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Hallmarks of T cell aging

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The aged adaptive immune system is characterized by progressive dysfunction as well as increased autoimmunity. This decline is responsible for elevated susceptibility to infection and cancer, as well as decreased vaccination efficacy. Recent evidence indicates that CD4$^+$ T cell–intrinsic alteratins contribute to chronic inflammation and are sufficient to accelerate an organism-wide aging phenotype, supporting the idea that T cell aging plays a major role in body-wide deterioration. In this Review, we propose ten molecular hallmarks to represent common denominators of T cell aging. These hallmarks are grouped into four primary hallmarks (thymic involution, mitochondrial dysfunction, genetic and epigenetic alterations, and loss of proteostasis) and four secondary hallmarks (reduction of the TCR repertoire, naive–memory imbalance, T cell senescence, and lack of effector plasticity), and together they explain the manifestation of the two integrative hallmarks (immunodeficiency and inflammaging). A major challenge now is weighing the relative impact of these hallmarks on T cell aging and understanding their interconnections, with the final goal of defining molecular targets for interventions in the aging process.

Age erodes every physiological function and affects most, if not all, cell types of our body through a series of mechanisms that range from the loss of genomic stability and epigenetic alterations to the loss of proteostasis, deficient nutrient signaling, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and deviant intercellular communication. Most of these 'hallmarks of aging'[1] have been defined in non-vertebrate animal models (such as nematodes and flies) that lack sophisticated adaptive immune systems, suggesting that the principal mechanisms of aging would precede the evolution of B and T lymphocytes and thus relegating these cell types to homeostatic functions that are not central to the core of the aging process.

Notwithstanding this conceptual construction, there is ample evidence in mice that T lymphocytes undergo major age-dependent changes that gradually compromise their physiological function, correlating with, and perhaps even explaining, the tendency to develop autoimmune, autoinflammatory, infectious, and malignant diseases in late life[2]. Thus, T cell aging may be one of the principal manifestations of 'immunosenescence', the time-dependent loss of immune-system vigor that compromises the elimination of noxious elements (such as microbes or malignant cells) while increasing unwarranted overreactions that lead to autoinflammatory and autoimmune disease[3]. Reflecting the fact that circulating (and, to a lesser degree, tumor-infiltrating) T lymphocytes are among the rare cell types that are easily accessible to biomedical investigation, abundant data from humans corroborate the idea that T lymphocytes undergo an important functional deterioration as health declines, placing this cell type in the limelight of human aging research[4].

Recent experiments performed in mice reveal that genetic strategies to accelerate T cell aging, such as the T lymphocyte-specific knockout of the mitochondrial transcription factor A (TFAM), causes not only an immunometabolic dysfunction that drives T cell senescence, but also a general, body-wide deterioration of health with multiple aging-related features, including metabolic, musculoskeletal, cardiovascular, and cognitive alterations[5]. Thus, premature aging of T lymphocytes maybe 'contagious,' driving a generalized acceleration of aging throughout multiple organ systems. Along similar lines, the immunodeficiency caused by knockout of perforin (which is required for the cytotoxic activity of T and natural killer (NK) cells) causes accelerated accumulation of senescent cells in multiple mouse organs, thereby speeding up the aging process, suggesting that the mere failure of immunosurveillance may precipitate whole-body senescence[6].

Driven by these considerations, we became interested in the specific mechanisms of T cell aging, as well as in the question of how the time-dependent deterioration of T lymphocytes might contribute to immunosenescence and the general aging process. Here, we propose the didactic distinction of ten hallmarks of T cell aging, including four primary hallmarks (thymic involution, mitochondrial dysfunction, genetic and epigenetic alterations, and loss of proteostasis) and four secondary hallmarks (reduction of the TCR repertoire, naive–memory imbalance, T cell senescence, and lack of effector plasticity), which together explain the manifestation of the two integrative hallmarks (immunodeficiency and inflammaging) (Fig. 1). Of note, these features of T cell aging are highly interconnected, meaning that they progress together, influence each other and give rise to common features of the aged immune system.

Thymic involution

One of the best-documented changes of the immune system during aging is the involution of the thymus, the major organ responsible for the generation of a highly diverse but selected T cell repertoire[7,8]. Thymic involution starts in childhood and peaks at around puberty in humans[9]. In mice, thymic involution appears to be more gradual, and there is evidence that the thymus can be functional in old mice[10–12]. Age-related thymic involution manifests through a disruption of tissue architecture, a reduction in thymic mass, and hence a decline in thymocyte numbers (Fig. 2). This results in diminished generation of naive T cells that reach the periphery, a compensatory clonal expansion of memory T cells, and a reduc-

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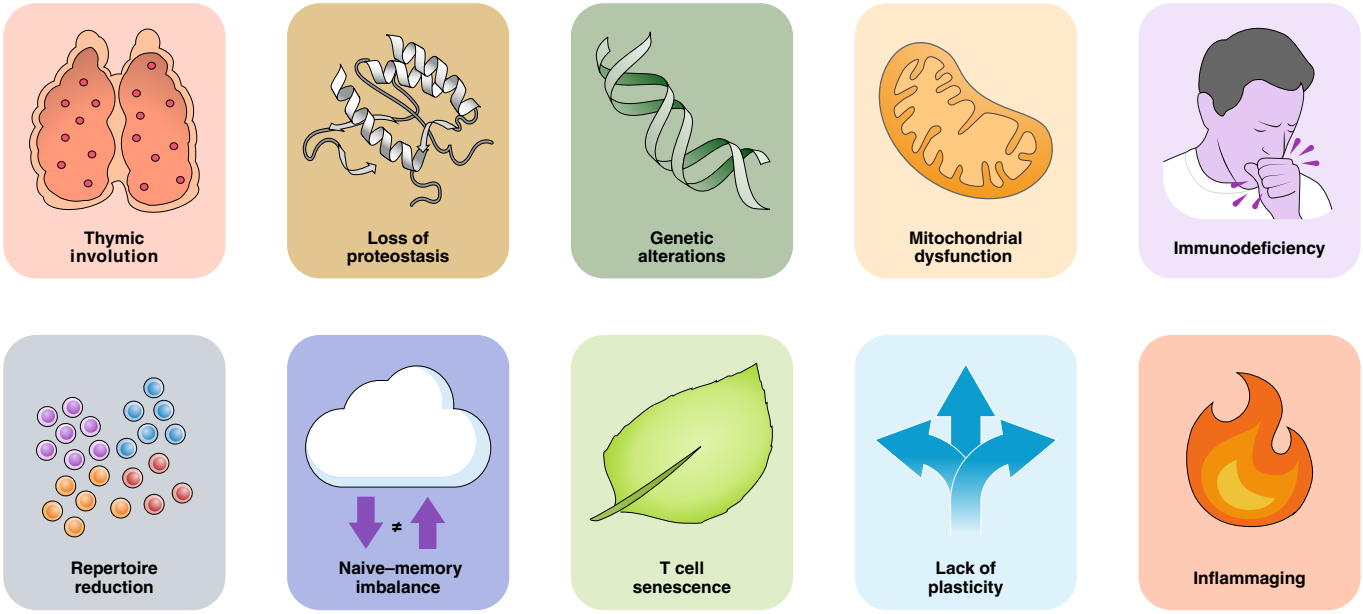

Fig. 1 | Hallmarks of T cell aging. The scheme enumerates the molecular hallmarks that define T cell aging.

tion in the diversity of the peripheral T cell repertoire, compromising the detection of pathogens. Increased levels of sex steroids and reduced production of growth factors, such as growth hormone, insulin-like growth factor-1, and keratinocyte growth factor (KGF), contribute to age-related thymic involution[13]. Accordingly, surgical or chemical castration resulting in the elimination of sex steroids induces a profound rejuvenation of the immune system. Conversely, physical stress, infection, obesity, pregnancy, and antineoplastic therapies accelerate thymic involution[14]. Exogenously administered cytokines from the interleukin-6 (IL-6) family (such as LIF, OSM, and IL-6 itself) or injections of the synthetic double-strand RNA polyinosinic:polycytidylic acid (pIC), mimicking viral infection, trigger thymic involution in young mice[15].

