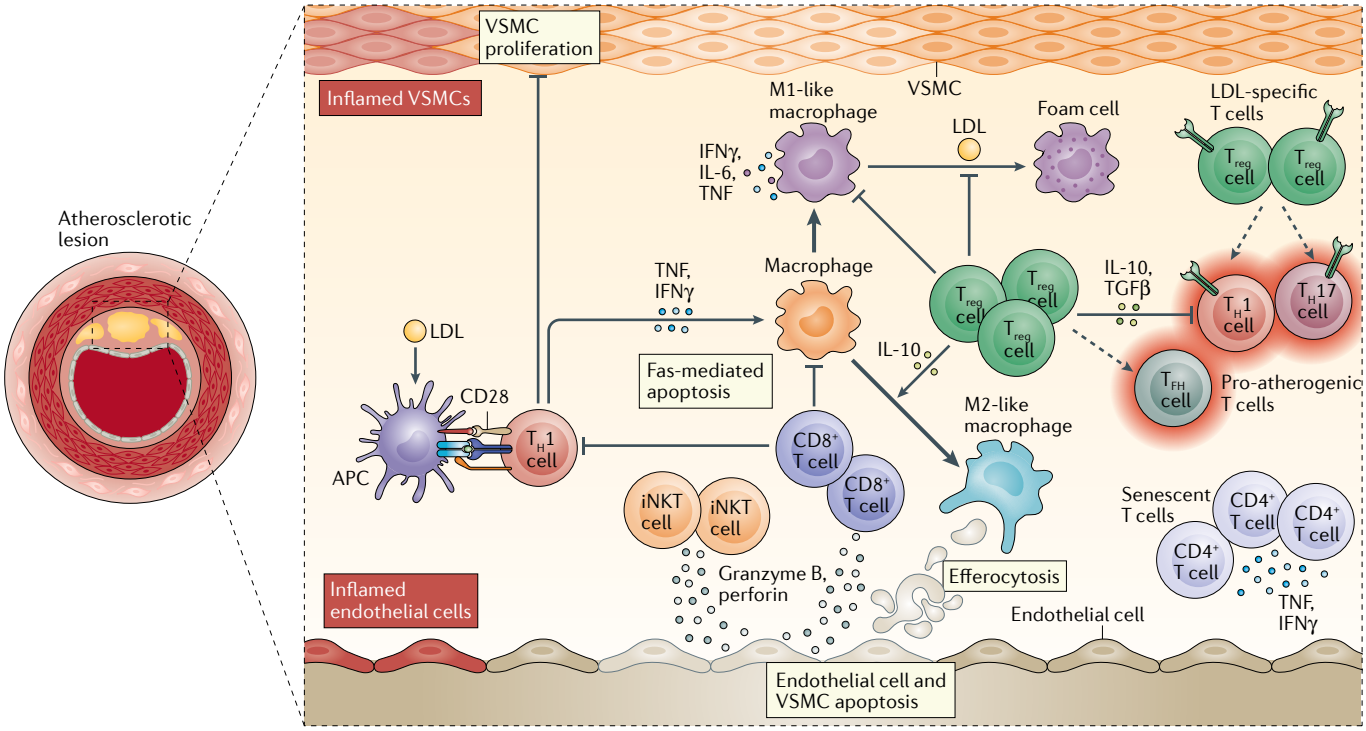

Fig. 2 | **T cell contribution to atherosclerosis.** During the progression of atherosclerosis, antigens derived from components such as low-density lipoprotein (LDL) are presented to naive CD4$^+$ T cells by antigen-presenting cells (APCs). This can lead to activation of antigen-specific CD4$^+$ T cells and their differentiation into T helper 1 (T_H1) cells that secrete interferon-γ (IFNγ) and tumour necrosis factor (TNF). T_H1-type cytokines inhibit the proliferative capacity of vascular smooth muscle cells (VSMCs) and amplify the inflammatory response by promoting differentiation of M1-like macrophages. Regulatory T (T_{reg}) cells inhibit the differentiation and proliferation of T_H1 cells, the acquisition of an M1-like phenotype in macrophages and the formation of macrophage-derived foam cells; at the same time, they promote the activation of pro-resolving (M2-like) macrophages. The conversion of T_{reg} cells into T follicular helper (T_{FH}) cells promotes atherosclerosis, as does the acquisition of T_H1 cell and T_H17 cell profiles by autoreactive T cells with a regulatory profile. Some activated T cells eventually acquire a senescent phenotype and exacerbate inflammation by releasing pro-inflammatory cytokines. In addition, CD8$^+$ T cells and invariant natural killer T (iNKT) cells contribute to plaque instability by exerting a cytotoxic activity against endothelial cells and VSMCs. TGFβ, transforming growth factor-β.

myocardial infarction and aneurysm, and the severity of these diseases negatively correlates with total T_{reg} cell numbers or function in mice and humans[48–50]. T_{reg} cells can prevent CVDs by several mechanisms[33,48] (FIG. 2). For instance, T_{reg} cells elicit anti-atherogenic effects by reducing the number of inflammatory macrophages, by blocking foam cell formation in mouse models of atherosclerosis[51] or through IL-10 and transforming growth factor-β (TGFβ)-dependent suppression of T_H1 cell proliferation[52]. In mice, T_{reg} cells can also promote atherosclerosis regression by secreting IL-10 that induces efferocytosis in the plaque and enhances the pro-resolving capacity of macrophages[53]. In a mouse model of aneurysm, T_{reg} cells downregulate MMP2 and MMP9 metalloproteinase activity and the release of pro-inflammatory cytokines such as CCL2 and IL-6, decreasing the incidence of aneurysms[54]. A specific subset of T_{reg} cells overexpressing the collagen-binding matrix protein SPARC ameliorate cardiac rupture after myocardial infarction in mice, through the induction of collagen production and maturation[55]. T_{reg} cells can also promote cardioprotection by inducing cardiomyocyte proliferation through secretion of molecules such as insulin-like growth factor 2 (IGF2), matrilin 2 (MATN2), fibrinogen-like 2 (FGL2) and IL-33 in murine models of myocardial infarction[56].

Autoreactive T cells also play a role in certain CVDs (FIG. 2). T cells recognizing the LDL core protein APOB initially present a regulatory transcriptional profile that progressively converts into a pro-inflammatory T_H1/T_H17 cell phenotype in mice and humans with atherosclerosis. Accordingly, adoptive transfer of these cells fails to protect against plaque formation in *Apoe*$^{-/-}$ mice[57]. In this regard, T_{reg} cells recognizing the α-myosin heavy chain (also known as myosin 6) play a cardioprotective role and improve cardiac function early after myocardial infarction[58].

The role of invariant natural killer T (iNKT) cells in CVDs is still open to discussion. The treatment with a CD1 lipid antagonist that inhibits iNKT cell activation ameliorates atherosclerosis by decreasing necrosis and inflammation in *Apoe*$^{-/-}$ mice[59]. Similarly, a reduced size of atherosclerotic lesions is observed in *Cd1*$^{-/-}$*Apoe*$^{-/-}$ mice[60]. Strikingly, cardiac remodelling is accelerated in hypertensive CD1-deficient mice owing to a decrease in IL-10, which in turn promotes fibroblast activation[61].

