Clinical Interventions in Aging

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REVIEW

T Cell Aging: An Important Target for Perioperative Immunomodulation

Haoning Lan, Songchao Xu, Huili Li, Ruijuan Guo, Zhong Feng, Yun Wang

Department of Anaesthesiology, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, People's Republic of China

Correspondence: Yun Wang, Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, No. 95, Yong' an Road, Beijing, 100050, People's Republic of China, Tel +86-10-63133069, Email wangyun129@ccmu.edu.cn

Abstract: Although T cells are crucially involved in maintaining immune function, their roles change with age. Furthermore, T cell aging has a unique onset and progression mechanism and several clinical indicators have been developed to detect it. Moreover, perioperative pain and stressful stimuli could affect the body's immune status, influencing patients' recovery. This article examines how preoperative and intraoperative complications influence T cell aging. These factors include conditions such as hypertension, diabetes, acute respiratory distress syndrome, hypoxemia, depression, pain, obesity, neurologic diseases, tumors, autoimmune diseases, as well as aspects like anesthetic modalities, types of surgery, and medications. This analysis could help identify groups at a high risk of perioperative T cell aging. For example, elderly cancer patients with multiple chronic diseases may be the most affected by T cell aging. We also discuss the effects of T cell aging on postoperative phenomena such as neurological dysfunction and recovery quality. Based on insights from this discussion, we deduced that prehabilitation, pharmacological treatment, and adoptive neuro-immunotherapy could modulate T cell aging in the perioperative period, thus improving clinical prognosis.

Keywords: perioperative period, T cell aging, immunomodulation, CD57, terminal effector memory T cells, senescence-associated secretory phenotype

Invasive perioperative procedures often trigger an inflammatory response in patients, stimulating immune regulatory mechanisms in their bodies. Patients' immune function gradually declines as they age due to the degeneration of immune organs, chronic infections and inflammatory senescence, mitochondrial dysfunction, protein homeostasis imbalance, and epigenetic alterations.[1] In addition to negatively impacting vital organ function in patients, imbalanced perioperative immune regulation could increase the incidence of postoperative infections and tumor metastasis recurrences.[2]

According to reports, appropriate anesthetic drugs and perioperative adjuvants could help improve innate and adaptive immune function. For instance, sevoflurane attenuated neutrophil recruitment and phagocytosis, whereas propofol exerted enhanced protective effects on neutrophil function. Furthermore, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), commonly used perioperative analgesics, upregulated Interleukin (IL)-10 (which has immunosuppressive properties) and downregulated IL-12 (which has anti-angiogenic properties).[3] However, due to a lack of appropriate immunomodulatory indicators, clinicians can only administer drugs to modulate perioperative immune function based on clinical experience. Although IL-6, calcitonin, C-Reactive Protein (CRP), absolute leukocyte value, and T cell ratio have been established as common immunomodulation targets, infections and drugs easily interfere with them; hence they cannot be employed to accurately quantify the immune reserve function. In other words, they are not optimal indicators of perioperative immunomodulation, a phenomenon that necessitates additional research. In addition to mediating adaptive immunity, T cells are also an important component of both humoral and innate immunity. T cells play a role in maintaining the cell pool, frequently processing endogenous signals and exogenous stimuli, reaching a new steady state, and preserving memory of previous antigen encounters.[4] Furthermore, the indicators of T cell could effectively reflect patients' immune reserve function. With increasing age, factors such as immune organ damage, chronic infection, and inflammatory senescence pose significant challenges to the intricate and delicate T cell system. Epidemiological studies have shown that the immune system in elderly individuals is weakened. For example, for the 2017/2018 flu vaccine

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season, the clinical effectiveness of the flu vaccine in preventing influenza was 68% in children, 30–40% in middle-aged adults, and only 17% in the elderly.[5,6] Although the overall immune capacity of the elderly population is diminished, there is considerable heterogeneity in immune function. Currently, there is a research gap in identifying elderly individuals with compromised immune function during the perioperative period and quantifying their residual immune capacity. T cell aging represents a promising approach to addressing this issue. First, as mentioned earlier, T cell function is an important indicator of immune function. Second, chronic diseases frequently observed in the elderly population are risk factors for T cell aging; thus, patients with multiple chronic conditions or tumors during the perioperative period are at high risk of immune decline. Third, evaluating T cell aging markers requires only peripheral blood extraction, making it highly practical for clinical applications. Fourth, T cell aging markers are quantifiable metrics that facilitate the assessment of immune function. Consequently, T cell aging is a vital indicator of perioperative immunity. Many prior investigations into T cell aging have relied on rodent models, but substantial disparities exist in immune patterns between rodents and humans. For example, in young adult rats, the majority of T cells originate from the thymus.[7,8] In contrast, for a 20-year-old male, less than 20% of T cells are derived from the thymus, and for a 50-year-old male, this proportion decreases to less than 1%.[9] Additionally, the lifespan of immature T cells in mice is limited to 6–11 weeks, whereas in humans, it extends to several years.[8] Therefore, this article focuses on clinical evidence related to the perioperative period while appropriately integrating findings from animal research. This article reviews the mechanisms, phenotypes, and clinical detection indexes of T cell aging. It also summarizes the preoperative and intraoperative factors that could help identify people at high risk of T cell aging. Furthermore, it discusses the impacts of T cell aging in the postoperative period and outlines the potential for modulating T cell aging in the perioperative period, to improve clinical prognosis.

Mechanisms of T Cell Aging

Unique T immune-related factors [immune organ damage (thymic degeneration and peripheral homeostasis disorders), long-term infections, and inflammatory senescence] and universal senescence-associated factors [genomic instability, epigenetic alterations, mitochondrial dysfunction and Oxidative Stress (OS), and protein homeostasis imbalance] are some of the influencing factors of T cell aging (Figure 1).

Immune Organ Damage and T Cell Aging

The thymus, the central immune organ, is responsible for T cell differentiation, development, selection, and maturation. It also secretes cytokines and hormones, thus regulating T cell immune function in peripheral lymphoid organs. Notably, thymus atrophies and thymocytes are always downregulated post-puberty. Thymic degeneration could reduce the output of thymic naïve T cells,[10] leading to a decrease in the number of peripheral naïve T cells and the diversity of T Cell Receptors (TCRs). This phenomenon implies that when the ability to fight against external pathogens is weakened, memory T cells will be upregulated as a means of compensating for the immune defense function.[11] Furthermore, autoreactive T cell upregulation following negative selection disruption could imply an increased risk of autoimmune diseases.[12] Besides the central immune organs, peripheral immune organs are also crucially involved in T cell aging. For instance, fibroblast reticulocytes in secondary lymphoid organs produce IL-7, which regulates T cell immunity. Additionally, lymph node-derived IL-7 deficiency somewhat mediated T cell apoptosis and depletion associated with lymph node fibrosis in individuals affected with the Human Immunodeficiency Virus (HIV) or the yellow fever virus.[8] Moreover, the combined analysis of chromatin accessibility and transcriptome suggested that silencing of the IL7R gene and the IL-7 signaling pathway could serve as potential biomarkers of $CD8^+$ T cell aging.[13] Therefore, impaired pathways or structural alterations in secondary lymphoid organs could also affect T cell aging.

Chronic Infection, Inflammatory Senescence, and T Cell Aging

Cytomegalovirus (CMV) infection is a key pathogenic driver of $CD8^+$ T cell aging.[14] According to research, in the elderly, CMV-specific T cells account for a significant proportion of $CD8^+$ T cells.[15] Furthermore, giant cell-associated latent infections could trigger a dramatic expansion of T cell clones, seizing ecological niches and biasing the TCR repertoire, thus diminishing protection against other antigens.[16] Additionally, with continued antigenic exposure and immune cell activation, Hepatitis B and C viruses, as well as HIV, could cause chronic infections. Through mechanisms such as topoisomerase inhibition or phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin 1