The inability of older people to restore immune function after insult induced by chemotherapy, ionizing radiation exposure, and infections (for example, with HIV-1) is coupled to increased morbidity and mortality. As a result, it is of paramount importance to develop strategies that enhance thymic output and promote immune reconstitution[16,17]. The prolongevity hormone fibroblast growth factor-21 (FGF21) protects against immunosenescence by delaying age-related thymic involution[18]. In young mice treated with KGF, also known as FGF7, the thymic epithelial cells (TEC) compartment transiently expands as immature TECs undergo differentiation. This leads to enhanced thymopoiesis and T cell export[18].

Extra supply of growth hormone or the energy-intake-regulating hormones leptin or ghrelin can prevent stress-mediated thymic atrophy[19]. Ghrelin infusion leads to a marked increase in thymic size, cellularity, and T cell output in old mice[20]. Interleukin-22 (IL-22) also drives thymic regeneration in mice[21]. Of note, people who practiced cycling at an intense level over the course of their life exhibit an increase in the frequency of naive T cells and recent thymic emigrants (RTE), as well as elevated circulating levels of the thymoprotective cytokine IL-7 (but low levels of IL-6, which promotes thymic atrophy), as compared with those levels in age-matched controls who do not practice regular exercise[22]. The TRIIM clinical trial on 9 healthy 51- to 65-year old men succeeded in causing thymic regeneration and an expansion of the pool of naive T cells by a combination of growth hormone, metformin, and dehydroepiandrosterone during 1 year[23].

Beside hormones and growth factors, thymic transplantation and adoptive cell transfer may stimulate thymopoiesis in mice[24]. When transplanted under the kidney capsule, TECs generated from FOXN1-overexpressing embryonic fibroblasts stimulate neoformation of ectopic thymi. Alternatively, TECs can be injected intrathymically to reverse the atrophy of aged thymi, a maneuver that reinforces the negative selection of self-reactive thymocytes, thus attenuating inflammaging and T cell senescence[25].

Of note, the precise mechanisms that drive normal age-related thymic atrophy and loss of thymic output are still largely elusive. Elucidation of these crucial pathways may pave the way to new strategies to prevent immunosenescence and to delay inflammaging.

Mitochondrial dysfunction

Mitochondrial dysfunction occurs in most tissues and cell types, including T cells, in aging humans and mice[5,26,27]. Although T cells from older individuals contain more abundant mitochondrial proteins than do those of young controls, they exhibit impaired oxidative phosphorylation, suggesting that dysfunctional mitochondria accumulate, probably due to their inefficient recycling by autophagy[27]. Persistent antigenic stimulation in chronic viral infections also impairs ADP-coupled oxidative phosphorylation[28]. Mitochondria are essential not only for bioenergetics and cellular metabolism (including the maintenance of the NAD/NADH ratio), but also for other functions. Thus, mitochondria are signaling hubs that produce, relay, and respond to reactive oxygen species (ROS) or calcium spikes[29,30]. These signaling pathways are dysregulated in aged T cells[31]. Mitochondrial dysfunction in T cells leads to the acquisition of a proinflammatory phenotype, through a combination of several molecular mechanisms, including the accumulation of inflammatory metabolites, epigenetic alterations, post-transcriptional protein modifications, and the release of mtDNA to the cytoplasm that activates the cGAS–STING pathway, culminating in the activation of the inflammasome and the transactivation of genes coding for proinflammatory cytokines[32]. In fact, glycolytic metabolism favors inflammatory responses through activation of PI3K–AKT–FOXO signaling[33], and aged T cells exhibit increased basal activation of PI3K–AKT–mTOR and MAPK signaling[34]. Accordingly, genetic deletion of *Mpc1* (an essential subunit of the mitochondrial pyruvate carrier), a maneuver that enforces aerobic glycolysis and reduces oxidative phosphorylation, skews thymocyte differentiation and ultimately promotes the expansion of excessively inflam-

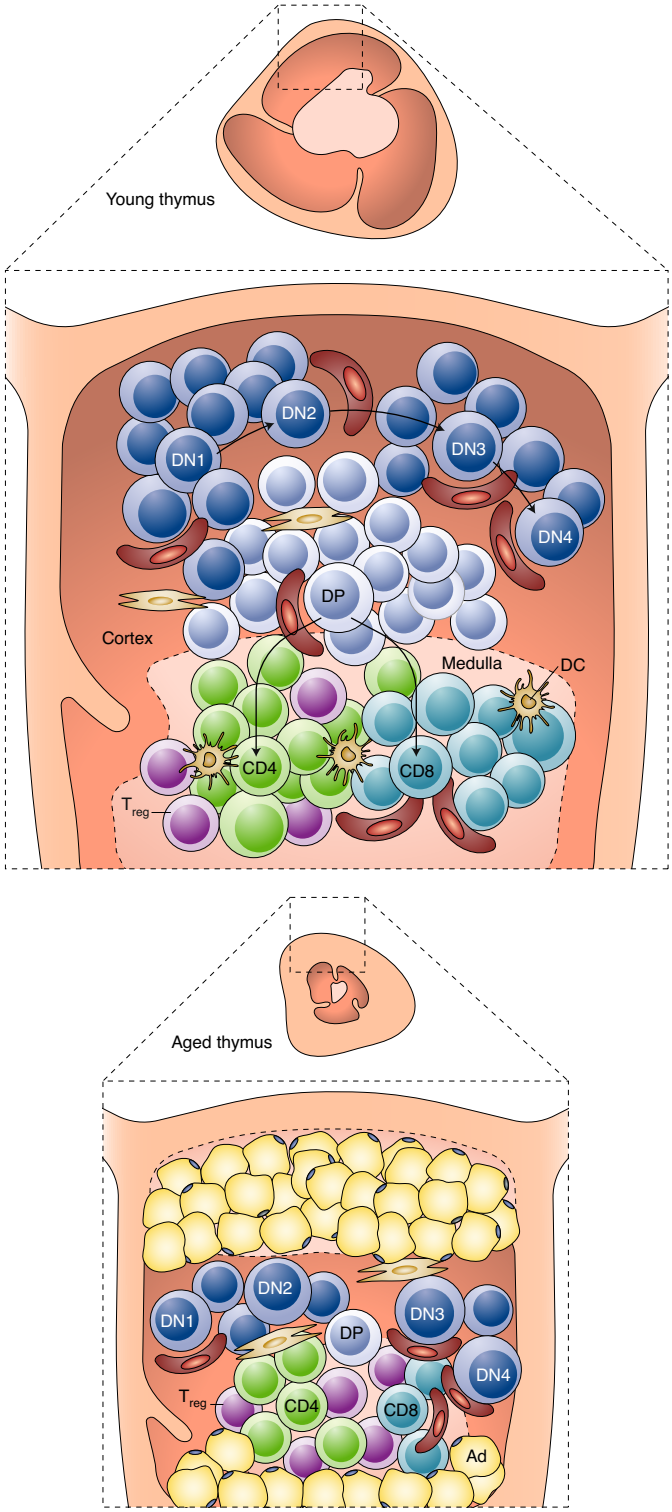

Fig. 2 | Thymus involution. With age, thymic cellularity gradually declines, commensurate with disruption of tissue architecture, reduced production of naive T cells, and reduction in the peripheral TCR repertoire. DN, double-negative $CD4^{-}CD8^{-}$ thymocytes; DP, double-positive $CD4^{+}CD8^{+}$ thymocytes; DC, dendritic cell; Ad, adipocyte. Figure created using BioRender.com.