Age-associated T cells have also been implicated in the pathogenesis of CVDs. In the blood of older

humans, increased numbers of CD4$^+$ T cells producing high levels of IL-17 and IFNγ, and bearing senescence features such as reduced expression of CD28 and increased levels of NKG2D, have been associated with metabolic risk factors for CVDs[62]. In fact, recent studies in humans established a correlation between cytomegalovirus seropositivity — a well-known driver of T cell senescence — and increased risk of suffering strokes, myocardial infarction, chronic heart failure and death owing to cardiovascular events[63,64]. Moreover, the presence of senescent T cells in the blood circulation has been associated with repetitive coronary events in patients with acute coronary syndrome or with detrimental cardiovascular episodes[62,65], and also predicts the development of cardiovascular events or mortality in patients with chronic heart failure[66,67]. Interestingly, a deeper characterization of circulating senescent T cells from patients with coronary artery disease and high risk factors for atherosclerosis has revealed that, in addition to pro-inflammatory cytokines, these cells express cytotoxic markers such as granzyme A, granzyme B and granulysin[68]. Importantly, different T cell subsets with features of senescence and exhaustion are present in human atherosclerotic plaques[35]. In fact, chronically activated senescent-like T cell clones in the atherosclerotic plaques of patients with coronary syndromes have been associated with plaque instability[69]. Interestingly, the transition towards a senescent phenotype in patients with acute coronary syndrome requires the proteasomal degradation of pro-apoptotic molecules such as BIM, BAX and FAS[70]. A causal pathogenic role of age-associated T cells in CVDs has been demonstrated in mice. In an angiotensin II model of hypertension, adoptive transfer of T cells from aged mice into young recipients accelerates cardio-renal damage through increased secretion of IFNγ, which promotes inflammation and fibrosis[71]. Recently, age-related cardiovascular alterations including aortic dilation, partial dissections and myocardial dysfunction have been reported in mice with premature T cell ageing caused by mitochondrial dysfunction[23]. These data suggest that senescent T cells could directly promote the development of CVDs.

T cells in metabolic dysfunction

During human ageing, the excessive fat deposition that occurs as a consequence of sustained calorie intake, in combination with gradual loss of muscle mass and insufficient physical activity, can ultimately precipitate chronic pathological conditions[72]. Importantly, T cells that reside in the adipose tissue are known to influence age-associated metabolic disorders, including obesity[73,74], type 2 diabetes[75] and insulin resistance[76].

CD4$^+$ and CD8$^+$ T cells specifically accumulate in visceral adipose tissue (VAT) and contribute to the pathology seen in aged mice[77], as well as in obesity and related metabolic conditions[74]. In this context, adipose tissue-resident T cells are more likely to undergo T_H1 cell differentiation, becoming detrimental producers of IFNγ[74,78,79]. In the initial stages of diet-induced obesity (DIO) in mice, CD4$^+$ T cells exert a protective effect on glucose homeostasis, leading to an early improvement in glucose tolerance and insulin sensitivity and controlling weight gain when transferred into HFD-fed mice lacking T cells. These metabolic improvements have been associated with the T_H2 cell polarization of the transferred T cells[78]. However, expansion of T_H1 cell[78] and T_H17 cell[80] populations in VAT promoted obesity-associated insulin resistance in humans and mice. Signal transducer and activator of transcription 3 (STAT3) is critically required for T_H17 cell differentiation and its functional ablation in T cells effectively prevents VAT inflammation and DIO, leading to improved insulin sensitivity and glucose tolerance in mice[76]. A massive infiltration of CD8$^+$ T cells occurs in the adipose tissue of HFD-fed mice with systemic insulin resistance, as a concomitant effect of a reduction in T_H2 cells and T_{reg} cells[73]. The secretion of perforin by CD8$^+$ T cells is important to limit the accumulation of IFNγ-producing CD4$^+$ and CD8$^+$ T cells as well as the expansion of CD8$^+$ T cells in inflamed VAT[81]. By contrast to this role of T_H1 cells and T_H17 cells in mediating obesity-associated insulin resistance, other studies suggest that predominant T_H1 cell responses are involved in adipose tissue remodelling and lipolysis. For instance, results from our laboratory indicate that the differentiation towards a T_H1 cell phenotype due to severe T cell mitochondrial dysfunction in mice results in an increased VAT lipolytic rate[23]. Accordingly, mice deficient in T-bet display increased intra-abdominal adiposity as well as decreased energy expenditure and physical activity, yet their glucose tolerance and insulin sensitivity are improved in comparison with their control counterparts[82].

T_{reg} cells with a unique transcriptomic signature are strikingly enriched in the VAT of lean mice compared with the VAT of obese mice with insulin resistance[77,83–85] (FIG. 3). The distinctive transcriptomic signature of the VAT-specific T_{reg} cell population that accumulates with age, which includes the upregulated expression of *Pparg*, *Gata3*, *Klrg1*, *Ccr2* and *ll1rl1* transcripts, has been found to appear long before their age-associated expansion[77,86] and to be reinforced until the age of 24 weeks, but gradually attenuated from week 40 (REF. [84]). By contrast, a dramatic shift into a different signature occurs in response to obesity, through a mechanism dependent on the phosphorylation of a specific residue of PPARγ[84]. In agreement with this, whereas fat-associated T_{reg} cells can have beneficial effects in improving certain metabolic parameters, such as insulin resistance, in DIO[79], they negatively affect age-associated metabolic parameters, for example, increasing fasting serum glucose and insulin levels as the mice age[85]. Notably, even the age-associated increase in mouse body weight and fat adiposity are reduced upon ablation of fat T_{reg} cells[85]. The accumulation of T_{reg} cells in ageing adipose tissue is a multistep process mediated by proliferation of certain clones coupled with enhanced survival. Transfer experiments using an engineered TCR-transgenic mouse model have revealed that this accumulation is driven by T_{reg} cell TCR specificity, with an important contribution of IL-33 signalling and the expression of FOXP3 and PPARγ[86,87]. Enhanced IL-33 signalling in VAT is achieved through different mechanisms. First, there is increased expression of the IL-33 receptor ST2 (encoded by *ll1rl1*) by VAT T_{reg} cells compared with splenic T_{reg} cells or with conventional CD4$^+$ T cells in

the VAT[85,86,88]. Second, increased IL-33 secretion by stromal cells in VAT is induced by PLZF$^+$ γδ T cell-derived IL-17 (REF.[89]). Third, there is a striking increase in the fraction of ST2$^+$ cells within the VAT T_{reg} cell compartment as a function of age[88]. Interestingly, IL-33 administration can rescue T_{reg} cell numbers and glucose tolerance but is unable to improve insulin sensitivity in different models of mouse obesity[88]. In this regard, the increased secretion of T_H1 cell-derived IFNγ, which is dependent on the higher expression levels of MHC class II by adipocytes in mice with DIO, interferes with the effects of IL-33 on the proliferation of T_{reg} cells in fat[79].