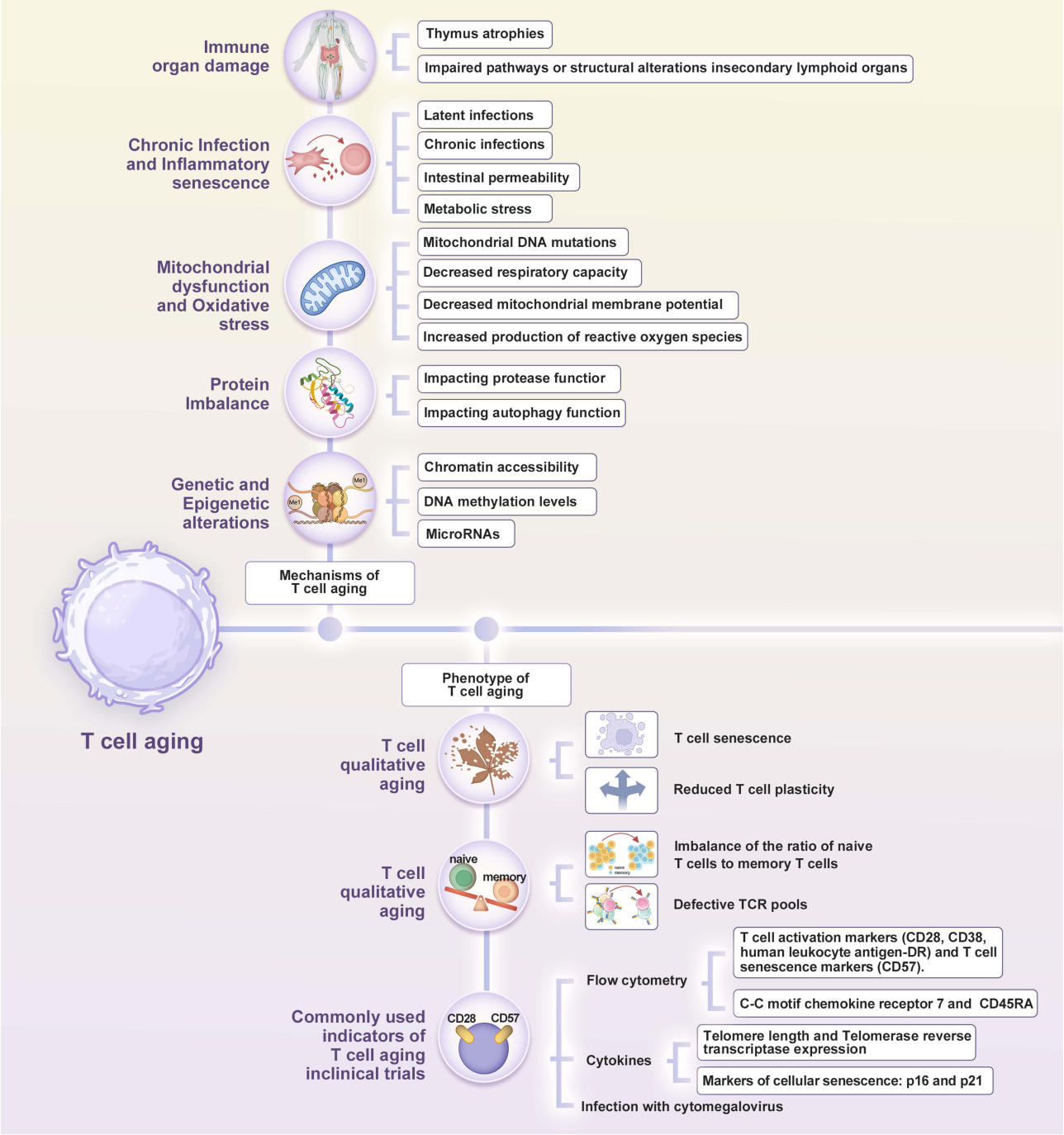

Figure 1 Mechanisms and Phenotypes of T Cell Aging.
Abbreviations: TCR, T Cell Receptor; CD, Cluster of Differentiation.

(mTORC1) signaling activation, chronic infections could lead to T cell aging-related manifestations such as DNA damage, telomere truncation, and metabolic abnormalities.[17,18]

Inflammatory senescence, a low-grade chronic inflammatory state that develops with age, has been associated with various age-related defects, such as increased intestinal permeability, chronic infections, metabolic stress, and senescent cell accumulation.[19] Multiple studies have established that inflammatory stimuli could induce naïve T cell differentiation. For instance, inflammatory factors IL-15 and IL-4 induced naïve T cells to differentiate into virtual memory T cells, which exhibited phenotypes comparable to those of antigen-induced memory T cells and exerted immune functions, such as bystander

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immunity.[20] It is also noteworthy that inflammation-induced T cell differentiation is diffuse. Various inflammatory factors (such as IL-6, IL-8, and TNF) can induce $CD8^+$ granzyme K^+ T cells, and granzyme K could lead to the senescence of peripheral cells such as fibroblasts.[21] Such inflammatory environments may also suppress the responsiveness of T cells to cytokines and other stimuli.[22] Notably, the secretion of inflammatory cytokines [such as IL-1β, IL-6, and Tumor Necrosis Factor (TNF)], and chemokines (such as CCL2 and IL-8) by senescent T cells could further exacerbate inflammatory senescence.[19]

Mitochondrial Dysfunction, OS, and T Cell Aging

Low doses of rotenone could suppress the Respiratory Chain Complex I (NADH Oxidoreductase) and upregulate Terminal Effector Memory T Cells (TEMRA Cells),[23] thus inhibiting mitochondrial function. This phenomenon highlights the potential direct effects of mitochondrial dysfunction on the proportion of senescent T cell subsets. The characteristic features of age-related mitochondrial dysfunction include mitochondrial DNA mutations, decreased respiratory capacity, decreased mitochondrial membrane potential, and increased Reactive Oxygen Species (ROS) production.[24] Besides inducing progressive changes in mitochondrial morphology, activity, and signaling function, these factors could also cause telomere wear and reduced enzyme repair activity, leading to decreased telomere length in T cells.[25] Apart from decreased telomere length, massive inflammatory factor secretion (a process mitochondria significantly mediate) is the other key hallmark of senescent T cells. In aged T cells, the altered membrane permeability of damaged mitochondria could promote the release of mitochondrial damage-associated molecular patterns, such as mitochondrial DNA, cardiolipin, or second mitochondria-derived activator of caspase. Mitochondrial DNA and cardiolipin could further activate inflammatory pathways such as the cyclic guanosine monophosphate -adenosine monophosphate synthase - stimulator of interferon gene pathway or the assembly of inflammasomes, promoting the release of Interferon Type I (IFN-I) molecules, TNF, IL-18, and IL-1β. On the other hand, second mitochondria-derived activator of caspase could switch the nonclassical nuclear factor-kappaB (NF-κB) pathway to the classical NF-κB pathway.[26] Notably, the genetic deletion of Mpc1 (a vital subunit of the mitochondrial pyruvate carrier) could intensify aerobic glycolysis and reduce Oxidative Phosphorylation (OPHOS), affecting thymocyte differentiation and ultimately promoting the expansion of hyperinflammatory T cells.[27]

Protein Imbalance and T Cell Aging

Proteasome and autophagy primarily mediate the degradation of misfolded or senescent proteins, and defects in either process could lead to T cell aging. Notably, elderly subjects exhibited calpain and tripeptidyl peptidase II downregulation in the proteasome pathway. Furthermore, protease function impairment, either by protease inhibitors or the specific knockdown of the mouse T cell Proteasome Subunit Non-ATPase-dependent Regulatory Granule 13 (PRG-13), increased in aged $CD4^+$ T cells in mice.[28] Moreover, defects in the tripeptidyl peptidase II gene (Evan's syndrome) have been associated with premature $CD8^+$ T cell immunosenescence,[29] a phenomenon that supports the tight link between proteasome activity and T cell aging. Furthermore, the autophagy blockade in the autophagy pathway could lead to the accumulation of depolarized mitochondria in $CD8^+$ T cells, limiting tissue-resident function.[30] Additionally, during senescence, mitochondrial dysfunction could persist due to autophagy impairment in $CD4^+$ T lymphocytes.[31]

Genetic and Epigenetic Alterations and T Cell Aging

Chromatin accessibility, DNA methylation levels, and microRNAs have all been established to influence the onset of T cell aging. According to research, chromatin accessibility is significantly altered during $CD4^+$ and $CD8^+$ T cell aging, resulting in the disruption of the IL-7R signaling pathway.[13] Furthermore, double-strand break repair nuclease meiotic recombination 11 homolog A (MRE11A) downregulation directly affects mitotic heterochromatin unraveling and leads to telomere damage, as well as increased levels of the aging markers Cyclin-Dependent Kinase Inhibitor 1 (CDKN1) and CDKN2A.[32] Notably, histone acetylation has also been established to influence chromatin accessibility. At the single-cell level, aged T cells exhibited increased histone acetylation heterogeneity, implying that altered chromatin accessibility could lead to functional and differentiation diversity in aged T cells.[33] It is also noteworthy that DNA methylation has recently gained increasing attention. Senescent $CD8^+$ TEMRA cells exhibited significantly altered DNA methylation levels, Furthermore, the methylation levels of immune senescence-related +6 off methylation sites correlated positively with the degree of immune senescence.[34] Finally, microRNAs were found to bind to messenger RNA molecules, inhibiting their translation or promoting their degradation, thus making them crucial regulators of immune function.