matory T cells[35]. Moreover, as is true for many other cell types, in T lymphocytes, age-associated mitochondrial decline is associated with the acquisition of a senescent phenotype. Thus, low-dose rotenone, which inhibits respiratory chain complex I, accelerates immunosenescence in human $CD4^{+}$ T cells[36]. Moreover, knockout of the mitochondrial transcription factor A (TFAM) in T cells results in precocious mitochondrial failure that resembles age-associated T cell dysfunction, accompanied by perturbed proteostasis and the acquisition of a type 1 helper T (T_H1) proinflammatory phenotype[37]. Importantly, TFAM-deficient T cells accelerate general aging and precipitate the manifestation of cognitive and physical disabilities, as well as profound cardiovascular alterations, altogether resulting in premature death. These findings suggest a central role for T cell metabolism in the control of organismal aging and longevity in mice. Mechanistically, it appears that the T_H1 phenotype of TFAM-deficient T lymphocytes exacerbates inflammaging, thus promoting paracrine senescence in multiple tissues[5].

Reduced mitochondrial fitness in regulatory T (T_{reg}) cells from HIV-infected people can be reversed by IL-15, which restores the expression of PGC1α and TFAM, thus stimulating mitochondrial biogenesis, and eventually enhancing the antiviral potency of HIV-specific $CD8^{+}$ T cells[38]. Treatment with the oral antidiabetic metformin, which is currently being evaluated for its antiaging effects in a clinical trial[39], enhances TFAM expression and mitochondrial function in mouse $CD8^{+}$ T cells, favoring the resolution of infection by *Mycobacterium tuberculosis*[40]. Similarly, T cell–specific overexpression of transgenic PGC1α not only sustains the structural and functional fitness of mitochondria, but also promotes $CD8^{+}$ T cell persistence, memory formation, and antigen recall potential. Thus, adoptive cell transfer of melanoma-infiltrating $CD8^{+}$ T lymphocytes (TILs) overexpressing PGC1α maintain higher mitochondrial activity and improved expansion when adoptively transferred into tumor-free hosts that then are rechallenged with melanoma cells. Through these effects, PGC1α improves the antitumor response[41]. Mitochondrial boosting strategies have been used to reinvigorate exhausted TILs[42,43].

For a rather small cohort of people, a correlation between old age and increased production of mitochondrial ROS by $CD8^{+}$ T lymphocytes has been reported[44]. Moreover, telomere shortening within the $CD8^{+}$ subset could be prevented in vitro by treatment with a ROS scavenger[44], pointing to a link between ROS and T cell aging.

Growth differentiation factor 15 (GDF15) is a mitokine generated in response to mitochondrial stress or dysfunction. Recent preclinical evidence suggests that GDF15 could maintain the immunosuppressive function of T_{reg} cells and protect against inflammaging[45]. Such data support the conjecture that interventions on endocrine factors, including GDF15, might provide a strategy for improving the immune tonus in older people.

In conclusion, converging, but still fragmentary, evidence favors the possibility that reinvigorating mitochondrial biogenesis may help avoid or correct the age-related derangement of T cell function.

Genetic and epigenetic alterations

As with any other cell type, T lymphocytes undergo genetic and epigenetic alterations with age. Chromosomal alterations accumulate in aging T cells, reflecting the increased incidence of T cell leukemia, which is more frequent in Japanese than in European individuals[46]. Mutations in hematopoietic stem cells (as they occur in clonal hematopoiesis) or lower-level lymphoid precursors affect T lymphocytes together with other blood cell types, depending on which level of the stem cell hierarchy the mutations have occurred[47]. Obviously, such mutations predispose to, or cause, the development of adult T cell leukemias and lymphomas.

Genomic instability of T cells may occur due to mitochondrial stress with overproduction of ROS and telomere attrition[44] as well as reduced activity of repair enzymes[48]. Thus, premature T cell aging associated with rheumatoid arthritis (RA) has been causally linked to the downregulation of the double-strand-break repair nuclease MRE11A, leading to telomeric damage, juxtacentromeric

heterochromatin unfolding, and upregulation of the senescence markers cyclin-dependent kinase inhibitor 1 (CDKN1A, best known as p21) and cyclin-dependent kinase inhibitor 2A (CDKN2A, best known as p16)[48]. Moreover, in immunodeficient mice carrying human synovia, adoptive transfer of MRE11A^{lo} T cells from people with RA caused synovial infiltration and inflammation, a phenomenon that was mitigated by MRE11A reconstitution[48].

All major T cell subsets, including CD8$^+$ α/β and γ/δ T cells, manifest an age-related reduction of telomere length[49], which in humans is profoundly influenced by chronic viral infection, in particular with cytomegalovirus (CMV)[50]. Idiopathic pulmonary fibrosis (IPF) is the most common manifestation of short-telomere syndrome in people. People with IPF who have undergone lung transplantation exhibit impaired T cell immunity against CMV[51], supporting the idea that defects in telomere maintenance can compromise T cell function. Accordingly, carriers of telomerase mutations may develop a T cell immunodeficiency that is associated with the upregulation of intrinsic and extrinsic apoptotic pathways and causes life-threatening opportunistic infections[52]. Conversely, T lymphocytes from 'high-performing' close-to-healthy centenarians are characterized by longer telomeres, higher telomerase activity, and an improved proliferative potential as compared to 67- to 83-year-old controls and low-performing centenarians[53].

Epigenetic alterations may accompany, and to some degree explain, T cell aging. Such epigenetic alterations affect DNA methylation as well as the histone code with its multiple post-translational modifications. DNA methylation age is particularly advanced in individuals with short leukocyte-telomere length (LTL), correlating with low levels of memory CD8$^+$ T cells and high levels of naive CD8$^+$ T cells[54]. In people, age-related epigenetic changes in the DNA methylome reportedly spike for the first time in the late thirties or early forties, with similar timing and magnitude in males and females; the second spike is earlier (by 5–6 years) and stronger in men, correlating with the reduced life expectancy of males[55]. Some of these epigenetic changes have clear functional consequences, as this has been documented for the interruption of the IL-7R signaling pathway occurring in memory CD8$^+$ cells[56].

Alterations in the expression level of specific micro-RNAs (miR) have also been linked to the aging process. For example, both human and mouse T cells manifest an age-related decline in one particular micro-RNA (miR), miR-181a, likely secondary to the decline of the transcription factors YY1 and TCF1 (refs. [57,58]). Conditional deletion of miR-181a in mature T lymphocytes recreates multiple defects in mice that resemble those observed in human T cell aging: upregulation of the negative regulator DUSP6–SIRT1, reduced T cell expansion, failing viral clearance due to impaired antiviral CD8$^+$ T cell responses, and insufficient recall responses coupled to a contraction of the TCR repertoire of memory CD4$^+$ T cells[58]. For example, mice lacking miR-146 develop chronic inflammation with elevated numbers of follicular helper T (T_{FH}) cells, germinal center (GC) B cells, and autoantibodies (against double-stranded DNA, but also multiple organ-specific antigens) that can be reversed by deleting miR-155 specifically in CD4$^+$ T cells[59]. Of note, the reduced lifespan of mice deficient for miR-146 in all their cells could be rescued by the CD4$^+$ T cell–specific knockout of miR-155 (ref. [60]). Consistent with the importance of mitochondrial dysfunction for T cell aging (see above), *miR-146a*$^{-/-}$ T cells exhibit enhanced aerobic glycolysis, which is reversed upon loss of miR-155 (ref. [60]).