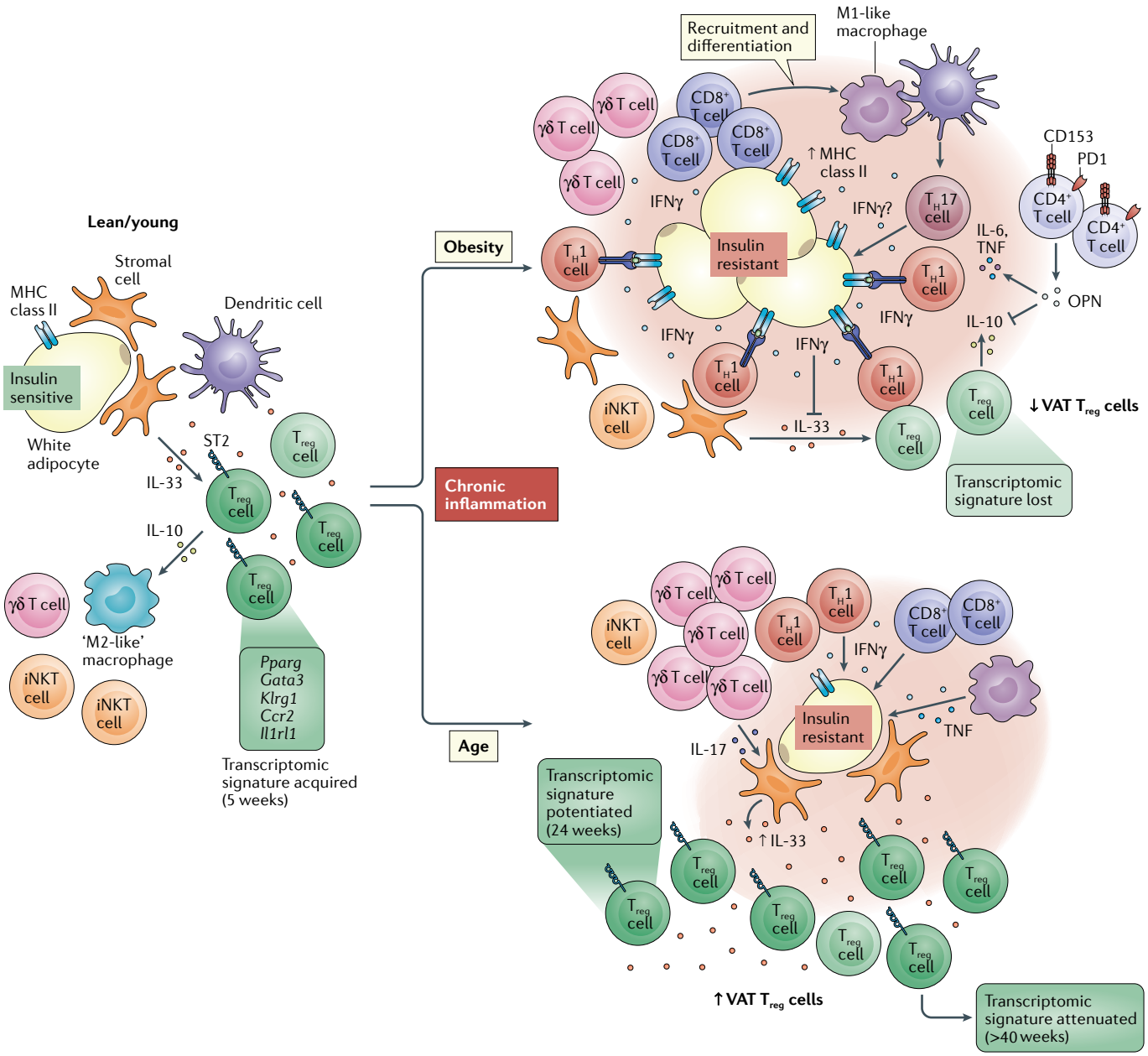

Fig. 3 | **T cell contribution to adipose tissue inflammation and pathology in obesity and ageing.** The distinctive early transcriptomic signature acquired by regulatory T (T_{reg}) cells in the visceral adipose tissue (VAT) of lean mice is enhanced and enriched during the age-related accumulation of VAT T_{reg} cells, whereas this signature is attenuated in late life (right bottom panel). By contrast, the VAT-specific T_{reg} cell transcriptional identity is lost with the induction of obesity, concomitant with a dramatic reduction in total T_{reg} cell numbers in VAT (right top panel). In the obese state, abundant CD8$^+$ T cells drive the recruitment and differentiation of M1-like macrophages and dendritic cells, which in turn promote T helper 17 (T_H17) cell differentiation that causes insulin resistance by affecting insulin receptor signalling. Increased expression of MHC class II molecules on the adipocyte surface stimulates interferon-γ (IFNγ) production by T_H1 cells, fostering inflammation and interfering with IL-33 signalling. Senescent CD153$^+$PD1$^+$ T cells also contribute to inflammation mainly by producing large amounts of osteopontin (OPN) that suppress IL-10 secretion by CD4$^+$ T cells. In lean adult mice, IL-17 secreted by PLZF$^+$ γδ T cells induces the production of IL-33 by stromal cells, enhancing IL-33 signalling through the ST2 receptor present on the surface of the VAT-specific T_{reg} cells. Pro-inflammatory cytokines such as IFNγ and tumour necrosis factor (TNF) that are derived from the increased numbers of T_H1 cells and CD8$^+$ T cells as well as from dendritic cells and M1-like macrophages negatively affect insulin sensitivity. In addition, both in ageing and in obesity, the numbers of γδ T cells and invariant natural killer T (iNKT) cells are increased and reduced, respectively.

Unconventional iNKT cell and γδ T cell populations are found at higher frequencies in adipose tissue compared with other tissues in steady-state conditions in humans and mice[89,90]. Studies in both species have revealed that in obesity γδ T cells are increased and iNKT cells are decreased in the adipose tissue and both subsets play a role in the development of insulin resistance[89–91]. In parallel with what is observed in obesity, an age-associated increase of γδ T cells and a decrease of iNKT cells occur in the VAT of mice between 5 and 28 weeks of age, concomitant with the age-associated accumulation of VAT T_{reg} cells[89] (FIG. 3). The balance of IFNγ and IL-10 production by two distinct subpopulations of adipose tissue-associated iNKT cells has been found to be important for preserving metabolic integrity. Whereas IL-10 produced by NK1.1$^-$ iNKT cells can restore metabolic function in obese mice, IFNγ secreted by NK1.1$^+$ iNKT cells stimulates the elimination of macrophages by natural killer cells to limit pathogenic expansion of macrophages in lean adipose tissue[92]. Interestingly, a ketogenic diet has recently been reported to induce the expansion of a metabolically protective γδ T cell subset in VAT that helps to restrain fat-induced acute inflammation[93].