Notably, miR-181a and miR-155 have been specifically highlighted as hot spots in the study of T cell aging. Specific deletion of miR-181a from mature T lymphocytes in a mouse model resulted in multiple defects comparable to human T cell aging, including upregulation of the negative regulator Dual-Specificity Phosphatase 6 (DUSP6)- Silent Mating Type Information Regulation 2 homolog 1 (SITR1) and impairment of antiviral $CD8^+$ T cell responses.[35] On the other hand, miR-155 was linked with an age-related upregulation of Toll-Like Receptor 5 (TLR5), leading to an enhanced inflammatory response in aged T cells.[36]

T Cell Aging Phenotype

In the bone marrow, Bone Marrow Pluripotent Hematopoietic Stem Cells (BM-HSCs) differentiate into lymphoid progenitor cells (also known as lymphoblasts), which enter the thymus through blood circulation and mature into initial T cells. The T cells then enter peripheral lymphoid organs and differentiate into effector T cells and memory T cells after the immune response. Notably, T cell aging entails dysfunction and subpopulation imbalance at the individual and overall cell levels respectively, with the former referred to as "qualitative aging" and the latter as "quantitative aging". Notably, the two aging mechanisms work synergistically to affect immune function in individuals (Figure 1).

Qualitative T Cell Aging

Qualitative aging, a manifestation of cellular senescence at an individual cellular level, is often evidenced by T cell senescence. Senescence manifestations in T cells include low telomerase activity, short telomeres, DNA damage, mitochondrial dysfunction, enhanced classical senescence hallmarks (eg, β-galactosidase), increased secretion of pro-inflammatory factors (eg, TNF and IFN -γ), decreased cell proliferation, and heightened cytotoxicity.[37] Furthermore, compared to immune cells, aged T cells exhibit unique senescence characteristics, including loss of TCR co-stimulatory receptors [eg, Cluster of Differentiation 27 (CD27) and CD28] and upregulation of terminal differentiation markers [CD57 and Killer Cell Lectin-like Receptor Subfamily G1 (KLRG1), Table 1].[38]

Table 1 Changes in CD Markers, Functions, Affected Signaling Pathways, and Transcription Factors of T Cells at Different Stages

Characteristic	Naïve	Central Memory	Effector Memory	EMRA/ Senescent	Functions
CD markers					
CD27	+++	++	±	–	Costimulatory molecule[39,40]
CD28	+++	++	±	–	Costimulatory molecule[39,40]
CCR7	+++	++	–	–	Coordinate the interaction between dendritic cells and T cells[39,40]
CD57	–	–	+	++	Terminal differentiation markers[39,40]
CD45RA	+++	++	–	++	Markers of naïve/terminally differentiated T cells[39,40]
KLRG1	–	–	+	++	Terminal differentiation markers[40]
Transcription factors					
p16	–	–	–	+	Cell cycle arrest[41]
γH2AX	–	–	–	++	DNA damage[23]
BCL-2	+++	++	+	±	Resistant to apoptosis[42]
IL-1β	–	–	++	–	Pro-inflammatory[43]
IL-18	–	–	–	++	Promote T lymphocyte activation[43]
Senescence					
Proliferative capacity	+++	+++	++	–	Cell cycle arrest[44]
Telomere length	+++	+++	++	±	DNA damage[44]
Telomerase	+++	++	+	–	DNA damage[44]
Signaling pathways					
P38/Erk/Jnk	–	–	±	++	Late T cell activation, proliferation[41]
PI3K/Akt/mTOR	+	+	+	±	Integrating nutrition and growth signals[45]
Lck-LAT-Zap70	+	+	+	±	T cells activation[41]

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Various T cell subpopulations differ in senescence sensitivity. For instance, $CD8^+$ T cells are more sensitive to senescence than $CD4^+$ T cells. Furthermore, $CD8^+$ terminally differentiated TEMRAs accumulate faster than $CD4^+$ cells. This phenomenon could be attributed to $CD8^+$ TEMRA cells being more susceptible to mitochondrial decline,[23] lower homeostatic naïve cell proliferation rates,[46] increased chromatin accessibility alterations,[13] and higher Tribbles Homolog 2 (TRIB2) abundance.[47] Furthermore, regulatory T cells (Tregs) are more severely senescent than effector T cells. Notably, DNA Damage-Binding Protein 1 (DDB1) and Cullin4- Associated Factor 1 (CAF1) are essential for Treg senescence inhibition via Glutathione-S-Transferase P (GSTP1)-regulated ROS production.[48]

Although T cell senescence is closely linked to T cell exhaustion, the two phenomena are distinct. Whereas senescent T cells undergo an irreversible cell cycle arrest, the reduced proliferative capacity of exhausted T cells is a reversible functional state disorder.[49] The expression profiles of the two phenomena are even more different. While senescent T cells exhibit CD28 and CD27 downregulation and CD57 and inflammatory factor upregulation, exhausted T cells show higher levels of inhibitory receptors [eg, Programmed Death 1 (PD-1), Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA4), T-cell immunoglobulin, and T Cell Membrane Protein 3(TIM3)] and lower levels of inflammatory factors (eg, IL-2 and TNF).[34,38]

Reduced T cell plasticity is the other important marker of T cell senescence. Besides their great proliferative potential and plasticity, young naïve $CD4^+$ T cells could differentiate into different lineages relatively freely. On the other hand, elderly naïve $CD4^+$ T cells have a specific differentiation tendency. Elderly naïve $CD4^+$ T cells exhibit Transforming Growth Factor-β Receptor 3 (TGF-βR3) upregulation; hence, their responsiveness to TGF-β increases with age, which, in turn, favors Th9 differentiation. Furthermore, aging naïve $CD4^+$ T cells respond to TCR stimulation, leading to Basic Leucine Zipper ATF-Like 2 (BATF2) and Interferon Regulatory Factor 4 (IRF4) upregulation and downregulation of inhibitors of DNA binding 3 and B Cell Lymphoma 6 (BCL6), all of which promote Th9 differentiation.[50] Aged naïve $CD4^+$ T cells also exhibit CD39 upregulation, which inhibits follicular helper T cell production.[51] Furthermore, due to an increase in miR-21 levels, aged naïve $CD4^+$ T cells are more likely to differentiate into inflammatory effector cells rather than follicular helper and memory T cells.[52] In addition to the differentiation capacity of naïve cells, T cell plasticity also entails an alteration in the functional efficiency of T cells. In aged mice, Tregs do not suppress conventional T cell function as efficiently as young Tregs.[48] Additionally, follicular helper T cells (T follicular helper) are inefficient in aged mice due to pathway defects.[53]

Quantitative T Cell Aging

One of the most striking phenotypes of quantitative T cell aging is an imbalance in the ratio of naïve T cells to memory T cells. On the one hand, naïve T cell pool maintenance depends on thymic output. Thymic degeneration, a phenomenon that occurs post-puberty, could lead to a decrease in the output of naïve T cells, resulting in a leaky naïve T cell pool.[4] On the other hand, naïve T cell pool maintenance also depends on homeostatic peripheral naïve T cell proliferation. Notably, naïve T-cell pool maintenance mechanisms differ significantly between humans and mice, with steady-state peripheral naïve T cell proliferation and thymic output dominating in humans and mice, respectively.[46] Furthermore, continuous antigenic stimulation could induce the conversion of naïve T cells into memory T cells; hence, the proportion of naïve T cells might gradually decrease with age. Besides antigenic stimulation, the peripheral lymphatic environment also influences the proportion of naïve T cells.

Perfect T cell immunity necessitates not just a sufficient number of T cells but also a diverse TCR pool to respond to new antigens. Both cohort and cross-sectional studies reported a decrease in TCR pool diversity with age[54] and a high degree of convergence in $CD4^+$ TCRs in the elderly.[55] These phenomena could be attributed to several factors. First, naïve T cells with neo-specific TCRs originate from the thymus and thymic degeneration correlates with aging. As a result, the decrease in the output of naïve T cells correlates with neo-specific TCRs from the thymus, potentially leading to decreased TCR diversity. Second, long-term chronic infections (such as CMV and influenza virus infections) could result in a disproportionate expansion of specific T cells, altering the proportion of cells with different TCR populations.[54] Third, due to the loss of wingless/β-catenin signaling, the human $CD4^+$ stem cell memory T lymphocyte pool might get depleted with age.[56] Reduced TCR diversity in naïve T cells is not entirely random and TCRs with a higher affinity for both self- and non-self-peptide-MHC complexes are more readily eliminated, probably because they are more readily converted to the "memory" phenotype.[55]