Altogether, these findings support the contention that a diverse array of genetic and epigenetic alterations contributes to T cell aging, which in turn may affect overall health status as well as longevity.

Loss of proteostasis

The destruction of misfolded or aged proteins is mediated by proteolytic enzymes, including proteasomes, or autophagy. Defects in either of these two systems can precipitate T cell aging.

In older people, the levels of expression of calpains and tripeptidyl peptidase II (TPPII) decline[61]. The genetic deficiency of TPPII (which causes a specific type of immunodeficiency, Evan's syndrome) is coupled to premature immunosenescence of CD8$^+$ T cells[62]. In aged mice, the activation of the proteasome by TCR signaling declines in CD4$^+$ T cells. Of note, T cell–specific knockout of the proteasome subunit *Rpn13* is sufficient to increase the frequency of senescence-associated PD-1$^+$CD4$^+$ T cells[63], supporting the idea that proteasome activity has a potent antiaging effect on T cells.

The sole mechanism that allows for the recycling of large protein aggregates and entire organelles is macroautophagy (to which we refer to as 'autophagy'), in which portions of the cytoplasm are enwrapped in two-membraned vesicles, the autophagosomes, which subsequently fuse with lysosomes for the bulk degradation of the luminal content. With age, autophagy tends to become insufficient due to a series of factors that likely include: the increase of nutrients (glucose and free fatty acids) and growth factors (insulin and IGF1) that accompany metabolic syndrome, in particular in the context of obesity, and overactivate the autophagy-inhibitory mTORC1 pathway[1,64]; the reduced activation of nutrient sensors, such as sirtuin-1, due to the age-associated decline of nicotinamide dinucleotide (NAD)[65]; reduced spermidine levels that are required for the hypusination-dependent translation of proautophagic proteins[66,67]; and reduced activation of proautophagic transfection factor cascades such as the FOXO1–TFEB axis[68]. Logically, autophagy can be reestablished by reduced caloric intake (by caloric restriction or intermittent fasting)[69] and provision of NAD precursors such as nicotinamide[70], as well as dietary supplementation of spermidine[66,67], resulting in an increase in healthspan and lifespan.

The age-dependent decline in autophagy also affects T cells. Memory T cells and T_{reg} cells, which depend on oxidative phosphorylation to a much higher extent than do effector T cells, are particularly vulnerable to autophagy inhibition, likely because autophagy plays an essential role in mitochondrial quality control[71]. Hence, an acquired autophagy defect may contribute to the decline of immunological memory and tolerance that accompanies old age, commensurate with the multipronged effects of autophagy on proteostasis and organelle homeostasis, metabolism, TCR-triggered proliferation, and the activation of senescence and exhaustion programs[72]. Pharmacological inhibition of autophagy interferes with the tissue-residence reprogramming of human memory CD8$^+$ T cells[73]. Moreover, activation of IGF1 receptor (IGF1R) augments mTORC1 signaling (which inhibits autophagy), increases aerobic glycolysis, and increases T_H17 differentiation over that of T_{reg} cells, and thus aggravates inflammatory and autoimmune phenotypes[74]. Genetic manipulations designed to inhibit autophagy in CD4$^+$ T cells, such as knockout of *Atg16l1* (autophagy-related protein 16-1) or *Pik3c3* (phosphatidylinositol 3-kinase catalytic subunit type 3, best known as Vps34), results in systemic inflammation with the loss of intestinal T_{reg} cells[75,76], a phenomenon that can be recapitulated by a T_{reg} cell-specific knockout of autophagy genes as well[77,78]. Hence, autophagy has anti-inflammatory effects that are mediated at least in part by T_{reg} cells.

In accord with this conclusion, provision of spermidine to human or mouse T cells differentiated in vitro or in vivo, respectively, favors the autophagy-dependent differentiation of naive CD4$^+$ T cells from a T_H17 toward a T_{reg} cell phenotype[79]. In mice, supplementing spermidine in drinking water also promotes homeostatic differentiation of T_{reg} cells in the gut[79]. Moreover, short-term administration of the mTORC1 inhibitor rapamycin improves the quality and magnitude of the CD8$^+$ T cell memory response to viral infection in mice[80] and improves immune responses to an influenza-virus vaccine in older people[81]. Pharmacological inhibition of mTORC1 also decreases the rate of infections (in particular of the respiratory tract) in older people[82]. In individuals belonging to families with exceptional longevity,

CD4+ T cells show improved activation-induced autophagic activity compared with those of age-matched controls[83].

Altogether, these results suggest that autophagy is an actionable target for counteracting T cell aging and that its induction may reduce inflammation but simultaneously improve the acuity of immune responses.

Reduction of TCR repertoire

The TCR repertoire shifts with age commensurate with multiple factors that change over time, namely: reduced generation of naive T cells by the thymus (see above); clonal hematopoiesis giving growth advantage to a fraction of T cells, irrespective of their antigen specificity; persistent selection by peripheral antigens, including those behind chronic viral infections such as cytomegalovirus CMV, causing 'memory inflation'; and senescence of T cell subsets that may result from limits to clonal expansion, perhaps linked to erosion of the telomeres[84,85]. This latter phenomenon may paradoxically abolish the immunodominance of high-affinity clones recognizing epitopes from CMV, thus favoring an evolution toward low-affinity clones[86]. In addition, recent work suggests that the pool of CD4+ human stem cell memory T lymphocytes (T_{SCM}) undergoes age-dependent attrition due to a loss of Wtn/ß-catenin signaling, commensurate with the systemic increase in the concentrations of Dickkopf-related protein 1, a natural inhibitor of the Wnt/β-catenin pathway[87].

Altogether, the available evidence suggests that both T cell–intrinsic and T cell–extrinsic factors contribute to a reduction in TCR diversity (particularly pronounced in the CD8+ T effector memory CD45RA+ (T_{EMRA}) subset) that compromises immune function and/or causes the disproportionate expansion of T cells specific for autoantigens or antigens encoded by persistent viruses (such as CMV and Epstein–Barr virus). This reduction in TCR diversity has been observed both in longitudinal and cross-sectional population studies[88].

Detailed analyses of large series of TCR sequences revealed that, in aging individuals, naive T cells exhibit a gradual reduction in TCRβ CDR3 length, NDN inserts, and the number of non-template added N nucleotides, together with a significant alteration of physicochemical properties of the central part of CDR3 loop. These alterations were found across CD4, CD8, RTE-enriched, and mature CD4 subsets of naive T cells. In contrast, an increase in 'publicity' (fraction of shared clonotypes) was observed in CD4+, but not CD8+, naive T cell repertoires[89]. These observations document a partial contraction of the α/β TCR repertoire. Of note, there is also an age-related shift from $V_\gamma9/V_\delta2$ to $V_\gamma2/V_\delta1$ memory T cells in humans that may be driven by peripheral selection[90] or by the intrinsic resistance of $V_\gamma2/V_\delta1$ cells to senescence[91].

Thus, the TCR repertoire undergoes subtle shifts and a partial contraction with age. However, at this stage it remains to be formally demonstrated whether such changes have major functional consequences and hence compromise the subtle balance between efficient foreign antigen recognition and avoidance of autoimmune reactions. Administration of IL-7 to humans increases in vivo TCR repertoire diversity, probably due to increased naive T cell proliferation[92]—suggesting the possibility of intervention on the age-related rarefaction of TCR diversity. Whether such an intervention will yield clinical benefits remains to be established.