The role of senescent T cells has also been studied in the context of metabolic diseases. In the VAT of obese mice, a distinct population of CD4$^+$CD153$^+$PD-1$^+$CD44^{hi}CD62L^{lo} senescent T cells is enriched and contributes to VAT inflammation by strongly activating expression of *Spp1*, which encodes osteopontin[16] (FIG. 3). Of note, adoptive transfer of these senescent T cells into lean VAT can trigger VAT inflammation and insulin resistance[16], and the removal of senescent T cells from the VAT of obese mice leads to improved glucose tolerance and insulin sensitivity[15]. In addition, higher numbers of CD4$^+$ and CD8$^+$ senescent T cells (CD44$^+$CD153$^+$) with enhanced production of TNF are found in the liver of aged mice, in association with higher fasting blood glucose and insulin levels[17]. In humans, the increased frequency of CD8$^+$CD57$^+$ or CD8$^+$CD28$^-$ senescent T cells in peripheral blood has been associated with the development of hyperglycaemia[94], and functionally impaired senescent CD4$^+$ and CD8$^+$ TEMRA cells (CD45RA$^+$CCR7$^-$) are significantly increased in the circulation of patients with type 2 diabetes[95]. Hepatic senescent CD8$^+$CD28$^-$CD57$^+$ T cells producing TNF, granzyme B and perforin are also increased in patients with type 2 diabetes and positively correlate with fasting blood glucose[17].

T cells in neurodegeneration

Thanks to the presence of the blood–brain barrier (BBB), the brain is probably the organ that is most isolated from the external environment. This isolation precludes the entry of exogenous toxic agents that could damage neurons. As low numbers of peripheral immune cells, including T cells, are found in the brain during homeostatic conditions, their role has remained underestimated for many years. However, potential immune cell entry into the brain parenchyma through the recently discovered meningeal lymphatic vessels[96,97] opens up the possibility of a wider range of T cell functions, even in the healthy brain, and growing evidence points to infiltrating T cells as regulators of important functions in the brain during pathology (FIG. 4). The identification of BBB breakdown as an ageing feature[98] suggests that the influx of T cells in the brain may be increased in older people. Furthermore, enhanced BBB breakdown occurs in age-associated neurodegenerative diseases[99]. Although the precise mechanisms mediating increased T cell infiltration during ageing remain to be elucidated, previous knowledge in neuroinflammatory diseases is starting to shed light on these. For instance, in patients with multiple sclerosis, T_H17 cells directly disrupt the BBB and infiltrate the central nervous system through a mechanism that is mediated by IL-17 and IL-22 signalling[100].

Recent evidence suggests that tissue resident memory T cells (T_{RM} cells) populate the white matter of middle-aged healthy humans[101,102]. In particular, CD4$^+$CD69$^+$CD103^{lo} T_{RM} cells are observed, together with CD8$^+$CD69$^+$CD103$^+$ T cells that express low levels of activation markers and increased levels of chemokine receptors for homing to peripheral inflammatory sites, such as CX_3CR1 and CCR5, as well as expressing PD1 and CTLA4 (REF.[101]). Other subsets of T cells also populate the brain parenchyma in healthy humans. These T cells are CD4$^+$CCR5^{hi} and express the VCAM1 ligand VLA4, which facilitates against-flow crawling in search of extravasation-permissive sites. Upon VLA4–VCAM1 binding, these T cells secrete granzyme K to induce local ICAM1 aggregation, facilitating transcellular endothelial transmigration[102]. In mice, resident T_H1 cells, T_H2 cells and T_{reg} cells patrol the epithelium of the choroid plexus and secrete IFNγ upon brain injury to regulate the entry of leukocytes[103]. These observations highlight a potential role for T cells in homeostasis and suggest that alterations in their levels or function may drive the altered cognition that occurs in older individuals.

Evidence for a role of T cells in regulating cognition has come from mechanistic studies in mice. Mice lacking T cells and B cells present with altered learning behaviour but preserved motivation and motor ability[104,105]. During performance of cognitive tasks, IL-4-producing T cells accumulate in the meninges. Consistent with the role of T cell-secreted IL-4 in maintaining meningeal myeloid cells in a resting state, IL-4-deficient mice harbour inflammatory myeloid cells and show cognitive impairment, which can be reversed by adoptive transfer of wild-type T cells[106]. Strikingly, microglial cells also require CD4$^+$CD69$^+$ brain T_{RM} cells to fully mature[107]. T cells can also directly control the appearance of anxiety-like behaviours as well as the development of proper social behaviour. Meningeal T cells, which are presumably responsible for IFNγ secretion, regulate neuronal connectivity and social behaviour by directly signalling to inhibitory neurons and, consequently, IFNγ receptor-knockout mice show profound social deficits[108]. In physically stressed animals, release of leukotriene B4 causes mitochondrial fission in CD4$^+$ T cells. This induces anxiety and depression via T cell-derived xanthine release, which activates the adenosine A1 receptor in oligodendrocytes of the amygdala[109]. Similarly, meningeal γδ T cells expressing CXCR6 promote anxiety symptoms through IL-17 signalling in cortical neurons[110], demonstrating that an exquisite tuning of

these signals is required to guarantee brain homeostasis and to preserve cognition. In addition, brain T cells could play a direct role in pathological conditions with impaired neurological function (FIG. 4). Recent studies have found increased numbers of IFNγ-producing $CD8^+$ T cells in neurogenic niches from older mice, suggesting a potential contribution to neurodegeneration[111]. After experimental ischaemic stroke, there is an accumulation of either brain-resident $CD44^{hi}CD62L^{lo}$ effector memory $CD8^+$ T cells[112] or double-negative ($CD3^+CD4^-CD8^-$) T cells[113], which favours inflammation and modulates microglial function. Accordingly, our results suggest that

