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T cell control of inflammaging

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A B S T R A C T

T cells are a critical component of the immune system, found in abundance in blood, secondary lymphoid organs, and peripheral tissues. As individuals age, T cells are particularly susceptible to changes, making them one of the most affected immune subsets. These changes can have significant implications for age-related dysregulations, including the development of low-grade inflammation – a hallmark of aging known as inflammaging. In this review, we first present age-related changes in the functionality of the T cell compartment, including dysregulation of cytokine and chemokine production and cytotoxicity. Next, we discuss how these changes can contribute to the development and maintenance of inflammaging. Furthermore, we will summarize the mechanisms through which age-related changes in T cells may drive abnormal physiological outcomes.

1. Introduction

The term inflammaging was introduced by Franceschi et al. over twenty years ago to describe an onset of a chronic pro-inflammatory state observed in older individuals even in the absence of an acute immune response [1]. It is often characterized by a progressive age-associated increase of serum inflammatory mediators. Among the most studied ones are cytokines IL-6, TNFα, and IL-1, and acute response molecules such as C-reactive protein [2]. More recent studies utilized unbiased plasma proteome profiling and discovered less widely known immunoregulatory factors that correlate with age (e.g., GDF15) [3]. Most of these molecules are required for protection against pathogens but become detrimental if elevated levels are sustained for prolonged periods. Indeed, numerous studies have associated the pro-inflammatory state with susceptibilities to age-associated diseases such as cancer, osteoarthritis, neurodegenerative and cardiovascular diseases, and others [2,4,5]. While many age-related dysregulations can be connected to inflammaging, the primary driver of this phenomenon is not known. Conceptually, corresponding theories can be separated into ones focusing on the immune system and ones investigating the impact of non-immune stromal cells. Among the latter, the suggested role of the senescent cells has been particularly intriguing due to a large overlap between molecules upregulated with age and senescence-associated secretory phenotype (SASP) [6]. However, with the immune system normally regulating both the onset and resolution of inflammatory responses, it can arguably be considered the most prominent player in the development of inflammaging.

Innate cells, especially macrophages, have been in the spotlight of aging research since the beginning of immunology as a field. Indeed, they were suggested to play a role in aging processes already by Ilya Metchnickoff [7]. Macrophages were also at the center of the theory by Franceschi et al. [1]. However, during the last decade, it became apparent that T cells might be the immune population most drastically affected by age. Both CD8 and CD4 T cells undergo significant re-modeling, including changes in cell populations and cell-intrinsic re-programming [8–11]. Due to the ability of these cells to directly kill infected or transformed cells and amplify immune response via massive cytokine production, T cell functions have to be tightly regulated. Thus, age-related changes in the T cell landscape have the potential to significantly contribute to and even drive the state of inflammaging. Here, we aim to summarize changes in pro- and anti-inflammatory functions of aged T cells known to date and to connect them to the systemic skew towards the inflamed state observed in old organisms. Given the canonical functions of T cells, we will consider the following routes of T cell-driven inflammatory phenotypes (Fig. 1). (1) Direct production of cytokines by T cells; (2) amplification of pro-inflammatory state of stromal and innate cells by T cell-produced mediators; (3) excessive or insufficient killing of non-immune cells that leads to either tissue damage or accumulation of stressed and senescent cells.

2. Age-related changes in cytokine production

Cytokines and chemokines are the primary mediators of inflammation, and the disbalance between pro- and anti-inflammatory molecules is a hallmark of inflammaging [12]. Among traditionally studied