Naive–memory imbalance

The quantity of unique antigens that T cells can identify is proportional to the number of clones present in the naive T cell pool, which is maintained by species-specific mechanisms in humans and mice. Although the proportion of RTEs declines with age, RTEs are readily detectable even in 2-year-old mice, suggesting that they contribute to the lifelong maintenance of the naive T cell pool[11]. Indeed, insufficient thymic output during aging leads to contraction of the compartment and eventually to holes in the murine T cell repertoire[11]. In contrast, in humans, thymic involution is more pronounced, meaning that the maintenance of naive T cell pool relies on peripheral division of existing clones rather than on de novo production of new ones[12,93]. Thus, in the absence of thymic output, naive T cells are considered to function as their own stem cells[2]. With age, the naive pool contracts along with the accumulation of highly differentiated memory cells, likely reflecting the exhaustion of stem cell-like pools in the T cell lineage. Mold et al. quantified nuclear-bomb-test-derived ^{14}C in genomic DNA to determine the turnover rates of CD4+ and CD8+ naive T cell populations, and found that these dynamics decline in healthy individuals as they age. Remarkably, CD8+ naive T cells exhibit reduced homeostatic proliferation in vivo relative to CD4+ naïve T cells[93]. However, as a caveat, it should be noted that knowledge on the naive–memory balance of T lymphocytes in humans is largely limited to the peripheral blood, which is far more studied than is the tissue-resident pool of T cells. Isolated studies point to an age-associated decrease in naive T cells in the gut-associated lymphoid tissue, as well as in lymph nodes and the spleen[94,95].

If naive T lymphocytes are considered quasi-stem cells, the mechanisms that compromise stem cell function during aging, such as loss of quiescence, increased differentiation, and senescence, may also subvert the maintenance of naive T cells[96]. Besides T cell–intrinsic defects, homeostatic proliferation can be compromised by impaired access to, or alterations in the architecture of, secondary lymphoid organs with age. Peripheral homeostasis of T cells depends on their recruitment to secondary lymphoid organs, where they encounter IL-7 produced by fibroblastic reticular cells[97]. The impact of IL-7 on naive T cell turnover is confirmed by the observation that therapeutic administration of high levels of IL-7 to people for as little as 1 week promotes a substantial rise in naive T cells[92]. IL-7 therapy induces CD4+ and CD8+ T cell expansion in vivo, with preferential increases in T cells bearing diverse TCR repertoire specificities. These effects are primarily mediated through increased proliferation and survival of peripheral T cells[92].

When quiescence is lost, naive T cells differentiate toward memory T cells. It has long been assumed that memory T cells accumulate with aging as a result of lifelong antigenic stimulation. However, this idea has been revisited since cumulative evidence supports the notion that cytokine-activated T cells, known as 'virtual memory T cells', present similar phenotypes to conventional antigen-experienced memory cells and accumulate with aging in mice[98,99]. Virtual memory T cells, are antigen inexperienced, present high affinity for self-antigens[100], and tend to develop features of cellular senescence[101]. Certain cytokines like IL-15 and IL-4 are essential for the differentiation of virtual memory T cells[100]. Aged CD8+ T cells are more prone to differentiate into virtual memory cells than are CD4+ T cells. It is therefore possible that the generation of virtual memory T cells favors the preferential erosion of the naive CD8+ T cell compartment. However, it is still uncertain whether this mechanism fully explains why the CD4+ T cell compartment is more resilient to age than its CD8+ counterpart[2,98,101].

Altogether, existing data suggest that, due to thymic involution, persistent antigen stimulation, and an inflammatory environment, there is an enrichment in memory (some of them antigen inexperienced) T cells and a decrease in the naive pool that is more prominent in the CD8+ compartment. This bias towards the memory phenotype compromises the response to new antigens. Thus, the age-related decline in number, diversity, and functionality of naive T cells presents significant challenges for developing efficacious vaccines for older people. Memory responses generated in youth or adulthood appear to be long-lasting compared with those generated in old age.

T cell senescence

Aging is accompanied by the accumulation of dysfunctional, terminally differentiated T cells. As a result of persistent lifelong antigen

stimulation, as occurs in particular in chronic virus infection, T cells acquire a senescent or exhausted phenotype that restricts T cell responses[102]. Although senescent and exhausted T cells share overlapping characteristics and are both defective in their TCR-triggered-proliferation, they are distinct in terms of molecular signaling and in their secretory phenotype. Senescent T cells secrete abundant proinflammatory factors, such as tumor necrosis factor (TNF), and osteopontin, reminiscent of an senescence-associated secretory phenotype (SASP).

Senescent T cells acquire additional features of senescence, including low telomerase activity and short telomeres; signs of DNA damage, such as γH2AX foci; apoptosis resistance; and β-galactosidase activity. Moreover, senescent T cells lose the expression of the costimulatory molecules CD27 and CD28 and upregulate the expression of terminal-differentiation markers, such as KLRG1 (ref. [84]). CD57 is another terminal-differentiation marker that has been used to identify human senescent T cells, colliding with the fact that CD57$^+$ T cells actively proliferate in vivo[103]. In accord with the idea that terminally differentiated T cells acquire a senescent phenotype, human T_{EMRA} cells exhibit many characteristics of cellular senescence, including decreased proliferation, defective mitochondrial function, increased secretion of TNF and interferon-γ, potent cytotoxic activity, and elevated p38 MAPK signaling[34].

The susceptibility of human CD4$^+$ and CD8$^+$ T cells to senesce differs, with CD8$^+$ T cells acquiring an immunosenescent phenotype faster than does the CD4$^+$ T cell compartment. T_{EMRA} cells are found in both the CD4$^+$ and CD8$^+$ T cell compartments. Although both subsets undergo the same phenotypic and functional changes with age, CD8$^+$ T_{EMRA} cells accumulate faster than their CD4$^+$ counterparts[84,104], perhaps due to differences in their metabolism. CD4 T_{EMRA} cells have fitter and healthier mitochondria, whereas CD8$^+$ T_{EMRA} cells are more prone to mitochondrial decline[36]. The tumor suppressor menin prevents T cell senescence by restringing cellular metabolism. *Menin*-deficient CD8$^+$ T cells present senescent features, including β-galactosidase activity. In these cells, mTOR complex 1 (mTORC1) signaling, glycolysis, and glutaminolysis are increased, and treatment with rapamycin prevents immunosenescence[105]. Sestrins are stress-sensing proteins that regulate T cell senescence[106,107]. In the CD8$^+$ T cell compartment, sestrins induce reprogramming of senescent-like CD8$^+$ T cells to innate-like killing activity. Thus, senescent-like T cells lose the signaling activity of the TCR and express a protein complex containing the agonistic NK receptor NKG2D and the NK adapter molecule DAP12, which promotes cytotoxicity against cells that expressed NKG2D ligands[107]. Cytotoxic CD4$^+$ T cells bearing KLRG1 and NK receptors and producing high levels of proinflammatory factors, including granzymes and perforin, have been identified in aged mice and supercentenarians[108,109]. Whether this age-associated T cell subpopulation displays additional senescent features, such as proliferative arrest, shortened telomeres, or signs of DNA damage, remains to be investigated.

Recently, it has been described that T_{reg} cells senesce more severely than do effector T cells during aging[110]. DDB1- and CUL4–associated factor-1 (DCAF1) expression is downregulated in aged T_{reg} cells. This pathway may be essential for buffering ROS levels through glutathione *S*-transferase (GSTP1). Thus, overexpression of GSTP1 and ROS scavengers reinvigorate the proliferation and activity of aged T_{reg} cells[110].

T cell senescence can be accelerated by chronic viral infection. Repeated T cell stimulation and extensive replication can induce telomere attrition and DNA damage, precipitating replicative senescence[84,111]. In fact, the percentage of senescent T cells is significantly higher in CMV-seropositive than in CMV-seronegative individuals[112]. In addition to replicative senescence, inflammatory stress signals, glucose starvation, or mitochondrial dysfunction may trigger premature senescence in T cells[5]. For example, virtual memory T cells express transcriptional and phenotypic markers of senescence in mice[101].