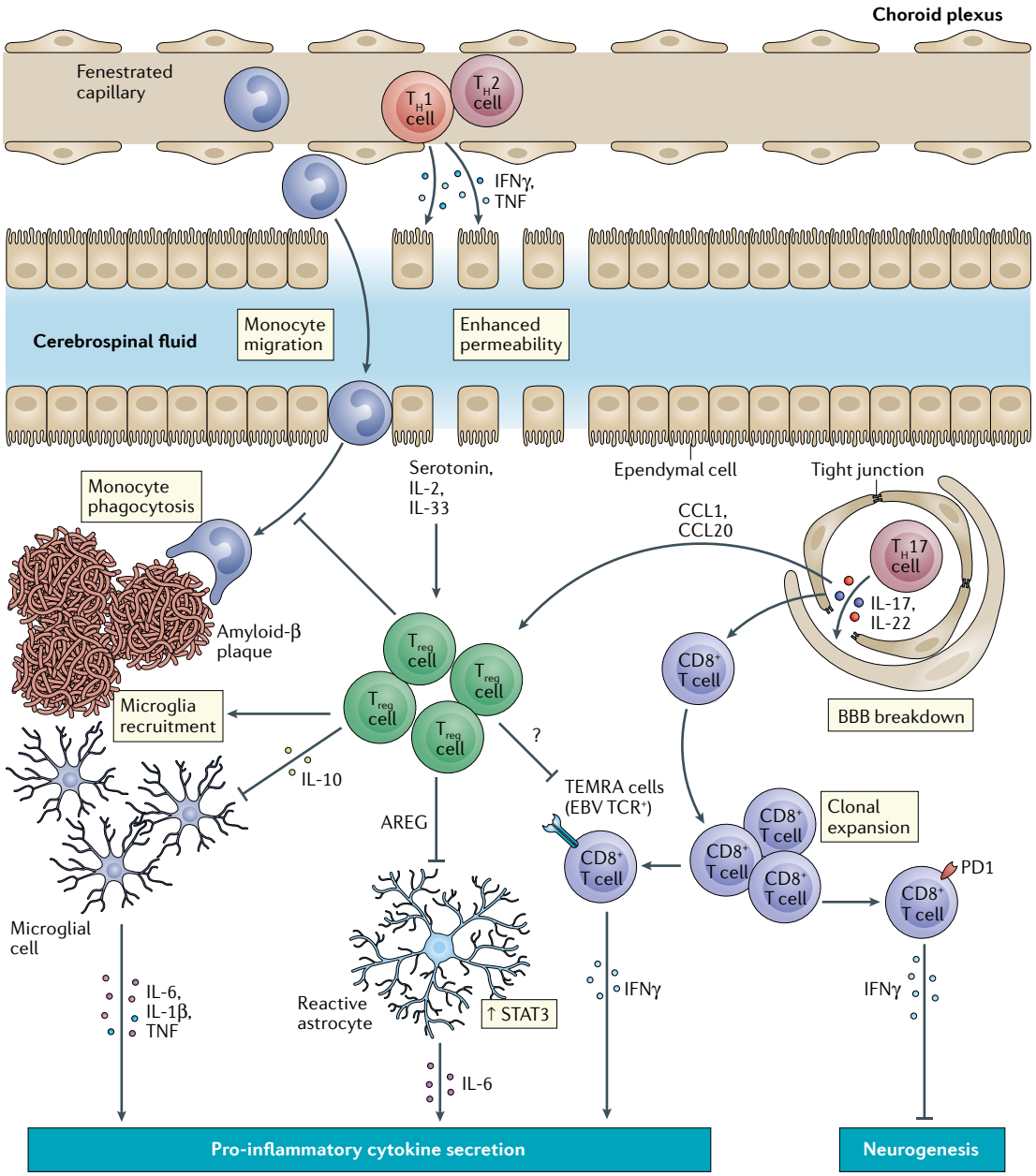

Fig. 4 | **T cells participate in age-related neurological disorders.** Blood–brain barrier (BBB) breakdown is facilitated by T helper 17 (T_H17) cells that secrete IL-22 and IL-17, promoting the entry of $CD8^+$ cells. Additionally, T_H1 cells and T_H2 cells induce the expression of adhesion molecules in choroidal ependymal cells by secreting tumour necrosis factor (TNF) and interferon-γ (IFNγ) that promote the access of myeloid cells into the parenchyma. During ageing, infiltrated $CD8^+$ T cells clonally expand and secrete IFNγ that hampers neurogenesis. In Alzheimer disease, $CD8^+$ T effector memory $CD45RA^+$ (TEMRA) cells harbouring T cell receptors (TCRs) that recognize Epstein–Barr virus (EBV) epitopes correlate with poor cognition. BBB breakdown also permits the entry of regulatory T (T_{reg}) cells in response to chemokines such as CCL1 and CCL20. T_{reg} cells can have both beneficial and detrimental roles. In Alzheimer disease, T_{reg} cells recruit phagocytic microglia to amyloid plaques while inhibiting the secretion of pro-inflammatory cytokines. However, T_{reg} cells can also counteract the entry of monocytes, which can phagocytose amyloid-β aggregates, through the choroid plexus. After stroke, T_{reg} cells can also protect against neuroinflammation by supressing astrocytes. AREG, amphiregulin; STAT3, signal transduced and activator of transcription 3.

metabolically stressed T cells with a pro-inflammatory phenotype cause cognitive and coordination alterations[23].

Increased numbers of clonally expanded brain $CD8^+$ TEMRA cells are detected in the brains of patients with Alzheimer disease, with these cells expressing TCRs that recognize two different antigens of Epstein–Barr virus. Remarkably, the presence of these cells has been inversely correlated with cognitive capacity[114]. Immunogenic responses against toxic proteins that accumulate in neurodegenerative diseases have been observed as well. In this regard, strong amyloid-β-specific T cell responses have been detected upon in vitro stimulation of peripheral blood mononuclear cells isolated from patients with Alzheimer disease or from healthy older individuals, with the most immunogenic epitopes mapping to amino acids 16–33 of the amyloid-β peptide[115]. Strikingly, despite the presence of T cells specific for numerous self-antigens (such as amyloid precursor protein, amyloid-β, tau, α-synuclein and transactive response DNA binding protein) in patients with Alzheimer disease, no notable differences compared with healthy age-matched individuals have been identified[116]. The role of T cell-mediated autoimmunity is better established in patients with Parkinson disease. In these patients, α-synuclein-derived epitopes trigger the development of specific T cells that drive effector and cytotoxic immune responses, even at preclinical stages of the disease[117,118].

The role of T_{reg} cells in the progression of neurodegenerative diseases remains controversial (FIG. 4). Transient conditional depletion of T_{reg} cells can promote amyloid-β plaque clearance in a mouse model of Alzheimer disease by inducing the recruitment of leukocytes through the choroid plexus[119]. In a different study, transient depletion of T_{reg} cells has been found to limit the recruitment of microglia towards amyloid plaques and accelerate the onset of memory loss without altering amyloid-β clearance. Peripheral administration of IL-2 can amplify the number of T_{reg} cells and restore the number of plaque-associated microglia, improving cognitive functions[120]. These studies suggest that resident microglia and monocyte-derived microglia differentially contribute to phagocytosis of amyloid-β aggregates and point to T_{reg} cells as important regulators of both cell populations during early stages of Alzheimer disease. In experimental ischaemic stroke, T_{reg} cells infiltrate the brain in response to CCL1 and CCL20, and promote neurological recovery through amphiregulin (AREG)-mediated inhibition of IL-6–STAT3 signalling in reactive astrocytes. These T_{reg} cells express unique genes related to the central nervous system such as *Hrt7*, which encodes the serotonin receptor 5-HT_7, and their amplification is dependent on IL-2, IL-33 and serotonin signalling[121]. In this disease model, T_{reg} cells also counteract neuroinflammation through IL-10-mediated suppression of TNF and IFNγ release by microglia and infiltrating immune cells[122].

T cells in tissue repair and regeneration

T cells contribute to barrier tissue maintenance as well as to the repair and regenerative responses that restore tissue homeostasis after sterile or infectious damage. In this context, age-associated alterations in T cell numbers and function may be associated with the poorer tissue regeneration that is seen with ageing.