T Cell Aging Indicators Commonly Used in Clinical Trials

Flow cytometry is often used in clinical research to categorize T cell subpopulations. Moreover, this approach is often used to quantify the degree of T cell aging in patients, primarily through two methods. First, based on the C-C motif Chemokine Receptor 7 (CCR 7) and CD45RA, T cells are classified into naïve cells, central memory cells, effector memory T cells (TEM), and TEMRA cells. In this method, patients are often evaluated for T cell aging based on changes in the ratio of the four types of cells or by focusing specifically on the ratio of TEMRA cells. Notably, cytokines such as CD31, CD103, and Protein Tyrosine Kinase 7 (PTK7) are sometimes added to naïve cells to assess thymic function.[40] Second, T-cell activation markers (CD28, CD38, and Human Leukocyte Antigen (HLA)-DR, among others) and T-cell senescence markers (CD57) are examined. Earlier clinical studies often employed $CD28^-$ or $CD57^+$ T cells alone to define T cell aging, but in recent years, T cell aging is mostly defined using $CD28^-$ $CD57^+$ T cells.[57] To ensure experimental reliability, these two cell groups are often evaluated simultaneously. Nonetheless, some differences have been noted between the two methods, with the former and latter tending to reflect "T cell quantitative aging" and "T-cell qualitative aging", respectively. There is a also difference in the reversibility of the two, with the cell cycles of TEMRA and $CD28^-$ $CD57^+$ T cells being reversible and irreversible, respectively. There were also differences in the phenotypes of the two methods. The stress-inducible protein sestrins in TEMRA provide a scaffold for Mitogen-Activated Protein Kinase (MAPK) pathway activation, enhancing the downstream activation of extracellular signal-regulated kinase, MAPK, p38, and c-Jun N-Kinase (JNK), while inhibiting mTORC1. For $CD28^-$ $CD57^+$ T cells, mTORC1, NF-κB, p38, and CCAAT/Enhancer Binding Protein β (C/EBPβ) are upregulated due to mitochondrial dysfunction and other factors, which mediate the differentiation of the senescence-associated secretory phenotype.[58] Besides cell sorting, cytokines are sometimes employed in testing the functional level of T cells. Specifically, they help in assessing the telomere length, telomerase reverse transcriptase expression in T cells, or cellular senescence markers, such as $p16^{INK4a}$ and $p21^{CIP1/Waf1}$.[59] For the rigor of the test, CMV expression is always tested more often to further exclude the effect of chronic infections on T cell aging.

Preoperative and Intraoperative Factors and T Cell Aging

Preoperative [hypertension, Diabetes, Acute Respiratory Distress Syndrome (ARDS), hypoxemia, depression, pain, obesity, tumors, and autoimmune diseases] and intraoperative (anesthesia methods, surgery types, and medications) factors can affect mitochondrial function and create an inflammatory environment, increasing the risk of T cell aging. Although the evaluation of these factors could help identify patient groups at high risk of T-cell senescence and allow for prompt intervention to avoid a poor prognosis, there are no clinical prediction models for quantifying the risk of T cell aging more accurately (Figure 2).

Hypertension and T Cell Aging

Hypertension is among the most common comorbidities in the perioperative period. According to research, T-cell-specific AT1 receptor deficiency can exacerbate angiotensin II–induced renal injury, increasing the accumulation of pro-inflammatory Th1 cells and upregulating IFN -c and TNFα in the kidney.[60] In hypertensive patients, T cells, especially $CD8^+$ T cells, showed senescence-associated features such as $CD28^-$ $CD57^+$, compared to their peers.[61] Additionally, both cellular assays and mouse models demonstrated that T cell aging accelerated Ang II–induced cardiovascular and renal fibrosis and promoted the expression of inflammatory factors and superoxide production in the target organs.[62] These findings suggest a tight link between T cell aging and both hypertension and damage to related organs. Moreover, although mice lacking T and B cells were not protected from Ang II–induced vascular abnormalities in a previous study, direct transfer of T cells restored vascular dysfunction.[63] Furthermore, compared to young T cells, conditioned cultures of aged T cells stimulated inflammatory factor expression and OS in Ang II-treated renal epithelial cells, although these effects were attenuated after IFN -c neutralizing antibody treatment.[62] Based on these research insights, targeting specific T cells could be a therapeutic avenue for managing elderly hypertension with comorbid end-organ dysfunction.

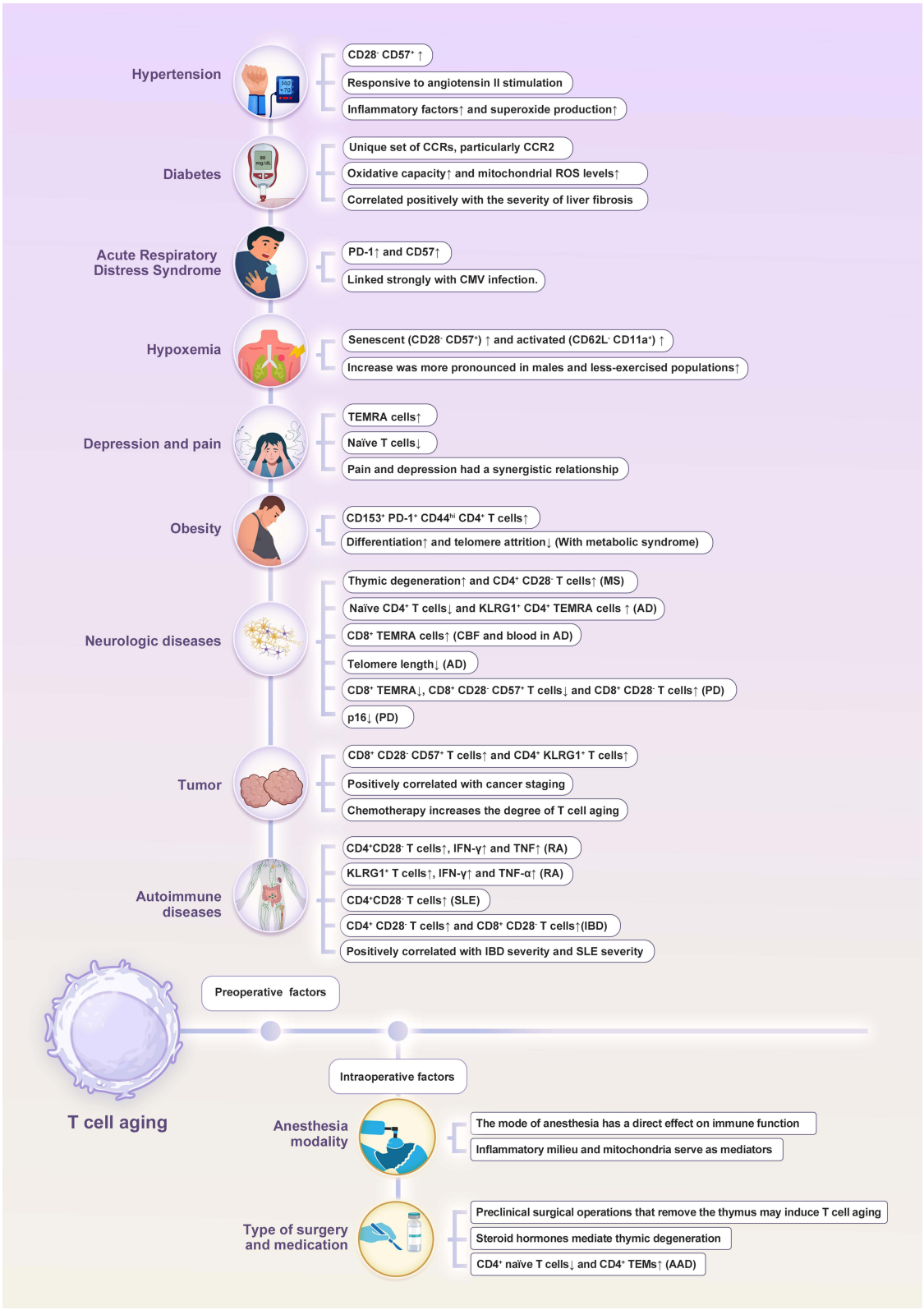

Figure 2 Preoperative and Intraoperative Factors Increasing the Risk of T Cell Aging.
Abbreviations: CD, Cluster of Differentiation; CCR, C-C motif Chemokine Receptor; ROS, Reactive Oxygen Species; PD-1, Programmed Death 1; CMV, Cytomegalovirus; TEMRA, Terminal Effector Memory T Cells; MS, Multiple Sclerosis; KLRG1, Killer Cell Lectin-like Receptor Subfamily G1; AD, Alzheimer's Disease; CBF, Cerebrospinal Fluid; PD, Parkinson's Disease; IFN, Interferon; TNF, Tumor Necrosis Factor; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; IBD, Inflammatory bowel disease; TEM, Effector memory T cells; AAD, Acute Aortic Dissection.

Diabetes and T Cell Aging

Diabetes is the other comorbidity common in the perioperative period. In previous research, insulin-resistant participants showed significantly more $CD28^-$ $CD57^+$ senescent T cell subsets in $CD4^+$ and $CD8^+$ T cells than those with lower resistance values, as assessed by the Insulin Resistance (IR) homeostasis model. Furthermore, the abundance of senescent $CD4^+$ and $CD8^+$ T cells and the IR index correlated positively with the severity of liver fibrosis.[64] Type 2 Diabetes (T2D) patients often have higher amounts of circulating aged T cells, a phenomenon that correlates with higher levels of systemic inflammation. This inflammatory milieu promotes the expression of a unique set of CCRs on aged T cells, particularly CCR2.[65] Another clinical study reported that mitochondria from $CD8^+$ T cells from T2D patients exhibited a higher oxidative capacity and mitochondrial ROS levels compared to age-matched controls. Furthermore, despite increased fatty acid uptake, T2D $CD8^+$ TEMRA cells exhibited impaired fatty acid oxidation, lipid droplet accumulation, and decreased AMP-Activated Protein Kinase (AMPK) activity.[66] These findings support the tight link between diabetes and T cell aging, with the latter being specifically linked with alterations in inflammatory responses and OS levels. Moreover, another clinical study involving pre-diabetic patients suggested that exercise stimulates naïve T cell production and mobilization, with differentiated TEMRA cells lost through apoptosis in the process.[67] Additionally, the Rosuvastatin+ezetimibe combination therapy downregulated aged $CD8^+$ T cells and increased the ratio of naïve to memory $CD8^+$ T cells in diabetic patients. Notably, this treatment's mechanism of action was not associated with improved lipid or glycated hemoglobin levels.[68] Therefore, exercise, diet, and pharmacotherapy may be leveraged to prevent diabetes-associated T cell aging.