Senescent T cells have been involved in the pathogenesis of certain age-related diseases, such as cardiovascular, metabolic, and neurodegenerative disorders. Adoptive transfer of old T cells into middle-aged mice accelerates angiotensin-induced cardiovascular damage and kidney fibrosis[113]. In obese mice, senescent T cells with a CD4$^+$CD44^{hi}CD62L^{lo}PD-1$^+$CD153$^+$ phenotype accumulate in visceral adipose tissues (VAT) where they play a crucial role in inducing chronic VAT inflammation and metabolic syndrome. Such effects depend on osteopontin because knockout of *Spp1* (the gene coding for osteopontin) in the donor mice abolished the pathogenic effects of adoptively transferred senescent T cells[114]. Vaccination with a CD153 peptide induces the production of anti-CD153 antibodies that then remove senescent T cells from obese mice, improving glucose tolerance[115]. In people with Alzheimer's disease, an increased frequency of T_{EMRA} is found in peripheral blood as well as in cerebrospinal fluid, and such T cells are often specific for Epstein–Barr virus antigens[116].

The PI3K and p38 MAPK signaling pathways are involved in the induction of T cell senescence. Hyperactive PI3 kinase signaling in primary immunodeficiencies accounts for the PI3 kinase delta syndrome (APDS), favoring premature accumulation of a CD57$^+$CD8$^+$ senescent T cell population[117]. Blocking p38 MAPK signaling can reverse some senescence-associated defects in T_{EMRA}, thus increasing their proliferation, telomerase activity, mitochondrial biogenesis, and autophagy[118–120]. Additionally, blocking KLRG1 signaling using antibodies against its ligand E-cadherin enhances CD8$^+$ T cell proliferation through the AKT-mediated induction of cyclins D and E and reduction in the expression of the cyclin inhibitor p27. In contrast, reduced telomerase activity is not altered by KLRG1 blockade[121]. miR-155 restrains CD8$^+$ T cell senescence by epigenetically repressing transcription factors driving terminal differentiation and exhaustion[122]. Phytochemicals such as polyphenols, probiotic microbes, and omega-3-fatty acids also reportedly reverse immunosenescence[123].

In sum, with age, senescent T cells with reduced immune but elevated proinflammatory functions accumulate. Depletion of such cells (senolysis) may provide interesting opportunities to intervene on aging and age-associated diseases, including metabolic syndrome and neurodegeneration.

Lack of effector plasticity

Differentiated CD4$^+$ T lymphocytes have classically been classified into distinct subtypes, including T_H1, T_H2, T_H9, T_H17, T_H22, T_{FH}, and T_{reg} cells. This paradigm has been recently reevaluated, giving rise to the idea that helper T lineages form a continuum of polarized phenotypes dictated by the antigenic challenge[124]. With age, T cells lose their quiescence and acquire a terminally differentiated stage, a phenomenon that may cause a bias in lineage commitment and therefore a loss in plasticity, compromising the capacity of the immune system to respond to new antigenic challenges. Human naive CD4$^+$ T cells from older individuals exhibit increased expression of transforming growth factor β receptor 3 (TGFβR3), thus activating the transcription factors PU.1, BATF, and IRF4 and favoring T_H9 differentiation[125].

On the basis of single-cell transcriptomics, the CD4$^+$ compartment of aging mice accumulates exhausted, cytotoxic, and activated regulatory cells, often with extreme anti- and proinflammatory properties, mainly within the T_H1 and T_H17 subsets[109]. Remarkably, the appearance of these subsets is associated with elevated circulating inflammatory cytokines (mainly interferon-β, IL-6, and IL-27), supporting an additional link between inflammaging and the aging-related changes of CD4$^+$ T cells[109]. Expansion of age-associated cytotoxic CD4$^+$ T cells has been identified in human supercentenarians[108]. In aged humans or mice, the CD8$^+$

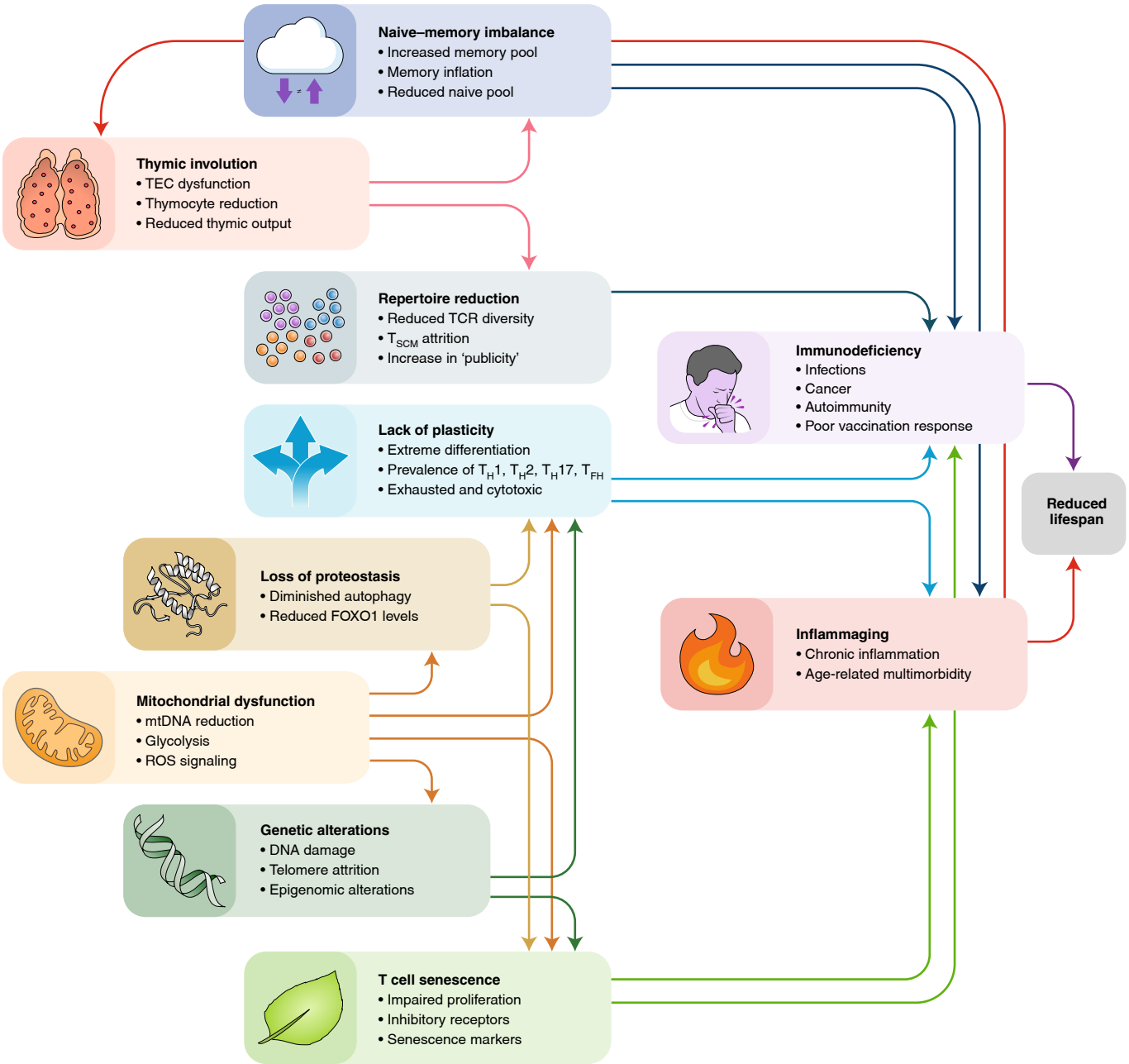

Fig. 3 | Features and consequences of T cell aging. Salient characteristics of each hallmark are listed, and the most important interconnections are indicated by arrows.

compartment is characterized by the expansion of an oligoclonal and exhausted ($TOX^+PD\text{-}1^+$) population of T cells that secretes granzyme K (GZMK), a factor that stimulates senescence in other cells, such as fibroblasts. Of note, this $CD8^+GZMK^+$ population is induced by an aged environment, as shown by heterochronic adoptive-transfer experiments (in which young $CD8^+$ T cells were injected into old mice), and correlates with markers of inflammaging, such as IL-6, IL-8, and TNF, in aged humans[126].