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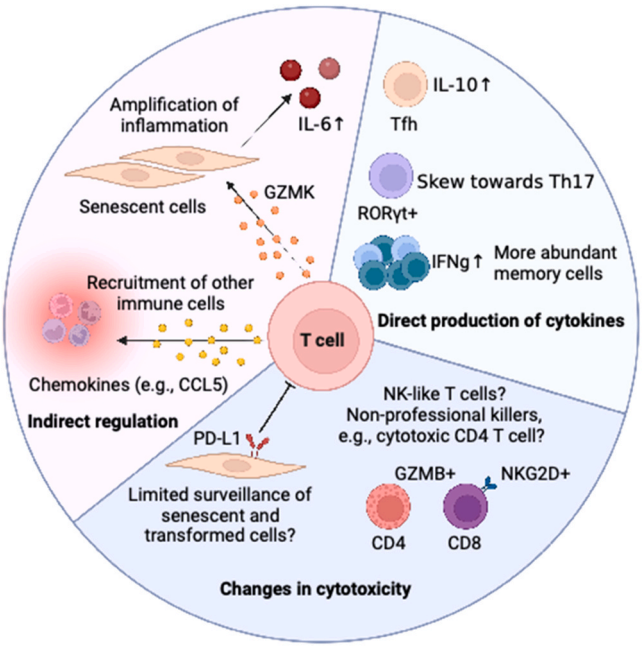

Fig. 1. Summary. Three major arms of T cell functionality include the production of pro- and anti-inflammatory cytokines, indirect amplification of inflammation through recruitment and regulation of other immune cells, and cytotoxicity. As all three branches have been reported to be affected by age, they all potentially contribute to the establishment of inflammaging.

cytokines, some are produced by T cells. For example, IFNg and TNFa are classically used to evaluate the functionality of CD8 and Th1 and Th17 CD4 T cells [13], while Tregs are important producers of anti-inflammatory IL-10 [14]. With advanced age, both the cell-intrinsic state of the cells and frequencies of different subpopulations change significantly. Here, we will review how these alterations affect the production of inflammaging-related mediators by aged CD4 and CD8 T cells.

T cells are the main producers of IFNg [15], – an inflammaging mediator implicated in developing age-related T cell-mediated phenotypes (see detailed discussion below). Naïve T cells are a dominant T cell population in young animals [9,10,16,17], and they require several days of activation and differentiation before they become cytokine-producing effectors [18]. On the other hand, rapid and enhanced production of cytokines, including IFNg, is a signature feature of memory T cells [19–21]. With the decline in naïve T cells being one of the most robust and well-characterized biomarkers of the immune system aging [8–10, 16,17,22,23], disbalance between naïve and memory populations of T cells can itself cause a hyperresponsive pro-inflammatory state in aged tissues. Indeed, when stimulated as bulk populations, both CD8 and CD4 T cells from old mice produced more IFNg compared to a young animal [9,24]. Moreover, sorted old memory T cells produced more IFNg than young memory cells, while data for naïve CD8 T cells is inconsistent [24, 25]. The same trend has been reported for circulating human T cells – production of IFNg was significantly enhanced upon anti-CD3 & anti-CD28 stimulation of bulk T cells isolated from older donors PBMCs [26]. IFNg and TNFa were also upregulated in old T cells stimulated with PMA and ionomycin [27,28]. Furthermore, cell-intrinsic changes in naïve CD4 T cells from older donors have also been observed. Activation of older CD4 T cells elicited a more effector-like phenotype characterized by lower levels of stemness marker TCF7 and decreased IL-2 production [29]. Thus, both cell-intrinsic and populational changes could explain increased production of IFNg and more data is necessary to delineate the specific contributions of each T cell subpopulation.

A need for population-specific analysis of cytokine production becomes especially pressing since the recent advances in single-cell technologies made it possible to gain insight into the complexity of the age-specific dynamic of T cell subpopulations with high granularity [30]. For instance, a subset of cytotoxic CD4 T cells has been identified in the spleen of old mice and circulation of extremely old human donors (supercentenarians) [31]. Based on the intracellular staining, these cells can produce higher amounts of IFNg and TNFa than regular effector memory CD4 T cells. The relative contribution of this novel population to the overall pro-inflammatory state remains to be defined, as well as stimuli that would trigger IFNg production by cytotoxic CD4 T cells in vivo. The latter could also differ between old and young organisms, as has been demonstrated for CD8 T cells that are more prone to antigen-independent bystander activation in aged mice. Specifically, old murine CD8 T cells produce IFNg upon in vitro treatment with IL-12, which is not observed for young cells [32]. This might indicate that in aging tissues, CD8 T cells can respond to danger signals in an innate fashion without TCR-specific activation, creating a positive feedback loop between innate and adaptive branches of the immune system.