ARDS and T Cell Aging

Longitudinal studies involving patients with Corona Virus Disease 2019 (Covid-19)-related ARDS revealed that patients had a 2-3-fold increase in blood effector T cell expression and that most effector T-cells expressed PD-1 (associated with failure) and CD57 (associated with senescence). Furthermore, the patients showed a surge of pro-inflammatory cytokines, waves of Th1 and Th2 activation, and a 15-fold increase in γδ T-cell and proliferating NK-cell populations.[69] It is also noteworthy that COVID-19-associated immune aging has been linked strongly with CMV infection. Compared to the healthy population, a previous study showed that patients with mild or asymptomatic COVID-19 in the unvaccinated and CMV-antibody-positive populations showed a significant upregulation of $CD28^-$ $CD57^+$ Chemokine C-X3-C-Motif Ligand 1 (CX3CR1) in $CD4^+$, $CD8^+$, and γδ T-cell subsets. Notably, this variability was not observed in the CMV antibody-negative or vaccinated populations,[70] probably because these two groups exhibited relatively weak immune activation and immune aging; hence, the small sample study could not yield positive results.

Hypoxemia and T Cell Aging

Short-term hypoxemia has been established to promote T cell aging. In previous research, the ratio of senescent ($CD28^-$ $CD57^+$) and activated ($CD62L^-$ $CD11a^+$) cells in peripheral blood increased significantly after intense exercise (up to maximal oxygen uptake). Furthermore, lymphocyte surface thiols, intracellular total glutathione levels, and reduced glutathione all decreased. There was also an enhanced peroxide-mediated mitochondrial membrane potential reduction, cysteine protease 3/8/9 activation, Poly-ADP ribose polymerase cleavage, and phosphatidylserine exposure. Notably, these phenomena were not observed after moderate-intensity exercise (up to 50% of maximal oxygen uptake) but were observed after moderate exercise in a hypoxic environment, becoming even more pronounced with decreasing oxygen concentration.[71] These findings collectively suggest that the hypoxic state increases the entry of senescent/activated forms of lymphocytes into peripheral blood while enhancing OS-induced lymphocyte apoptosis by decreasing cellular antioxidant levels during exercise. In another study, exercise to the point of volitional fatigue was followed by a 42.4% and 45.9% increase in senescent $CD4^+$ and $CD8^+$ T lymphocytes, respectively. Furthermore, males and less-exercised populations showed more pronounced levels of exercise-induced acute T cell aging.[72] These findings suggest that during the perioperative period, especially in the anesthesia induction and maintenance phases, special attention should be paid to monitoring the blood gases of patient groups at a high risk of hypoxemia, including males, patients with airway difficulties, Chronic Obstructive Pulmonary Disease (COPD) patients, and debilitated patients, to reduce hypoxia-induced T cell aging and avoid related adverse outcomes.

Depression and Pain and T Cell Aging

According to reports, T cells are crucially involved in psychiatric regulation. In a previous study, compared to the healthy population, patients with major depression showed a higher proportion of TEMRA cells. Furthermore, patients with major depression showed a lower proportion of naïve T cells compared to the normal population. This phenomenon was more pronounced in the CMV-positive cohort, highlighting the potential link between depression and a more pronounced T cell aging.[73] Similarly, in an Irritable Bowel Syndrome (IBS) patient cohort, the depressed group showed a significantly lower number of circulating T cells than non-depressed patients, implying that the co-morbid state of pain and depression had a more detrimental effect on immune status than the disease alone.[74] The finding also suggested that patients with poor chronic pain control or psychiatric disorders such as depression were potential candidates for T cell aging, and that extra attention should be paid to such groups during the perioperative period.

Obesity and T Cell Aging

A high-fat diet will promote the accumulation of aging T cells ($CD153^+$ $PD\text{-}1^+$ $CD44^{hi}$ $CD4^+$ T cells), and this subset will increase visceral adipose tissue inflammation by producing osteopontin.[75] Obesity has been established to promote T cell senescence via several mechanisms. First, chronic stimulation by leptin and free fatty acids in the blood, repetitive antigenic stimulation, stress response, and hypoxia could all directly induce $CD4^+$ T cell exhaustion.[76] Second, obesity promotes thymus enlargement through growth factors such as the Insulin-like Growth Factor (IGF); however, this is only temporary as the thymus decline intensifies after 6–7 months, ultimately inducing T cell aging.[77] Third, obesity induces OS and inflammation, leading to telomere shortening and ultimately T cell aging.[78] Finally, obesity could trigger widespread gene expression changes in multiple organs[79] and DNA methylation changes in blood leukocytes,[80] leading to immune dysfunction and T cell aging. Notably, metabolic syndrome could further accelerate T cell aging in obese individuals. In previous research, obese patients with metabolic syndrome exhibited increased $CD8^+$ T cell differentiation and shorter $CD4^+$ T cell telomere length compared to those without metabolic syndrome.[81] It is also noteworthy that surgical interventions could temporarily reverse accelerated T cell aging in cases of metabolic syndrome. Following bariatric surgery, the increased thymic output and accelerated T cell differentiation trend in obese patients would be suppressed, with patients with metabolic syndrome experiencing a more pronounced effect of the surgical intervention.[81,82] This phenomenon suggests that the risky events associated with T cell aging in obese patients could be surgically prevented during the perioperative period, especially in those with metabolic syndrome.

Neurologic Diseases and T Cell Aging

In previous research, patients with multiple sclerosis exhibited features of T cell aging such as accelerated thymic degeneration and upregulation of $CD4^+$ $CD28^-$ cells.[83,84] Moreover, clinical studies demonstrated that senescence and systemic elevation of late memory T and B lymphocytes were some of the key manifestations in individuals with faster amyotrophic lateral sclerosis progression and medullary involvement.[85]

Notably, T cell aging has also been strongly associated with Alzheimer's Disease (AD). In previous research, the percentage of naïve $CD4^+$ T cells in the peripheral blood of AD patients decreased, whereas that of KLRG1-expressing terminally differentiated memory $CD4^+$ T cells increased.[86] Furthermore, another study revealed that compared to the normal population, AD patients exhibited higher levels of $CD8^+$ TEMRA cells in the Cerebrospinal Fluid and blood.[87] Additionally, AD patients showed a significantly shorter telomere length of peripheral blood T cells than the non-Alzheimer's population. Moreover, the telomere length was found to correlate negatively with the serum TNF-α level, the proportion of $CD8^+$ $CD28^-$ T cells, and the level of apoptosis.[88] These findings collectively highlight the crucial involvement of T cell aging in various neurodegenerative diseases. It is also noteworthy that AD patients and the elderly often show the upregulation of A-β-specific T-cells.[89] In another study, these cells penetrated the brain parenchyma and contributed to AD development in mice.[90]

There have also been some links between T cell aging and Parkinson's Disease (PD). In a previous study, compared to the normal population, PD patients showed significantly lower levels of peripheral blood $CD8^+$ TEMRA and $CD8^+$ $CD28^-$ $CD57^+$ T cells, significantly higher $CD8^+$ $CD28^-$ expression, and lower expression levels of the cellular

senescence marker p16. Furthermore, the two groups showed no significant differences in T cell telomere length, Telomerase Reverse Transcriptase (TERT) activity, or thymic migration.[57,59] In another study, PD differed significantly from most of the aforementioned neurologic disorders regarding the state of T cell aging, a phenomenon attributable to the overreaction of the more active, less senescent T cells to PD-associated antigens, such as α-synuclein.[91]

Tumor and T Cell Aging

Numerous clinical trials have shown that the tumor microenvironment influences the distribution of T cell subsets, by increasing the proportions of $CD8^+$ $CD28^-$ T cells and $CD8^+$ $CD57^+$ T cells in the blood circulation of patients with head and neck cancer, lung cancer, pleural mesothelioma, and lymphoma.[92] This suggests that the tumor microenvironment may modulate the T cell aging. Meanwhile, the number of typical T-cell senescent subpopulations ($CD8^+$ $CD28^-$ $CD57^+$ T cells) in the circulation of lung cancer was reported to be highly elevated relative to levels in the normal population, and the proportion of T cell aging subpopulations in patients with the advanced stage was significantly higher compared with that of patients with early stage.[93] Similarly, the expression of KLRG1 on $CD4^+$ T cells increases with tumor progression in patients with renal clear cell carcinoma,[94] further demonstrating that the tumor microenvironment influences T cell aging. Meanwhile, studies have demonstrated that chemotherapy increases the degree of T cell aging in tumor patients.[95] Collectively, the aforementioned clinical trials have shown that the proportion of T cell aging is significantly higher in tumor patients, especially those with advanced tumors and following chemotherapy treatment. Therefore, researchers should formulate interventions during the perioperative period thereby improve T cell aging and prevent perioperative adverse events, ensuring good prognostic outcomes.