Although the number of T_{reg} cells increases in aged mice, they are less efficient in suppressing conventional T cell function than are young T_{reg} cells[110]. Importantly, quenching ROS reinvigorated the proliferation and activity of aged T_{reg} cells[110]. Similarly, in aged mice, there is a rise in the number of T_{FH} cells[127], which, however, become inefficient B cell helpers, perhaps due to defective signaling pathways[128].

In brief, aging of T lymphocytes is associated with a decrease in plasticity coupled to a terminal-differentiation phenotype, compromising their elasticity to combat novel challenges. In tumor immunology, the functional efficacy of T cells infiltrating tumors has been resuscitated by induced progenitor stem cell (iPSC) technology[129]. Whether a similar approach may be chosen to restore the plasticity of aged T cells remains to be determined.

Immunodeficiency

Progressive immunodeficiency due to reduced TCR repertoires, shifts in the proportion between naive, effector/memory, and T_{reg} cells, and an accumulation of ever-less-efficient senescence-associated or exhausted T cells may explain the old-age-associated susceptibility to severe, and sometimes lethal, bacterial or viral infections. Moreover, deficient immune (and T cell) function also likely

contributes to the pathogenesis of noncommunicable diseases, like cancer or arteriosclerosis. Indeed, mathematical models suggest that the increased risk of cancer linked to the aging process might be better explained by a reduction in thymic output (with a consequent decline in immune function) than by an increase in somatic DNA mutations[130]. Thus, the escape from immune control due to T cell immunodeficiency might be the principal driver of the manifestation of cancer, in line with the observation that immunodeficiencies accelerate the development of carcinogen-induced carcinomas[131]. A reduction in thymic function (deduced from a decrease in RTE) has also been associated with an increased risk for long-term mortality after kidney transplantation[132]. However, since uremia associated with end-stage renal disease itself triggers thymic aging[133], as well as telomere shortening on peripheral leukocytes[134], the cause–effect relationship between these phenomena may be bidirectional. The amount of signal-joint T cell receptor excision cycles in T lymphocytes, a molecular marker of RTE, was found to negatively correlate with the progression of coronary artery disease[135], illustrating yet another association between immunodeficiency and age-associated disease. Again, it is still unclear whether this latter association reflects a causal relationship.

It can be speculated, yet remains to be formally demonstrated, that deficient T cell function contributes to the accumulation of senescent (non-immune) cells in different tissues due to a failure in the clearance of such cells. At this point, the only study dealing with this possibility has investigated perforin-deficient mice that lack the cytotoxic activity of T cells but also NK and NKT cells[6]. Moreover, one of the major strategies of senescent skin cells to avoid immune clearance involves the upregulation of HLA-2, which interacts with the inhibitory receptor NKG2A, expressed by differentiated CD8$^+$ T cells and NK cells[136]. Thus, at this point, there is no formal demonstration that the specific dysfunction of aged T cells would compromise the clearance of senescent cells, thereby precipitating the aging process. As such, further experimental evidence is required to confirm a hypothetical T cell–specific immunosurveillance defect that contributes to the general aging process.

Inflammaging

Inflammaging, a term first coined in 2000 by Claudio Franceschi, refers to the state of low-grade chronic inflammation that develops with age. It is characterized by high serum concentrations of inflammatory cytokines and mediators such as C-reactive protein (CRP), IL-6, IL-8, and TNF[137]. Inflammaging is associated with increased risk of age-related multimorbidity and mortality[138,139]. Although inflammaging was initially considered a biomarker of age-related conditions, accumulating evidence suggests a cause–effect relationship between inflammaging and age-related tissue deterioration. Clinical trials demonstrated that some nonsteroidal anti-inflammatory agents, as well as neutralization of IL-1 and TNF, retard the manifestation of cardiovascular pathologies[138].

Inflammaging has been attributed to a combination of age-related defects, such as increased gut permeability, chronic infections and the accumulation of senescent cells[140]. Recent evidence suggests that the time-dependent deterioration of T lymphocytes actively contributes to inflammaging either in a direct way, through the production of inflammatory cytokines[5] and the failure to eliminate senescent cells[6], or in an indirect way, by affecting the function of distinct myeloid cell populations, including macrophage subtypes, or by modulating gut permeability.

Metabolic stress in T cells suffices to accelerate inflammaging[5]. Accelerated inflammaging occurs in mice with mitochondrial dysfunction in CD4$^+$ T cells due to a defect in TFAM. *Tfam*$^{fl/fl}$ *CD4Cre* mice exhibit low body weight, kyphosis, metabolic syndrome, cognitive and physical disability, and profound cardiovascular alterations, including cardiac atrophy and aortic wall remodeling, resulting in premature death. Of note, blockade of TNF with etanercept prevented systemic senescence and muscle, cardiovascular, and cognitive alterations that are normally observed in *Tfam*$^{fl/fl}$ *CD4Cre* mice. Thus, TNF-dependent inflammaging contributes to the frailty and premature ageing of *Tfam*$^{fl/fl}$ *CD4Cre* mice[5].

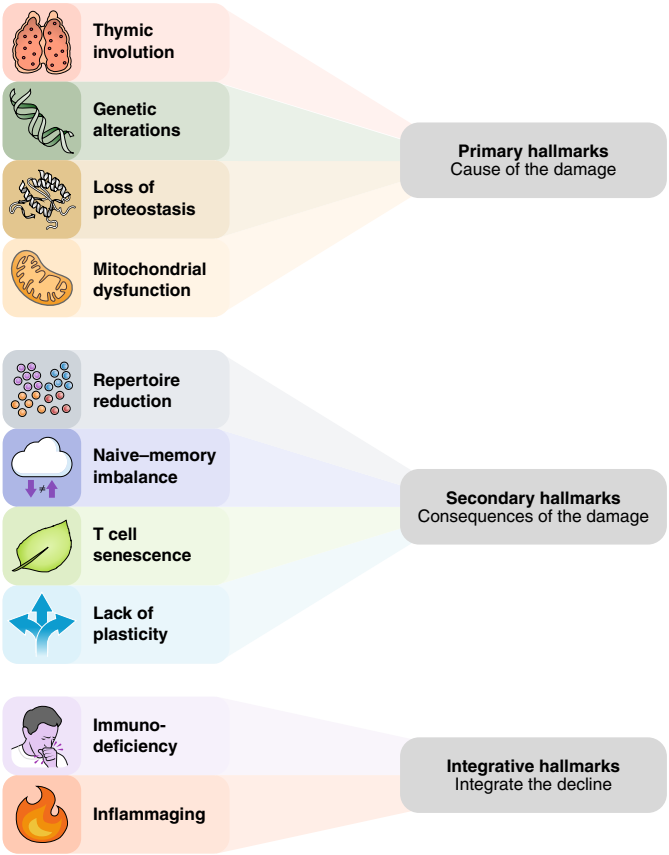

Fig. 4 | Classification of the hallmarks. The proposed hallmarks of T cell aging are grouped into three different categories according to their hierarchical position in the process. Adapted from Lopez-Otin et al.[1].