Another critical aspect of T cell compartment aging is dysregulation of T cell differentiation trajectories, especially in the context of CD4 T cells. CD4 T cells are vigorous cytokine producers and are required to orchestrate appropriate immune responses for each type of pathogen. In advanced-age mice, CD4 T cells tend to skew towards the Th17 trajectory. Indeed, upon stimulation, both total splenocytes and CD4 T cells isolated from the lymphoid organs of old mice produce 3–4 times more IL-17 on both protein and transcriptional levels [33,34]. Moreover, both resting and activated old CD4 T cells express higher levels of Th17 program master regulator RORgt [33]. Enhanced IL-17 signaling and production have also been observed in total lymphocytes from border tissues, such as lamina propria and skin [34,35]. Importantly, this bias towards Th17 lineage is established already in naïve CD4 T cells from old mice since they differentiated into IL-17-producing Th17 effectors more effectively than naïve cells from a young animal [33,34]. Furthermore, naïve CD8 T cells from aged mice respond to Th17 differentiation conditions as well and can produce IL-17, while almost no young CD8 T cells do so [34]. A similar overall phenotype has been reported in recent human studies. Circulating total CD4 T cells from older donors produce higher levels of IL-17 and other Th17-associated cytokines IL-21, IL-22, and IL-6 in response to activation [34,36,37]. An age-associated increase in IL-21 production has been also reported for PMA and ionomycin-stimulated human PBMCs [38]. Interestingly, the increase of IL-17 production by old human CD4 T cells is alleviated if they are activated in the presence of metformin, suggesting a metabolic pathway as a potential avenue for T cell rejuvenation [36].

The skew towards the Th17 phenotype is relevant to multiple autoimmune inflammatory conditions and is often associated with a more aggressive phenotype [13,39]. In the context of aging, Th17-biased naïve CD4 T cells from old mice can cause more severe and exacerbating colitis when transferred into a Rag1-deficient recipient [34]. However, the physiological relevance of T cells to aging phenotypes in other models remains elusive. For instance, while total IL-17 is overproduced in old animals in a model of post-traumatic osteoarthritis, the absolute number of CD4 T cells in an affected old group is ~5 times lower compared to young ones [40]. This suggests that an alternative age-associated source of IL-17 contributes to the phenotype. In another inflammatory settings, aged mice were protected against experimental autoimmune uveitis [41]. While aged CD4 T cells expressed more IL-17 and Th17 CD4 T cells were more abundant at the baseline, they failed to produce GM-CSF, which ameliorated the disease. Along the same lines, the reduction of G-CSF production in response to E. coli has been reported for whole blood from elderly donors [42].

Conflicting phenotypes in physiologically relevant models can also be explained by an age-associated change in the production of cytokines with an anti-inflammatory role. For example, in humans, bulk T cells from older donors produce more IL-10 than young T cells [27,43]. In mice, age-related increase in IL-10 is systemic and can be observed in serum alongside pro-inflammatory cytokines such as IL-6 [9,44,45]. In

old mice, T follicular helper (Tfh) T cells are the major producers of IL-10 under homeostatic conditions [44]. Human data is consistent with this observation and shows that old Tfh cells produce ~4 times more IL-10 than any other subset in a young donor [44]. Importantly, antigen-specific IL-10-producing Tfh emerge upon vaccination in aged mice, and blockade of IL-10 signaling can restore antibody production to youthful levels [44]. The mechanism behind the age-related increase of IL-10 is not fully known, but it has been demonstrated that aged IL-6 KO mice have low serum IL-10 and reduced numbers of IL-10-producing Tfh cells. This suggests that the increase in IL-10 can be a compensatory mechanism responding to rising inflammaging.