Autoimmune Diseases and T Cell Aging

The commonly reported autoimmune diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD). A previous study demonstrated that the percentage of $CD4^+CD28^-$ T cells was increased in the peripheral blood of RA patients, whereas $CD4^+CD28^-$ T cells in the peripheral blood of RA patients generated more IFN-γ and TNF compared to regular $CD4^+CD28^-$ T cells.[96] Elsewhere, the $CD4^+CD28^-$ T cells were not detected in the synovial fluid of RA patients, but $KLRG1^+$ T cells (a typical T-cell senescence phenotype) were recorded in the synovial fluid of RA patients and spondylarthritis patients. This subset of T cells produces large amounts of IFN-γ and TNF-α.[96,97] In patients with SLE, the number of $CD4^+CD28^{--}$ T cells (a typical T-cell senescence phenotype) was significantly increased and the percentage of senescent T cells correlated significantly with SLE activity and disease severity.[98] Similarly, high proportions of $CD4^+$ $CD28^-$ T cells and $CD8^+$ $CD28^-$ T cells were detected in patients with IBD, and the ratio of $CD4^+$ $CD28^-$ T cells to $CD8^+$ $CD28^-$ T cells serve as an important indicator of IBD severity.[99] These studies provide evidence that autoimmune diseases influence T cell aging, and that the progression of autoimmune diseases will may influence T cell aging, necessitating careful preoperative operation.

Anesthesia Modality and T Cell Aging

Several clinical studies have shown that patients with colorectal cancer administered with a general anesthesia combined with epidural anesthesia compared to general anesthesia exhibit positive changes in NK cells, $CD4^+$ cells, and $CD4^+/CD8^+$ ratio.[100] This indicates that the mode of anesthesia has a directly effect on immune function. It can also alter the inflammatory milieu and trigger mitochondrial dysfunction. To prevent inflammation, general anesthesia combined with epidural anesthesia positively regulated IL-6, IL-8, IL-10, and TNF-α in patients with colorectal cancer.[101,102] Modification to the inflammatory environment is accompanied by changes in the expression profile of healthy mesenchymal stem cells and genes influencing the survival of lymphocytes.[103] Senescent mesenchymal stem cells that produce inflammatory factors impair the function and clonogenicity of young hematopoietic stem cells.[104] It has been reported that general anesthesia lead to mitochondrial dysfunction by altering mitochondrial morphology and distribution, increasing mitochondrial ROS production, mitochondria-mediated regulation of cell death pathways, and mitochondria's ability to clear misfolded proteins.[105] As previously mentioned, mitochondrial dysfunction may promote T cell aging either directly or indirectly by inducing excessive production of ROS, affecting telomerase wear, and excessive inflammatory expansion. This demonstrates that mitochondria also serve as a mediator between anesthesia and T cell aging.

Type of Surgery and Medication and T Cell Aging

Studies have demonstrated potential association between the type of surgery and T cell aging. First, T cell aging is strongly associated with thymic hypoplasia, and preclinical surgical operations that remove the thymus may induce T cell aging, and hence, clinicians should pay attention to patients with a history of this surgery, and perform a long-term postoperative follow-up.[106] In other studies, it was observed that sex steroid hormones mediate thymic degeneration by driving steroid signaling in thymic epithelial cells,[107] and thus, additional attention should be paid to patients receiving long-term hormone therapy preoperatively. Second, patients with acute Stanford type-A aortic dissection exhibited reduced proportion of $CD4^+$ naïve T and increased proportion of $CD4^+$ TEMs on admission compared to healthy volunteers,[108] suggesting that T cell aging may occur in all patients undergoing critical surgery and that additional clinical studies are needed to confirm the existence of T cell aging in patients undergoing other types of critical surgeries. As mentioned earlier, tumors is a high-risk factor for T cell aging, therefore, patients undergoing tumor-related surgery need to be monitored for potential T cell aging.

T Cell Aging and Postoperative Factors

T cell aging leads to poor prognosis by inducing perioperative neurologic dysfunction and impairing postoperative recovery. Therefore, additional clinical studies are needed to further explore the association of T cell aging with the remaining postoperative factors (Figure 3).

T Cell Aging and Postoperative Neurologic Dysfunction

Accumulating studies have demonstrated a link between T cell aging and postoperative cognitive dysfunction. In a model of neurocognitive impairment induced by internal fixation of tibial fracture in aged mice, circulating Tregs were increased accompanied by elevation of plasma inflammatory factor levels. Infusion of Tregs from young mice partially restored blood-brain barrier damage and alleviated postoperative cognitive dysfunction in aged mice. Compared with Tregs from young mice, differentially expressed genes were enriched in the TNF signaling pathway and the cytokine-cytokine receptor interaction pathway,[109] implying that T cell aging may lead to postoperative cognitive dysfunction. T cell aging influences postoperative cognitive dysfunction via several mechanisms. First, a higher proportion of senescent cells in the brain increases the

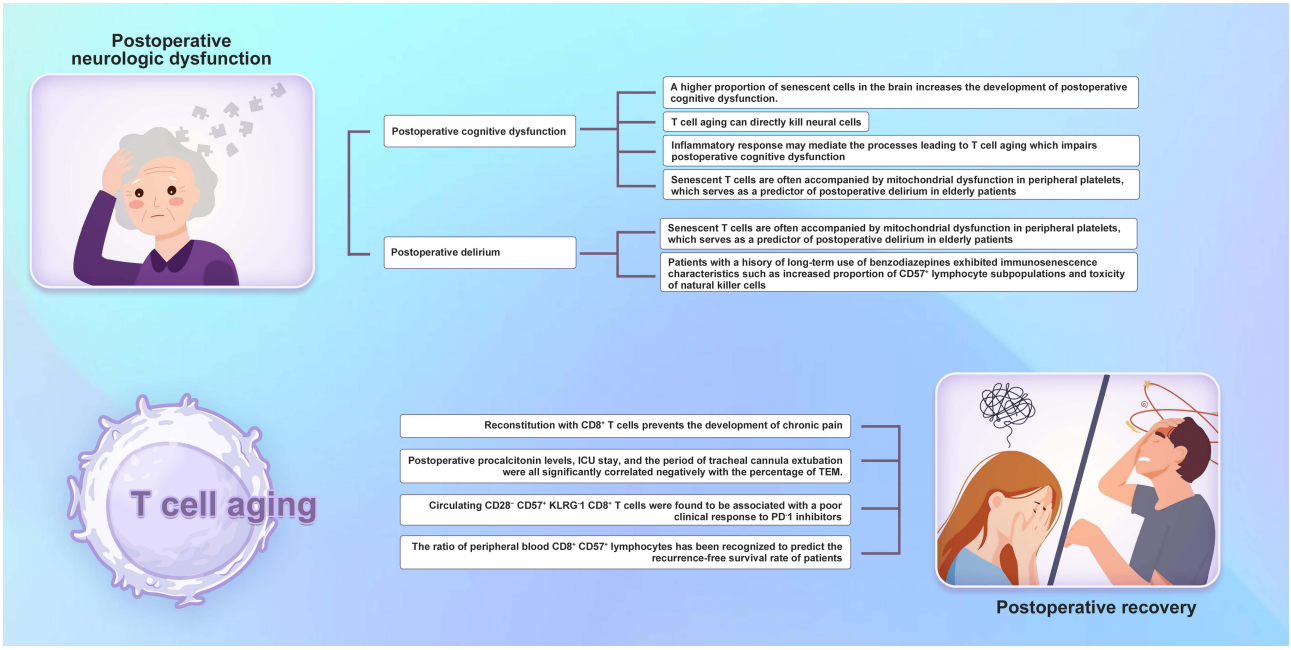

Figure 3 Postoperative Factors Associated with T Cell Aging.
Abbreviations: CD, Cluster of Differentiation; TEM, Effector memory T cells; KLRG1, Killer Cell Lectin-like Receptor Subfamily G1; PD-1, Programmed Death 1.