T cell control of barrier tissue maintenance. Immune responses at barrier tissues need to protect against harmful agents and environmental insults but ensure tolerance to commensal microorganisms and innocuous antigens. Indeed, T_{RM} cells[123], T_{reg} cells[124] and γδ T cells[125] are abundant in the skin and the intestine, the two largest barrier tissues in mammals. Several T cell subsets have been implicated in barrier tissue maintenance, and chief among these are γδ T cells. Although present in low frequency in circulating blood and secondary lymphoid organs, γδ T cells are plentiful in barrier tissues[125]. They produce regenerating factors such as keratinocyte growth factor (KGF) and IGF1 to regulate tissue homeostasis and promote epithelial cell proliferation[126,127]. Intestinal γδ T cells also promote epithelial integrity by secreting mediators such as TGFβ1, TGFβ3 and prothymosin β4 (REF.[128]). Of note, the proportions of pro-healing γδ T cells and levels of anti-inflammatory mediators diminish in the gut of aged mice[129]. Pro-inflammatory and colitogenic T_H17 cell responses occurring at controlled levels can also contribute to maintain gut tissue integrity[130], but need to be tightly modulated by signals such as IL-33 (REFS[131,132]). In the skin, cytotoxic $CD8^+$ T cells expressing IL-17 or IFNγ accumulate in steady-state conditions in non-human primates and in humans, which suggests a role for this T cell subset in tissue homeostasis[133].

Effects of T cells on tissue repair after injury. γδ T cells promote wound healing and limit tissue damage in the skin of mice[134] and humans[135] by producing factors such as KGF and IGF1. Importantly, in contrast to T cells isolated from acute human wounds, both αβ and γδ T cells from non-healing chronic skin wounds that frequently affect older patients and patients with diabetes are functionally impaired[135]. In addition, wound healing is impaired in the skin of aged mice owing to impaired function of dendritic epidermal T cells, which have the ability to promote re-epithelialization after injury[136].

T_{reg} cells have also been implicated in diverse repair and maintenance processes, including, for instance, skin wound healing[137], skeletal muscle protection[138,139] or epithelial proliferation during lung recovery[140]. The reparative potential of T_{reg} cell-secreted AREG, a ligand of the epidermal growth factor receptor, has been proven in various models, including muscle and lung injury[141,142] and colitis[143]. T_{reg} cells also facilitate lung repair after injury by secreting KGF and inducing epithelial cell proliferation[144]. Strikingly, mature T_{reg} cells in zebrafish infiltrate regenerating tissues, undergo population expansion and produce organ-specific regenerative factors, namely neuregulin 1 in the heart, IGF1 in the eye and neurotrophin 3 in the spinal cord[145].

In mice, skin commensals also drive the accumulation of $CD8^+$ T cells that predominantly secrete IL-17 rather than IFNγ[133] and can accelerate wound healing in the skin[146]. A decline in such T cell responses may occur in aged individuals and contribute to impaired wound healing, and this will be an interesting area for

future research. Ageing accelerates the accumulation of CD8$^+$ T cells in the circulation that display highly cytotoxic senescent phenotypes and this could drive immune-mediated pathology in human skin lesions[147,148].

Regarding bone regeneration, the age-associated loss of bone mass represents a problem for the older population and, indeed, bone fractures heal less effectively in older mice and humans[149]. Studies in a humanized mouse model involving the transfer of human peripheral blood mononuclear cells and subsequent osteotomy[149] showed reduced bone volume fraction and mineral density post surgery in mice reconstituted with higher proportions of terminally differentiated TEMRA cells. This supports the importance of a more naive T cell compartment for the healing capacity of bone.

T cell regulation of stem cells controls tissue regeneration. Balanced self-renewal and differentiation of stem cells is crucial for tissue homeostasis and can be highly influenced by T cell-derived cytokines. Consistently, the contribution of different T cell subsets to stem cell function is paramount in tissues with high renewal demand. In this regard, skin T_{reg} cells expressing high levels of the Notch ligand Jagged 1 directly drive Notch-dependent hair follicle stem cell proliferation[150]. By contrast, pro-inflammatory cytokines enhance muscle stem cell expansion[151], suggesting that fine-tuning between the action of T_H1 cells and T_{reg} cells is required to progress through the distinct stages of muscle regeneration. Although anti-inflammatory cytokines such as IL-10 promote epithelial integrity and intestinal stem cell (ISC) renewal[152] (FIG. 5), pro-inflammatory cytokines can induce ISC differentiation and may promote gut barrier disruption. In support of this, T cell-mediated intestinal damage and IFNγ-induced ISC apoptosis in murine and human organoids have recently been reported[153,154], whereas low concentrations of TNF boost mucosal development in human fetal intestines[155]. Hence, an excessive pro-inflammatory environment can lead to stem cell depletion[152], which may drive age-related changes in intestinal architecture and functionality.

T cell regulation of gut microbiota

A dysregulated gut microbiota has been linked with unhealthy ageing and age-related chronic inflammatory diseases[156]. Considering the role of T cells in adjusting the ISC fate and gut integrity[152], together with their capacity to control the gut microbiota, the microbiota–T cell interaction has turned into a promising therapeutic target in age-related diseases. T cells promote local, fine-tuned IgA responses in germinal centres that guarantee tolerance to commensal microorganisms[157]. At a glance, germinal centre responses require a balanced contribution of T_H17 cells and T_{reg} cells, which acquire T_{FH} cell[158] and T follicular regulatory cell[159] phenotypes in Peyer's patches, respectively. T_{FH} cell differentiation in mouse germinal centres is also orchestrated by a subset of γδ T cells expressing CXCR5 (REF.[160]). Importantly, MYD88 signalling and the expression of the transcription factor MAF in T_{reg} cells prevent exacerbated T_H17 cell responses and promote IgA-dependent responses that enforce commensalism[161,162]. Recently, iNKT cells have been shown to control the IgA repertoire via regulation of the gut microbiota, and iNKT cells also regulate intestinal T_{reg} cell function[163]. Taken together, these findings suggest that T cells help to maintain a healthy and balanced gut microbiota, and dysregulated T cell responses leading to gut dysbiosis[164] may underpin inflammatory conditions associated with ageing.

Indeed, recent research has identified microbial dysbiosis, gut hyperpermeability and bacterial translocation as instrumental to late-life health[165]. Defective germinal centres and defects in antigen-specific IgA are seen in older people[166], and dysfunctional T_{FH} cell and excessive T follicular regulatory cell activity in the germinal centres of aged mice may affect gut microbiome remodelling during ageing[167,168]. The loss of host–microbiota symbiosis, along with the breakdown of the intestinal barrier during ageing, could prompt gut bacterial products to spread systemically, contributing to inflammageing and generating a pathological feedback loop that amplifies this unresolved inflammatory response[169,170] (FIG. 5). Notably, disturbed gut microbial communities and bacterial translocation in individuals infected with HIV correlate with the prevalence of age-related comorbidities. Mechanistically, these factors chronically stimulate T cells, which could contribute to immunosenescence and frailty in the host[171,172]. Nonetheless, T cell-dependent IgG responses against the gut microbiota have been found to increase with age in mouse peripheral blood, suggesting a protective mechanism to prevent systemic damage in an event of bacterial traslocation[173]. Hence, T cells are potential regulators of older-age wellness by modulating host–microbial symbiosis.