Along Tfh cells, there are other potential sources of IL-10 in old mice. Old B cells were shown to produce IL-10 by several reports [44,45]. Also, aged CD8 T cells express IL-10 on a transcriptional level [25]. Of note, while regulatory T cells (Tregs) are dispensable for the age-associated increase in IL-10 levels [44], they expand dramatically in old mice and might contribute to the regulation of inflammaging by other means [9,46,47]. In mouse spleen, the expansion of the Treg population can be observed already in 74 weeks old mice, with about a third of all CD4 T cells being FOXP3 positive. However, Tregs remain stable in non-lymphoid tissues and do not accumulate [9,46]. Interestingly, the percentage of splenic PD1^{+} Tregs also increases with age, potentially reflecting their more activated status [9,47]. Indeed, a recent deep single-cell profiling of murine CD4 T cells from aged mice revealed that activated Tregs form a transcriptionally distinct subpopulation of regulatory cells that grows ~10 times with age [48]. Functionally, these cells are superior to their resting counterparts as measured by the ability to suppress the proliferation of naïve T cells in vitro [48,49].

In humans, there is also evidence of an age-associated increase in the production of IL-4 – a characteristic cytokine for type 2 immune responses. Activated CD8 and CD4 T cells from older donors produce more IL-4 [26–28], and this effect is more pronounced when bulk PBMCs are stimulated [50].

3. Cytotoxicity and aging

The ability of T cells to directly eliminate abnormal cells is a cornerstone of protective immunity, especially against cancers and intracellular pathogens. Under the assumption that the immune system becomes dysregulated as we age, it would be plausible to hypothesize that immune surveillance will also become less efficient in older organisms. This, in turn, can lead to the accumulation of abnormal cells, including senescent ones. The relationship between senescent cells and age-associated inflammation has been studied extensively [51–53]. Multiple components of senescence-associated secretory phenotype (SASP) increase with age systemically, and depletion of senescence cells by pharmacological or genetic tools decreases age-related inflammation and other morbidities (comprehensively reviewed by Borghesan et al. [53]). To investigate whether a defect in cytotoxicity causes abnormal accumulation of senescent cells, Ovadya et al. examined old mice deficient in perforin [54]. These mice accumulated large amounts of senescent cells in tissues by the age of 24 months, as was shown by measuring classical markers of senescence (e.g., senescence-associated-β-galactosidase staining and p16 expression). Old perforin-deficient mice also developed significantly worsened inflammation compared to age-matched controls and lost overall fitness and integrity of multiple systems. Interestingly, excessive immune infiltration was also observed in perforin-deficient animals that formed immune foci populated by T and NK cells in various tissues. One can speculate that senescent cells attracted cytotoxic lymphocytes that then failed to eliminate them and only further exacerbated the inflammatory state driven by SASP, causing further tissue damage and senescent cell development. While many mechanistic details of how T cells control senescence remain unknown, this study provided evidence of cytotoxic cells' importance in maintaining aging tissues. Moreover, T cell-based therapies have been suggested to eliminate senescent cells in aging and other models. For example, a fraction of senescent cells expresses PD-L1 on their surfaces, therefore, inhibiting T cell-driven killing [55]. Treatment of aged mice with blocking antibodies against PD-L1 enables T cell-mediated cytotoxicity against these cells and results in a decreased senescence burden and improvement of some physiological parameters, such as hepatic lipidosis.