development of postoperative cognitive dysfunction. Aging $CD8^+$ T cells present with features of elevated natural killer cell lectin-like receptor subfamily C member 1 and PD-1 and decreased perforin binding, which may potentially contribute to senescent cell escape.[110–112] Senescent $CD8^+$ cells are not only less capable of clearing senescent cells but also promoting the senescence of other brain cells via granzyme K and TNF-α, which may exacerbate the accumulation of senescent cells in the brain.[21,113] Collectively, these findings indicate that long-term T cell aging increases the proportion of senescent cells in the brain, which in turn enhances the risk of postoperative cognitive dysfunction. Secondly, T cell aging can directly kill neural cells and senescent $CD8^+$ T cells in the brain have also been shown to directly promote axonal and myelin degeneration via granzyme B and IFNγ-mediated microglia activation,[114,115] and $CD4^+$ $CX3CR1^+$ T cells and $CD8^+$ $CX3CR1^+$ T cells. In addition, they are close to cleaved cysteinyl aspartate specific proteinase-3^+ oligodendrocytes,[116,117] indicating that aging T cells may directly lead to oligodendrocyte death and demyelination. Therefore, aged T cells kill neuronal cells and trigger degenerative brain changes enhancing the occurrence of postoperative delirium. Thirdly, inflammatory response may mediate the processes leading to T cell aging which impairs postoperative cognitive dysfunction. Brain inflammation has been associated with increased expression of the chemokine CX3C motif ligand 1 in the cerebrospinal fluid,[116] and therefore, $CD4^+$ $CD28^-$ T cells highly expressing CX3CR1 migrate to sites of inflammation in response to chemokine signals. Aged $CD4^+$ T cells acquire an extreme pro-inflammatory phenotype, which upregulates IL17, IL9, IL1-β, IFN -γ, and the chemokine CX3CR1, while also downregulating CCR7.[118] IL-17 triggers cognitive and synaptic deficits and damages the cerebral blood barrier.[119,120] As a classic inflammatory mediator, IL1-β regulates neuronal survival and growth, and neuroplasticity.[121] The levels of IL-9 were found to be negatively correlated with inflammatory activity, serving as an indicator of neurodegenerative and progressive disorders.[122] Finally, in 5xFAD transgenic mice, CCR7 deletion caused deleterious neurovascular and microglia activation, thereby reducing lymphatic in-flow and cognitive deficits.[123]

T cell aging has been linked to occurrence of postoperative delirium. Firstly, senescent T cells are often accompanied by mitochondrial dysfunction in peripheral platelets, which serves as a predictor of postoperative delirium in elderly patients.[124] Application of WS635, a mitochondrial function-enhancing agent, or transferring B cells attenuates anesthesia- and surgery-induced delirium-like alterations via the transmicrotubule-associated protein tau-PT217 pathway.[125] These findings demonstrate that mitochondrial dysfunction is a potential mediator of T cell aging and postoperative delirium, making it a potential therapeutic target. Mitochondrial dysfunction may contribute to accumulation of inflammatory metabolites, epigenetic alterations, post-transcriptional protein modifications, and release of mitochondrial DNA into the cytoplasm, which activates the cyclic guanosine monophosphate -adenosine monophosphate synthetase-stimulator of interferon genes signaling pathway, stimulating activation of inflammasome vesicles and transcriptional pro-inflammatory cytokine gene activation.[126] Activation of immunoinflammatory pathways and reduction of negative immunoregulatory mechanisms are linked to surgery-induced delirium.[127] Therefore, the inflammatory response may be a more important mediator of T cell aging associated with postoperative delirium. Notably, the timely application of drugs such as dexamethasone can inhibit the inflammatory response thereby avoid postoperative delirium and prevent T cell aging. Second, patients with a history of long-term use of benzodiazepines exhibited immunosenescence characteristics such as increased proportion of $CD57^+$ lymphocyte subpopulations and toxicity of natural killer cells,[128] demonstrating that intraoperative use of benzodiazepines may trigger postoperative delirium via the T cell aging pathway. Therefore, patients at increased risk of T cell aging, benzodiazepine use should be minimized during the perioperative period, thereby reducing the risk of delirium.

T Cell Aging and Quality of Postoperative Recovery

Numerous investigations have shown that T cell deficiency will delay the time to remission of chemotherapy-induced peripheral neuralgia, chronic arthritis, and other types of pain, whereas reconstitution with $CD8^+$ T cells prevents the development of chronic pain.[129,130] This implies that T cell aging is a risk factor for the occurrence of postoperative pain. Postoperative pain is often accompanied by negative emotions such as depression and frustration. Compared with normal mice, recombinant activation of genes 2 gene-deficient mice (mice lacking adaptive immune cells) showed significantly delayed regression of mechanical anomalous pain, spontaneous pain, and depressive-like behavior induced by complete Freund's adjuvant. CD3 T^+ transplantation can ameliorate the aforementioned pain and depression delays, whereas NSAIDs do not achieve similar effects.[131] This demonstrates that T-cell regulation participates in the co-morbid mechanisms underlying the development of pain and depression and is an irreplaceable target for formulating co-morbid therapy.

Patients with acute aortic coarctation exhibited increased percentage of TEM compared with healthy volunteers, and a significant negative correlation was observed between the percentage of TEM and the time of extubation from the tracheal cannula, ICU stay, and postoperative procalcitonin levels.[108] This demonstrates that the percentage of T-cell subpopulations can predict various near-term postoperative indices. The 15-item Quality of Recovery Inventory (QoR-15) is a commonly used tool for evaluating short-term postoperative recovery, including five dimensions of indicators: pain, physical comfort, physical independence, psychological support, and emotional state. As discussed, T cell aging may be linked to physical independence, pain, and emotional factors, potentially impacting the quality of postoperative recovery. However, robust RCTs are required to validate this conclusion. Additionally, T cell aging could also influence long-term prognosis. In patients with advanced non-small cell lung cancer, large numbers of circulating $CD28^{-}$ $CD57^{+}$ $KLRG^{-}1$ $CD8^{+}$ T cells in the peripheral blood were found to be associated with a poor clinical response to PD-1 inhibitors.[132] Similarly, the ratio of peripheral blood $CD8^{+}$ $CD57^{+}$ lymphocytes has been recognized to predict the recurrence-free survival rate of patients with nonmuscular invasive bladder cancer treated by transurethral tumor resection combined with intravesical instillation of IL-2,[133] suggesting that T cell aging has a negative effect on the long-term prognosis of patients, although fewer studies have demonstrated the association between T cell aging and long-term prognosis in non-neoplastic disease.

Perioperative Modulation of Targeted T Cell Aging

A randomized controlled trial demonstrated that 8 weeks of yoga improved the Disease Activity Score for Rheumatoid Arthritis (DAS28-ESR), reduced the proportion of Th17 cells and T cell aging subpopulations, down-regulated RORγt, IL-17, IL-6, CXCL2, and CXCR2, and up-regulated FoxP3 and TGF-β transcription, and maintained immune homeostasis.[134] Another clinical study found that 6 weeks of endurance strength training enhanced the proportion and absolute value of susceptible T cell aging in elderly patients.[135] The aforementioned trials indicate that engaging in moderate-intensity preoperative exercise can enhance the immune environment and decrease the proportion of senescent T cells in most older adults, ultimately leading to better postoperative outcomes (Figure 4). Furthermore, patients at higher risk for anesthesia may