The disrupted configuration and metabolic activity of the intestinal microbiota have emerged as central players in numerous non-communicable inflammatory pathologies, with special emphasis on age-associated diseases such as obesity, atherosclerosis and neurodegenerative disorders. A well-balanced mutual dialogue between T cells and microbiota is essential for host metabolism. CD4$^+$ T cell control of microbiota has been observed to adjust host glucose and fat metabolism[174] and to confer protection against obesity[30]. Furthermore, microbiota-specific CD4$^+$ and CD8$^+$ T cells improve HFD-induced insulin resistance by restoring the gut microbiota[175]. Strikingly, gut dysbiosis induced by both a HFD and a ketogenic diet results in the depletion of intestinal T_H17 cells, which are known to attenuate metabolic syndrome[176,177]. Related to this, γδ and T_H17 T cells have been recently reported to limit gut dysbiosis and bacterial translocation in obese mice through the IL-17 and IL-23/IL-22 axes[31,178,179]. In fact, the T_H17 cell axis has also emerged as a major therapeutic target to prevent cardiovascular events, in a study showing that restoring gut microbiota sensitive to a high-salt diet improved hypertension by modulating the T_H17 cell subset[180]. In the same direction, the IL-23/IL-22 axis may contribute to gut microbiota homeostasis, leading to protection from diet-induced atherosclerosis[181]. Additionally, a boost of intestinal T_{reg} cell responses ameliorates atherosclerotic lesions[182] and post-ischaemic neuroinflammation[183], posing the T cell–microbiota

Dysbiosis
Abnormal shifts in the microbiota composition and in the associated microbiota-derived metabolites.

Bacterial translocation
The leakage of viable bacteria and/or their by-products from the intestinal lumen to peripheral tissues, such as the mesenteric lymph nodes, the adipose tissue or the liver.

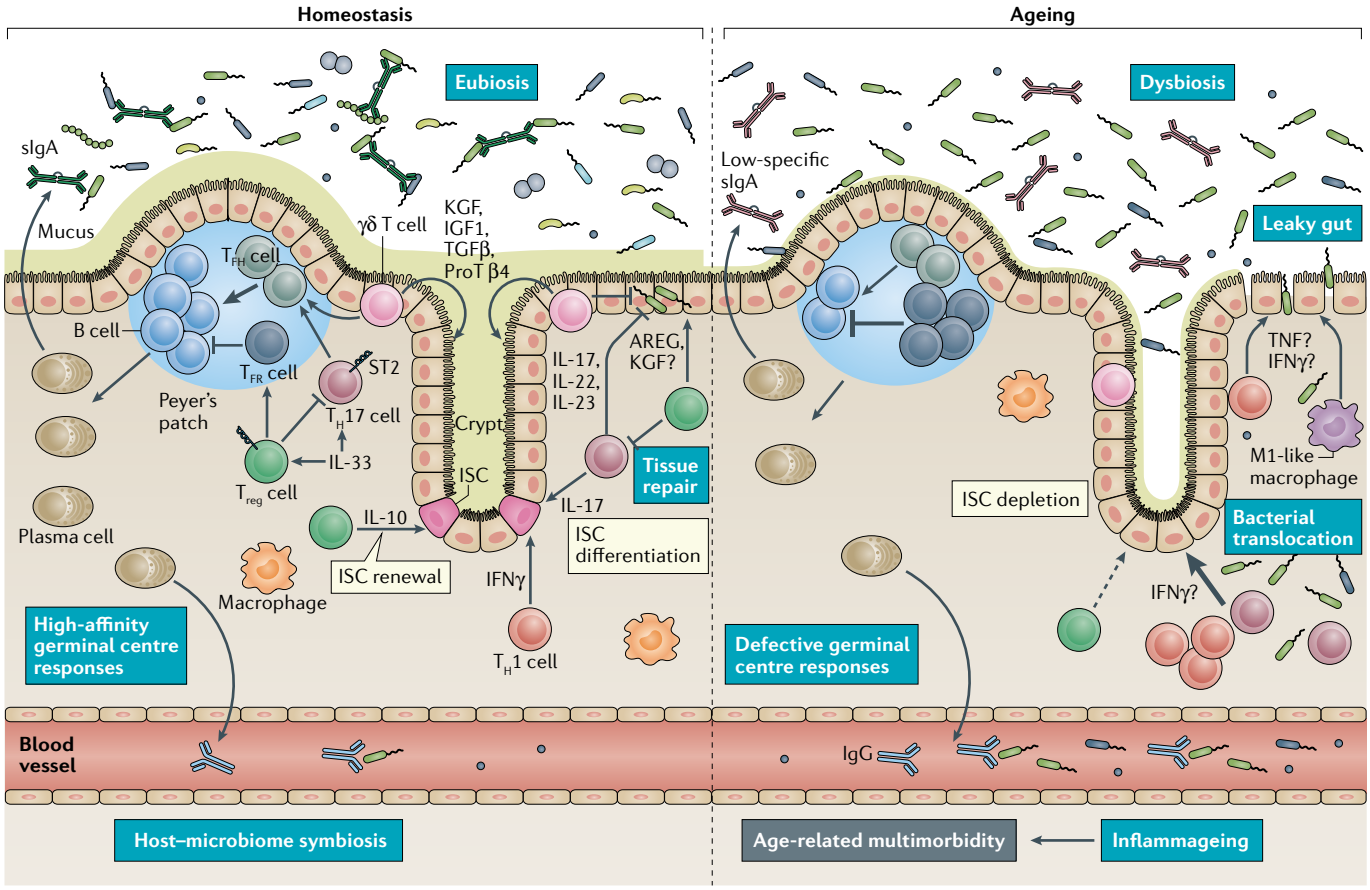

Fig. 5 | **T cell control of gut homeostasis is lost during ageing, driving inflammatory pathologies.** Maintenance of gut homeostasis is coordinated by the activity of intestinal T cells. The fine-tuned secretion of anti-inflammatory and pro-inflammatory cytokines by T cells ensures balanced intestinal stem cell (ISC) self-renewal and differentiation that support the high turnover rate of the intestinal epithelium. In addition, the pro-maintenance roles of regulatory T (T_{reg}) cells, T helper 17 (T_H17) cells and γδ T cells favours tissue homeostasis and restricts the leakage of microbially derived products. On the other hand, a homeostatic T follicular helper (T_{FH}) cell to T follicular regulatory (T_{FR}) cell ratio, together with the contribution of T_H17 cells, T_{reg} cells and γδ T cells, orchestrate fine-tuned germinal centre responses, which establish host–microorganism symbiosis through the secretion of microbiota-specific IgG and local high-affinity IgA from plasma cells. Nonetheless, this mutualistic relationship is lost during ageing owing to an aberrant germinal centre T cell composition, which could support perturbations in gut microbial communities. Gut dysbiosis enhances gut permeability, along with a pro-inflammatory T cell environment that could drive ISC depletion due to excess of differentiation or apoptosis. Consequently, bacteria and their by-products could translocate into circulation contributing to inflammageing, which is linked with a myriad of age-related cardiometabolic and neurologic pathologies. AREG, amphiregulin; IFNγ, interferon-γ; IGF1, insulin-like growth factor 1; KGF, keratinocyte growth factor; ProTβ 4, prothymosin β4; sIgA, secreted IgA; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

axis as a target for the treatment of cardiovascular and neurological pathologies.

Given the relevance of gut dysbiosis in age-related chronic diseases and the tight and reciprocal relationship between T cells and microbiota, further research is needed to define the precise role of T cells in ageing disorders through the control of the gut microbiota.