With increasing evidence of the importance of T cell-mediated cytotoxicity in normal aging, there is a need for a better understanding of how aging influences the ability of T cells to perform killing. In mice, one study reported that old CD8 T cells were significantly faster and more efficient in killing cancer cell targets after TCR-stimulation [56]. While the endpoint percent of killing is similar between old and young T cells, the killing speed is almost twice higher for effector cells isolated from older animals. This is not only due to compositional changes since comparison of memory subsets from old and young mice yields similar results, suggesting a cell-intrinsic change in old CD8 T cells to drive the phenotype. Mechanistically, degranulation between ages is comparable but old cells release more perforin and granzymes than young cells, making killing almost four times more efficient. In humans, some older data indicates that old T cells might be more cytotoxic in antibody-mediated cellular cytotoxicity (ADCC), and this effect is sex-specific [57]. ADCC is a mechanism usually utilized by NK cells, and what receptor allows T cells to bind antibodies is unknown. However, along the same line, it was recently suggested that, with age, more CD8 T cells acquire an innate-like phenotype resembling NK cells [58]. Specifically, a subpopulation of terminally differentiated CD27-CD28- CD8 T cells accumulates in the circulation of older individuals [59] and expresses NK receptors [58]. Functionally, these cells can kill target cells independently of MHC I, using NKG2D receptor to recognize the target. Signaling through NKG2D can activate these cells to produce granzyme B and, to a lesser extent, IFNg. While this adaptation can help facilitate the clearance of senescent and pre-cancerous cells, it also can potentially lead to non-specific killing and cause autoimmune-like pathology and promote inflammation. Similarly, with memory cells becoming dominant in the elderly, the overall cytotoxic capacity of CD8 T cells increases [60]. Coupled with the higher vulnerability of older stromal cells [61], it can potentially predispose the tissues to excessive damage during an inflammatory response.

CD8 T cells and NK are canonical cytotoxic lymphocytes, but with age, other cells might acquire the ability to kill. Single-cell profiling of old mice and human T cells discovered a subpopulation of cytotoxic CD4 T cells [31,48]. In the mouse spleen, this is the most expanded with age population, and it comprises almost 10 % of total CD4 T cells in older animals [48]. Expansion of the cytotoxic CD4 subset has also been reported in the circulation of supercentenarians [31]. While there is no experimental evidence yet that these cells can lyse a target, their transcriptional signatures and protein expression data demonstrates high levels of granzymes and perforin. Furthermore, an increase in cytotoxicity has been observed even for naïve CD4 T cells from older individuals. Upon activation, older naive CD4 T cells had defects in lysosomal activity and abnormal exosome secretion. Exosomes collected from the supernatant of in vitro activated old CD4 T cells contained a high amount of GZMB and were sufficient to induce apoptosis in target cells [62].

4. Indirect regulation of cytokine production by aged T cells

T cells can facilitate inflammaging indirectly by producing mediators that enhance the secretion of canonical aging-related molecules by other cells. Single-cell profiling of aging murine tissues enabled the discovery of an age-associated population of CD8 T cells absent in young mice but a dominant population of CD8 T cells in old animals [9]. These cells produce a range of inflammatory mediators with a signature molecule, granzyme K (GZMK). The exact function of GZMK is not fully understood. Although it is not cytolytic, GZMK can serve a role in amplifying inflammation [63]. Indeed, if treated with GZMK alone or in

combination with IFNg, fibroblasts start to produce IL-6 [9]. This effect is even more pronounced in senescent cells that accumulate with age. The addition of GZMK to senescent cells in vitro dramatically increases the secretion of various SASP components, such as IL-6, CCL2, and CXCL1 [9]. Other subsets of T cells can also promote senescence and amplify SASP. Th17 CD4 T cells have been shown to induce senescence when co-cultured with normal fibroblasts [40]. Moreover, senescence driven by the Th17 secretome is more inflammatory compared to other senescence models. For example, in this model, *Il1a*, *Il1b*, *Tnf*, and *Il6* are significantly upregulated relative to irradiation-induced senescence. Interestingly, differentiation of CD4 T cells in the presence of senescent fibroblasts led to increased IFNg production, suggesting a positive feedback loop between T cell differentiation and senescent cells.