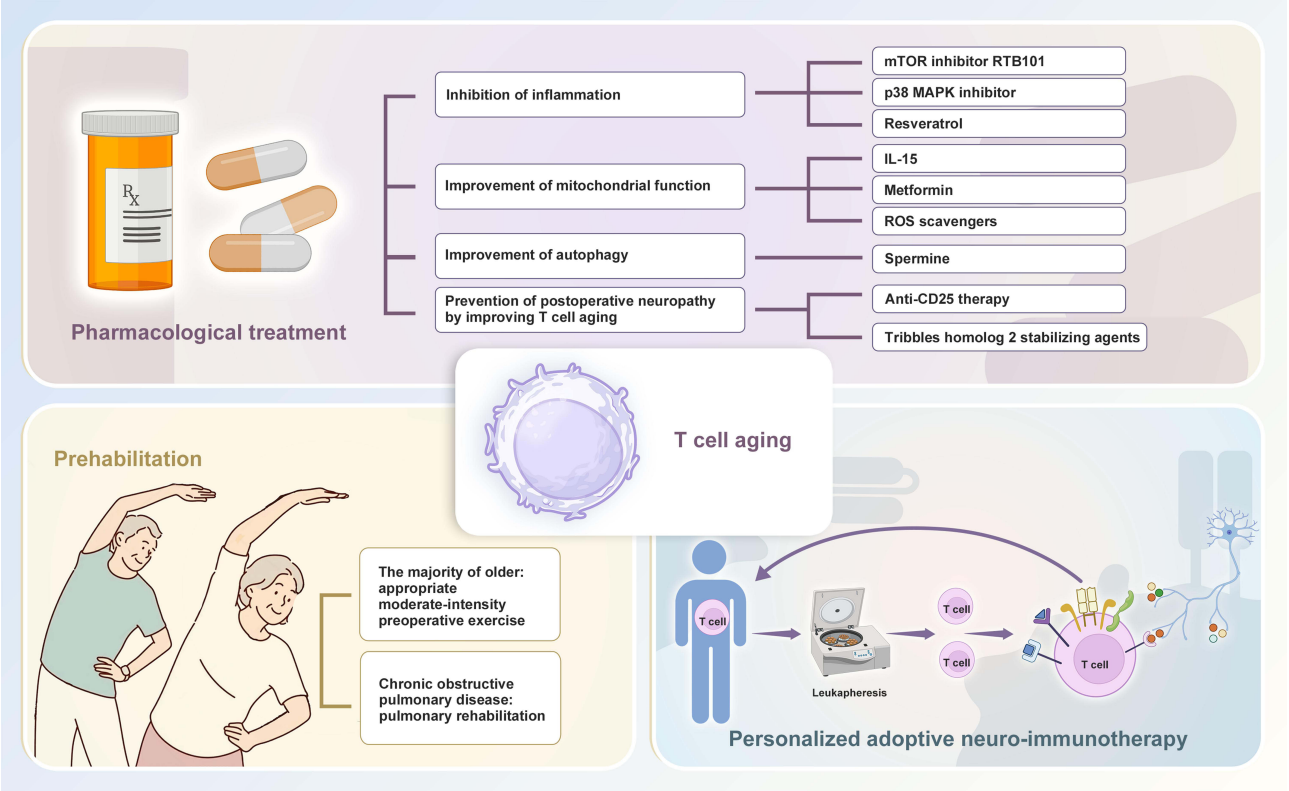

Figure 4 Perioperative Regulation Targeting T Cell Aging.
Abbreviations: mTOR, Mammalian Target of Rapamycin; MAPK, Mitogen-Activated Protein Kinase; IL, Interleukin; ROS, Reactive Oxygen Species; CD, Cluster of Differentiation.

experience an increased likelihood of T cell aging. Clinical studies have reported that more than 12 weeks of pulmonary rehabilitation significantly improved lung function, quality of life, and T-cell immune indices such as $CD3^+$%, $CD4^+$%, and $CD4^+$%/$CD8^+$% in patients with chronic obstructive pulmonary disease compared with the normal population.[136] This demonstrated that prehabilitation may be more effective in suppressing T cell aging in anesthetized high-risk patients.

Based on the mechanisms of T cell aging, future research should aim to develop agents for inhibiting inflammation, improving mitochondrial function, and autophagy. Meanwhile, strategies that alleviate postoperative neuropathy by improving T cell aging should be explored. It has also been reported that IL-15 treatment improved mitochondrial adaptation of Treg cells in HIV-infected patients, thereby restoring peroxisome proliferation-activated receptor-γ-coactivator 1α and mitochondrial transcription factor A. It also stimulated mitochondrial biosynthesis and enhanced the antiviral efficacy of HIV-specific $CD8^+$ T cells.[137] Metformin upregulates the expression of mitochondrial transcription factor A and mitochondrial function in $CD8^+$ T cells in mice, thereby inhibiting *Mycobacterium tuberculosis infection*, and also improves TH17 inflammatory features by activating autophagy and improving mitochondrial bioenergetics in T cells.[138] It is currently being investigated in clinical studies for potential anti-aging treatment.[139] Treatment with ROS scavengers restored the immunosuppressive functions of senescence and DNA damage-binding protein 1- and Cullin4- associated factor 1-deficient Treg cells.[48] Targeting the NF-κB, mTORC, and p38 MAPK pathways in the aging-associated secretory phenotype may inhibit inflammation, and further research is advocated to explore these possibilities. Animal experiments have shown that rapamycin improves the quality and intensity of $CD8^+$ T cell memory responses to viral infection in mice.[140] Findings from clinical trials have revealed that a low-dose mTOR inhibitor RTB101 is well-tolerated and up-regulates IFN-induced antiviral responses in elderly patients, making it an ideal agent for preventing aging.[141] Inhibition of p38 MAPK partially restored the proliferative capacity of TRMRA by improving telomerase activity, and thus p38 MAPK is also a potential research direction.[142] Chronic consumption of resveratrol has been shown to reverse pro-inflammatory cytokine profiles and oxidative DNA damage in senescent hybrid mice.[131] Regarding the enhancement of autophagy, spermine intake emerges as a promising research avenue, given that autophagy deficiency is linked to reduced levels of nicotinamide dinucleotide and a decline in spermine, which is necessary for the hypo-uridylation-dependent translation of pro-autophagic proteins. Animal experiments have revealed that spermidine promotes homeostatic differentiation of Treg cells in the intestine,[143] but subsequent clinical trials are needed to validate its feasibility as a treatment for T cell aging and prevent postoperative neuropathy. Anti-CD25 therapy maintains the infantile pattern of T cells by depleting Treg or by shifting chromatin accessibility to a younger individual state, thereby regulating neurological functions such as cognition.[123,144] Tribbles homolog 2 is an important regulator of T cell naivety, and agents that stabilize its activity have shown potential to treat neurodegenerative diseases in clinical studies.[47,145]

Personalized adoptive neuro-immunotherapy is a novel personalized cellular immunotherapy for patients with aging, tumors, neurodegenerative diseases, and chronic infections.[146] The therapy initially evaluates the responsiveness of various neurotransmitters and neuropeptides to T cells in the patient's peripheral blood, assessing both beneficial increases or decreases in T cell protein expression levels and enhancements in T cell functional responses. Subsequently, a substantial number of T cells are isolated from the peripheral blood and infused back into the body after being exposed to the appropriate neurotransmitters and neuropeptides.[147] The T cells interact with neurotransmitters or neuropeptides and does not involve unnatural activation, expansion, genetic manipulation, or other processes, making a safe intervention.

Conclusions

In the aging process, immune organ degeneration, long-term infection, inflammation aging, mitochondrial dysfunction, protein homeostasis imbalance, and epigenetic alterations are the underlying causes of T cell aging, which will lead to phenotypes such as T cell senescence, reduced T cell plasticity, imbalance of the ratio of naïve T cells to memory T cells and defective TCR pools. Future studies are anticipated to clarify the relationship between the triggers of T cell aging and to distinguish between primary and secondary changes. This understanding will aid in identifying optimal molecular targets that may slow or interrupt the aging of T cells. In the future, further research can be carried out in the following areas to deepen the understanding of the clinical significance of T cell aging: First, preoperative and intraoperative factors, such as hypertension, diabetes, acute respiratory distress syndrome, hypoxemia, depression and pain, nervous system diseases, obesity, tumor, autoimmune diseases, anesthetic methods and medications, as well as types of surgery,

have been identified as predictive factors for high-risk groups of T cell aging. However, there is no robust clinical prediction model available to evaluate the relative importance of various perioperative indicators for T cell aging. Future studies should focus on developing rigorous prediction models to quantify the risks associated with these preoperative and intraoperative factors. Second, preliminary basic experiments and limited clinical research suggests that T cell aging may be linked to multiple adverse outcomes, such as postoperative neurological disorders. However, additional large-scale clinical investigations are required to elucidate the relationship between T cell aging and overall postoperative recovery quality, as well as long-term prognosis. Our research team is currently conducting a cohort study examining the association between T cell aging and postoperative recovery quality in elderly patients with colorectal cancer. This study will help directly investigate the association between T cell aging and postoperative recovery quality, as well as screen for clinically significant indicators of T cell aging. Third, surgery and anesthesia may potentially harm the human body and accelerate T cell aging, which warrants further exploration. Finally, prehabilitation, pharmacological interventions, and personalized adoptive neuroimmunotherapies can improve clinical prognosis by regulating T cell aging. In the future, a comprehensive and tailored strategy for regulating T cell aging could be developed for individual patients. For anesthesiologists, appropriate nerve blocks (eg, stellate ganglion block) and specific anesthesia techniques (eg, intravenous anesthesia instead of volatile anesthesia) may influence the state of T cell aging and contribute to improved clinical prognosis. In summary, given the increasing global aging population, in-depth research into T cell aging is of great significance for facilitating perioperative transitions and achieving healthy aging.

Abbreviations

IL, Interleukin; OS, Oxidative Stress; TCRs T, Cell Receptors; CMV, Cytomegalovirus; mTORC1, Mammalian target of rapamycin 1; TNF, Tumor Necrosis Factor; TEMRA Cells, Terminal Effector Memory T Cells; ROS, Reactive Oxygen Species; IFN-I, Interferon Type I; NF-κB, Nuclear factor-kappaB; CD, Cluster of Differentiation; KLRG1, Killer Cell Lectin-like Receptor Subfamily G1; PD-1, Programmed Death 1; Tregs, Regulatory T cells; CCR 7, Chemokine Receptor 7; TEM, Effector memory T cells; MAPK, Mitogen-Activated Protein Kinase; T2D, Type 2 Diabetes; CX3CR1, C-X3-C-Motif Ligand 1; AD, Alzheimer's Disease; PD, Parkinson's Disease; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; IBD, Inflammatory bowel disease.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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