T cell-based immunotherapies

Strategies that target pathogenic T cells could open up new therapeutic avenues for age-associated diseases (FIG. 6). These approaches range from using broadly immunosuppressive drugs, such as calcineurin inhibitors or TNF antagonists, to the use of anti-CD3 antibodies to directly target T cells. More sophisticated approaches could selectively remove pathogenic, highly activated or senescent T cells. With respect to this, vaccination with the CD153 antigen has been validated as a long-lasting approach to prevent the accumulation of senescent T cells in the adipose tissue and to ameliorate obesity-related parameters in mice[15]. On the other hand, T cell-dependent removal of senescent cells can be promoted by using engineered T cells expressing a chimaeric antigen receptor that enables them to specifically recognize and remove senescent cells[184]. Additionally, the immune response can be manipulated by using immune checkpoint regulators. These strategies, which have revolutionized the field of immunotherapy for cancer and autoimmunity, could also have a place in the field of geroscience[185,186].

Novel strategies that target metabolic pathways in specific T cell subsets have also emerged in recent years. Regulation of immunity through small molecules or the diet has already been proposed to treat metabolic disorders[187], autoimmunity[188] or inflammatory diseases[189]. Future work is required to investigate whether such approaches are also useful in age-related diseases (FIG. 6). Metformin treatment induced autophagy in $CD4^+$ T cells and promoted their skewing towards a non-inflammatory

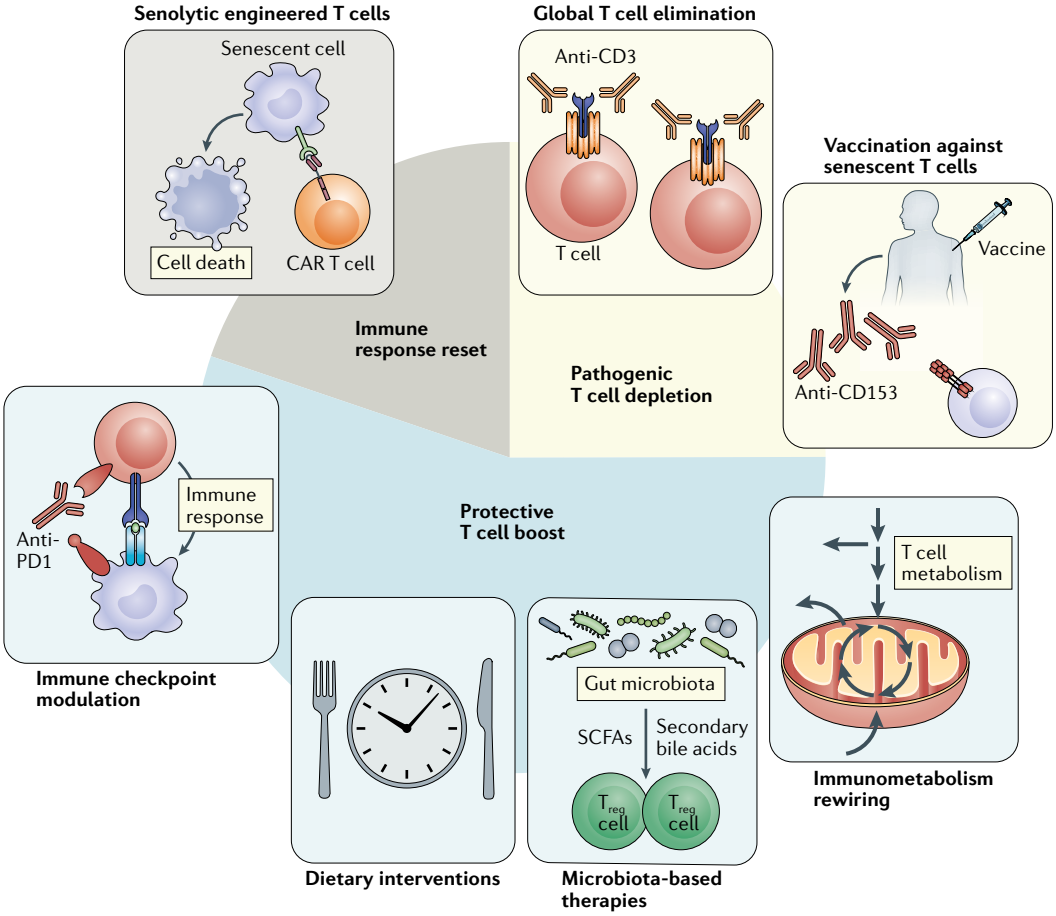

Fig. 6 | **T cell based-immunotherapies to increase resilience to age-related diseases.** Emerging therapeutics aim to delay the onset of age-associated pathologies through the control of T cell responses. These approaches could include a wide range of strategies aimed at resetting the immune system, depleting pathogenic T cells or promoting T cell protective responses. To dampen pathological T cell activity, general approaches aimed at reducing global T cell function or numbers have been proposed. Alternative strategies have been designed to specifically target senescent T cells, for example, vaccination against $CD153^+$ cells. Protective T cell responses can be triggered through the modulation of T cell metabolism or the implementation of diet and microbiota-based interventions (for example, calorie restriction mimetics). In addition, the administration of immune checkpoint modulators (such as anti-PD1 antibodies) could modify the outcome of the T cell immune response. Finally, the immune system could be exploited to deplete senescent cells by using senolytic engineered chimeric antigen receptor (CAR) T cells. SCFAs, short-chain fatty acids; T_{reg} cells, regulatory T cells.

state, preventing the T_H17 cell differentiation observed in older mice and improving inflammageing[24]. Similarly, mTOR inhibitors such as rapamycin can elicit important immunomodulatory effects on T cells, inhibiting T_H1 cell, T_H2 cell and T_H17 cell differentiation while promoting T_{reg} cell differentiation[190,191]. NAD^+ precursors improve mitochondrial metabolism in exhausted T cells[7] and prevent inflammageing[23].

Finally, microbiota-based interventions have recently flourished as promising anti-ageing therapies[192,193]. The modulation of the T cell–microbiota crosstalk could be exploited to preserve gut integrity and to prevent bacterial translocation and its associated inflammageing, ultimately delaying age-related diseases[156,194].

Concluding remarks

Recent findings that T cells regulate inflammageing and drive systemic senescence suggest key roles for these cells in age-associated diseases. Pro-inflammatory subsets, such as T_H1 cells and T_H17 cells, are generally linked with pro-ageing events, whereas T_{reg} cells are more likely to promote rejuvenating events. However, the role of certain T cell subsets can be strongly dependent on the context or the tissue. Importantly, the balance of the contribution of the different T cell subsets will ultimately dictate the global outcome. Among age-associated T cells, mainly senescent T cells stand out as major drivers of self-tissue cytotoxicity and sustained pro-inflammatory cytokine production, promoting the accumulation of senescent cells and eventually leading to tissue and organ failure. T cell metabolic imbalance is a strong mediator of these effects that drive age-related multimorbidity. Overall, a breakdown of immune tolerance resulting from T cell malfunctioning might be a major component of many conditions that are prevalent in older people. Therefore, emerging therapeutic approaches based on T cell immunotherapies are arising as promising key tools to delay the onset of age-associated pathologies.

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