Aged T cells are also avid producers of various chemokines, which can significantly change the immunological landscape, especially in tissues. Overproduced by age-associated CD8 T cells GZMK [9], discussed above in the context of inflammation, can affect cell trafficking by inducing ICAM-1 expression on endothelial cells and facilitating diapedesis into tissues through otherwise non-activated endothelium [64]. CD8 and CD4 T cells from old mice also remarkably upregulate the production of CCL5, also known as RANTES [9,48,65]. The pleiotropic effects of CCL5 can affect numerous immune cell types that express its receptors, and more data is required to establish the physiological consequences of CCL5 overproduction in old mice. Besides abnormal trafficking and recruitment of pro-inflammatory cells, e.g., monocytes, into tissues, CCR5 signaling might directly re-program affected cells. In the old bone marrow, CCL5 has been suggested to affect hematopoiesis and promote a skew toward myeloid lineage [66]. Another age-associated chemokine CXCL9 [22] is IFN-inducible [67], so it is plausible that its upregulation might be driven by excessive IFNg secretion by T cells. CXCL9 can affect endothelial cells and might increase arterial stiffness in aged mice [22]. Overall, the indirect effects of T cells might have implications beyond classically discussed T cell functions. More data is needed to evaluate T cell-specific contribution to aging and identify intermediate mediators. We will discuss examples of proven systemic outcomes of T cell aging in the next section.

5. Systemic outcomes of T cell aging

While our understanding of phenotypical changes in the T cell compartment has significantly improved, very few studies have been able to mechanistically connect observed cellular phenotypes to systemic age-related dysfunctions. Several recent reports have utilized genetic mouse models to address whether premature aging of the immune system and specifically T cells, is sufficient to drive multimorbidity and inflammaging. For example, it has been shown that a hematopoietic lineage-specific defect in DNA repair increases circulatory inflammatory mediators, drives the accumulation of senescence markers in multiple organs, and causes tissue damage [68]. Another study generated a mouse with declined mitochondrial function restricted to T cells [69]. T cells in this model are skewed towards glycolysis and characterized by increased production of IFNg and TNFa, partially mimicking the aging phenotype. Strikingly, this defect caused severe multimorbidity and significantly shortened the mouse lifespan. T cells with dysfunctional mitochondria were sufficient to drive multiple morbidities, including severe cardiovascular alterations, such as abnormal histological parameters of the heart, increased heart rate and cardiac stress markers, reduced cardiac output, and decreased blood pressure. This model also demonstrated an association of defective T cells with metabolic and cognitive decline. Interestingly, this phenotype was at least partially recovered by a TNFa blockage, suggesting that T cell-mediated inflammaging can drive systemic aging phenotypes. A recent study used T cell-specific depletion of *Rip1* to induce excessive T cell apoptosis, thus modeling the age-related decrease in naive T cells [70]. T cells in these mice are drastically depleted across both lymphoid and non-lymphoid tissues, show a tendency towards a memory phenotype, and exhibit a pro-inflammatory state with increased production of IL-17 and IFNg. This study provides another piece of evidence that abnormal T cells are sufficient to shorten lifespan and accelerate the onset of age-associated morbidities (e.g., osteoporosis), tissue senescence, inflammaging, as well as dampen the overall fitness of an animal.

T cells' contribution to multiple aging diseases has been studied extensively in recent years [11]. Since even diseases prevalent in the geriatric population are customarily modeled using young animals, it is particularly challenging to pinpoint which age-dependent alteration in T cells contributes to a natural pathology. The genetic models discussed above are instrumental in establishing that faulty T cells alone can cause age-associated phenotypes. However, there is still much to learn about how this damage occurs in each case. Comparison of aged *Rag1* knock-out (KO) mice that lack lymphocytes to age-matched wild-type controls allowed to shed light on the mechanism behind T cell-driven damage to optic nerve axons [71]. Mice that lack all lymphocytes or, more specifically, CD8 T cells suffer less axonal loss and alterations. Lymphocyte deficiency also improves coordination and cognitive performance in old animals. Mechanistically, aging CD8 T cells rely on antigen-specific Gzmb-mediated cytotoxicity to cause damage to the optic nerve, and systemic inflammation further exacerbates this effect. In the subventricular zone neurogenic niche, infiltration of clonally expanded CD8 T cells correlates with increased IFNg signaling, potentially dampening the proliferation rate of neural stem cells [72]. A similar phenotype has been shown in the white matter of aged mice, where IFN-responsive ($STAT1^{+}$) oligodendrocytes and microglia co-localized with infiltrating CD8 T cells [73]. Induction of excessive IFN-signaling depends on CD8 T cells since aged Rag1 KO and CD8 KO mice have fewer $STAT1^{+}$ cells. Physiologically, the reduction of IFN-signaling in knock-out mice coincided with increased white matter density, suggesting that brain-infiltrating CD8 T cells promote pathology in old mice.