Besides its contribution to age-related tissue damage, inflammaging may also inhibit antigen-specific immunity and reduce vaccination effectiveness[140]. Accordingly, tissue-specific immunity can be restored in older adults by short-term inhibition of inflammatory responses, with a p38 MAPK inhibitor[141,142].

Paradoxically, together with inflammaging, the circulating levels of IL-10, a potent anti-inflammatory cytokine, increase in aged individuals[143]. IL-10 likely plays an important role to counteract inflammaging and promote healthy aging. IL-10-producing T cells bear markers of T_{FH} cells and are present in both mice and humans. IL-21 is critical for maintaining this balance, as mice deficient in IL-21 have decreased IL-10 (and lose IL-10-producing T_{FH} cells) but increased IL-6, pointing to a complex crosstalk among cytokines that fine tune the inflammatory tonus[143].

Obviously, there is much interest in developing drugs that dampen inflammaging. The mitokine GDF15 is induced by mitochondrial dysfunction and organ injury and coordinates tolerance to inflammatory damage[144]. In GDF15-deficient mice, aging is accompanied by severe adiposity, liver injury, and hepatic fat deposition. Although GDF15 is not required for T_H17 cell differentiation, GDF15 contributes to T_{reg}-mediated suppression of conventional T cell activation and inflammatory cytokines[45]. GDF15 is induced by metformin, perhaps explaining (some of) its antidiabetic and antiaging effects[145]. Metformin, which activates the AMP-activated protein kinase signaling pathway, has been successfully used as a long-term therapy in people with diabetes. Recently, it has been

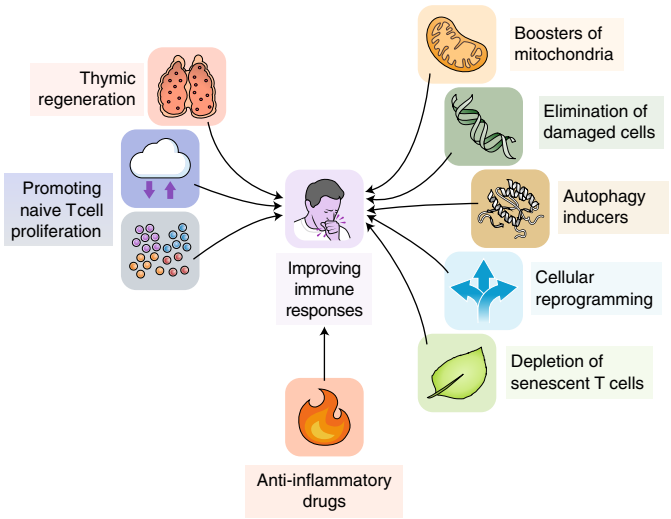

Fig. 5 | Interventions that might improve T cell aging. Therapeutic approaches that may delay some of the hallmarks of T cell aging are indicated. Adapted from Lopez-Otin et al.[1].

reported that metformin ameliorated the T_H17 inflammaging profile by increasing autophagy and improving mitochondrial bioenergetics in T cells, both in vitro and in people[146]. As an alternative strategy, long-term, low-dose resveratrol reversed phenotypes of immunosenescence and inflammaging in old mice, as it corrected the age-associated elevation of 8-hydroxy-2′-deoxyguanosine, a marker of oxidative DNA damage[147]. Attempts to combine different strategies involving anti-inflammatory drugs, senolytics, and immune checkpoint inhibitors are underway for optimal blocking of inflammaging[140].

Briefly, inflammaging can be partially attributed to dysfunctional or senescent T cells. Ameliorating inflammaging should be an intense research focus in the coming years to prevent both the onset of age-related diseases and the decline in immune responses.

Conclusions

With age, the immune system loses the capacity to mount rapid and precise responses against new antigenic, infectious, or neoplastic challenges, and its capacity to recall and refine memory responses is reduced; it instead engages in futile proinflammatory and autoimmune reactions. Aged T cells acquire a proinflammatory state that sustains inflammaging, thus accelerating pathologies that constitute the leading causes of human frailty and mortality, such as cardiovascular and metabolic diseases, chronic kidney disease, nonalcoholic fatty liver disease, and neurodegenerative disorders[139]. In fact, recent evidence supports the relevance of T cell fitness for preventing Alzheimer's disease[116], as well as cardiovascular and metabolic disorders[148]. Understanding the interconnections among the ten hallmarks of T cell aging will help to elucidate new strategies to boost immunity in older people and to prevent the undesired consequences of chronic inflammation.

The hallmarks of T cell aging can be grouped into three distinct categories, based on their hierarchical interconnections. Four primary hallmarks (thymic involution, mitochondrial dysfunction, genetic and epigenetic alterations, and loss of proteostasis) account for the initial damage. Four secondary hallmarks (reduction of the TCR repertoire, expansion of the memory pool, lack of effector plasticity, and T cell senescence) are consequences of the primary hallmarks. Finally, the two integrative hallmarks (immunodeficiency and inflammaging) crystallize the consequences of the age-linked T cell derangement, channeling them into functional deficiencies (Fig. 3). For example, thymic involution, one of the primary hallmarks, contributes to the appearance of at least two of the secondary hallmarks, rarefaction of the TCR repertoire and expansion of memory over naive T cells, and it may also facilitate the accumulation of senescent T cells[149,150]. The other primary hallmarks—mitochondrial dysfunction, loss of proteostasis, and genetic alterations, are interconnected to some extent, though without a clear hierarchy. Thus, mitochondrial dysfunction can promote autophagy decline and vice versa[37]. The secondary hallmarks are T cell–intrinsic and affect different facets of their function, namely their clonality/specificity (TCR repertoire), their level of differentiation following a temporal sequence (naive/memory imbalance), and their proliferative competence and function (immunosenescence), as well as bias in their activity (loss of plasticity). These different facets are interrelated. For example, each of the different categories of naive/memory, senescent and non-senescent, or more or less biased T cell populations can be differentially affected by the reduction of the TCR repertoire. Similarly, the SASP may be both the cause and the consequence of plasticity loss. It is well possible that the integrative hallmarks engage in feedforward loops that accentuate primary and secondary hallmarks, thus driving the aging process, locking it into a chronically advancing pace. Thus, inflammaging can accelerate thymus involution and precipitate secondary hallmarks (Fig. 4). Hence, a major challenge is to understand the relative importance of each of the hallmarks of T cell aging and to clarify their interconnections, with the final goal of defining optimal molecular targets for attenuating or interrupting the aging process. Indeed, some of the processes accounting for T cell aging are druggable (Fig. 5). However, it remains to be determined which strategies will be most effective and how they can be advantageously combined.

Theoretically, T lymphocyte aging might involve immune-cell-intrinsic processes, alterations in lymphoid organs, host-intrinsic metabolic or neuroendocrine factors outside of lymphoid organs, smoldering infections, and shifts in the intestinal microbiota—meaning that it is intrinsically difficult to distinguish the precise cause of age-associated T cell dysfunctions, which are interlocked[151]. To elucidate this problem, heterochronic adoptive-transfer experiments (that is, the reconstitution of old mice with young T cells or vice versa), transplantation of lymphoid organs between mice of different ages, heterochronic parabiosis (that is, the connection of the circulatory systems among young and old mice), and fecal microbial transplantation should be explored in a systematic fashion. Similarly, the organism-wide effects of T cells should be studied in more detail, not only by genetic strategies that accelerate T cell aging, but also by maneuvers that block or reverse the aging phenotype of T lymphocytes. Would the rejuvenation of the T cell compartment suffice to delay organismal aging in its entirety, or at least some of its manifestations? An affirmative response to this question might have vast consequences for immunological research and practice.

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Competing interests

G.K. is the scientific cofounder of three biotech companies dealing with age-related diseases: everImmune, Samsara Therapeutics, and Therast Bio.

Additional information

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