Excessive IFNg production by aged T cells is also pathological in settings of cardiovascular damage. Angiotensin II-induced kidney, heart, and vascular injuries depend on T cells since *Rag1* KOs show almost no fibrotic areas after infusions [74]. Transferring old T cells before the treatment leads to worse outcomes, suggesting that aged T cells cause more tissue damage in this model than cells isolated from young donors. This effect depends mainly on IFNg since the Cas9-mediated deletion of *Ifng* before the transfer abrogates the pro-fibrotic phenotype. Another example of T cells being detrimental in aged but not young animals comes from studying flu. Depletion of CD8 T cells during the resolution phase of infection showed that cytotoxic T cells establish an unresolving inflammation and increase fibrosis in the lungs of old but not young animals [75]. Although further studies are required to understand the exact mechanism, T cell-related and IFN signatures are the most elevated in aged lungs two months post-infection.

6. Conclusion and future perspectives

While phenotypical age-associated changes in the T cell compartment have been extensively described using various approaches (especially in mice), data on functional outcomes of T cell aging, such as their role in the induction of inflammaging, is more limited. However, descriptive studies and the existing functional data summarized in this review already conclude that aged T cells exhibit a range of dysregulated features compared to young T cells, including changes in cytokine production patterns. Genetic models of T cell function that partially mimic aged T cell phenotypes demonstrate that abnormal T cells alone can drive systemic deterioration beyond inappropriate responses to infections and cancers. Specific contributions of T cells into establishing inflammaging and other age-related processes and overall decline remain not fully understood. Importantly, since in different contexts, age-associated changes in T cell responses can depend on various regulators and promote different outcomes, it is unlikely that a universal therapeutic strategy could be translationally effective. Moreover, the

variability of how the immune system ages in different individuals increases with advancing age groups. Thus, a more personalized approach to managing T cell-driven aging phenotypes might be needed.

Another aspect of T cell-driven aging phenotypes that is beginning to emerge and is currently rather understudied is a change in T cell trafficking and localization patterns. For instance, multiple reports of detrimental IFN-gamma signatures observed in the aged brain can be driven by dysregulated recruitment of T cells into the normally immune-privileged organ [72,73]. Indeed, in other models, old tissues have been shown to abnormally upregulate chemokine CXCL13, which leads to the recruitment of damaging CD8 T cells and worse outcomes [76,77]. Notably, while this aging phenotype is T cell-dependent, young T cells transferred into old mice can elicit a similar response [76]. Thus, in some models, the underlying cause of T cell-driven damage can be not old T cells per se but their improper recruitment and activation in the tissues. This avenue seems especially promising for human studies since most of the data so far is generated from blood samples. With aging altering tissue immune composition and even introducing more complex tertiary lymphoid structures into non-immune organs [78], dissecting how this change affects human organs homeostasis is especially intriguing.

Finally, understanding the drivers of aging phenotypes in T cells will potentially deliver druggable targets to ameliorate detrimental changes and rejuvenate the compartment. Mechanistic details of T cell aging and ability to target corresponding upstream regulators of will also answer the ultimate question of whether the rejuvenation of T cells is sufficient to improve healthspan and, more specifically, reduce inflammaging.

Declaration of Competing Interest

The authors declare no competing interests.

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