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REVIEW

An in-depth understanding of the role and mechanisms of T cells in immune organ aging and age-related diseases

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T cells play a critical and irreplaceable role in maintaining overall health. However, their functions undergo alterations as individuals age. It is of utmost importance to comprehend the specific characteristics of T-cell aging, as this knowledge is crucial for gaining deeper insights into the pathogenesis of aging-related diseases and developing effective therapeutic strategies. In this review, we have thoroughly examined the existing studies on the characteristics of immune organ aging. Furthermore, we elucidated the changes and potential mechanisms that occur in T cells during the aging process. Additionally, we have discussed the latest research advancements pertaining to T-cell aging-related diseases. These findings provide a fresh perspective for the study of T cells in the context of aging.

T cell | aging | immune organ | age-related diseases

Introduction

The aging population is a global and significant social issue, and promoting healthy aging is a goal of human medicine. In the elderly stage, the immune function of the body typically declines with age, rendering older individuals more susceptible to various infectious and malignant diseases. Therefore, it is crucial to enhance the immune function of elderly people and delay immune system aging to promote healthy aging.

Immune aging is a broad and complex subject that encompasses a variety of cellular changes, but when we narrow our focus to T-cell aging, we delve into a specific aspect that has profound implications for immune function. T cells, as a critical component of the adaptive immune response, undergo aging processes that can significantly affect their ability to respond to infections and tumors. By examining the intricate mechanisms underlying T-cell aging, we can better understand the decline in immune responses observed with advancing age. For instance, T lymphocyte-specific knockout of mitochondrial transcription factor A (TFAM) has been shown to cause not only immunometabolic dysfunction that drives T-cell senescence but also a general deterioration of health throughout the body, accompanied by multiple aging-related features, such as metabolic, musculoskeletal, cardiovascular, and cognitive alterations (Desdín-Micó et al., 2020). These findings suggest that premature aging of T lymphocytes may have a systemic impact on aging, accelerating the aging process in multiple organ systems.

Furthermore, immune cell aging not only affects innate and adaptive immunity but also potentially impacts organ aging, thereby accelerating the normal aging process (Yousefzadeh et al., 2021). In conclusion, T lymphocytes have been implicated in driving systemic aging, and modulating impaired immune cells may be a means to delay the progression of aging.

T lymphocytes are derived from lymphoid precursor cells originating in the bone marrow. They undergo differentiation and maturation in the thymus and are distributed throughout the immune organs and tissues of the body via the lymph and blood circulation to exert their immune functions. Multipotent stem cells in the bone marrow transform into lymphoid precursor cells, which migrate to the thymus. Under the influence of thymic factors, these cells undergo a series of orderly differentiation processes, gradually developing into T cells with a T-cell receptor (TCR) repertoire capable of recognizing various antigens. TCRs can be classified into two types based on the combination of TCR chains: αβ T cells composed of α and β chains, which are the main components of T cells, and γδ T cells composed of γ and δ chains.

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T lymphocytes that enter the thymus go through three stages: $CD4^+$ and $CD8^+$ double-negative (DN) T lymphocytes differentiate into double-positive (DP) T cells. DP cells undergo positive selection and negative selection to acquire major histocompatibility complex (MHC)-restricted recognition ability and self-antigen tolerance and develop into single-positive (SP) T cells with the surface markers CD4 and CD8. These SP T cells then migrate to peripheral lymphoid organs to settle (Touraine et al., 1977).

Upon activation of naïve T cells in the periphery, further differentiation of CD4 T cells occurs under the influence of cytokines and their microenvironment, giving rise to subpopulations with different biological functions known as helper T cells (Th). Th cells can be classified as Th1, Th2, Th17, Th9, or follicular helper T (Tfh) cells, depending on the type of cytokine secreted. Additionally, there are regulatory T (Treg) cells and cytotoxic T cells, which are a group of $CD8^+$ T cells with cytotoxic activity (Jenkinson, 1982). Different subpopulations of T cells play distinct roles in different anatomical sites and pathological processes, regulating and even converting each other and collectively participating in the fine regulation of immune responses in the body.

Numerous reviews on the role of T lymphocytes in aging have been published recently (Jain et al., 2023; Mao et al., 2024; Mittelbrunn and Kroemer, 2021; Møller et al., 2022; Nguyen and Chauhan, 2023; Zheng et al., 2023). In this discussion, we focus on recent evidence supporting the role of T lymphocytes in immune organ aging and their contribution to the occurrence and progression of age-related diseases. Specifically, we examined age-related changes in various immune organs and tissues, such as the thymus, spleen, lymph nodes, and tonsils, as well as the characteristic changes in several T-cell subsets and the TCR repertoire during aging. We also delve into the roles of T lymphocytes in age-related diseases and explore the applications and advances of T lymphocytes for anti-aging strategies. Understanding the mechanisms of T-cell aging and finding ways to delay aging are crucial for maintaining the health of immune function in the human body.

Aging of immune organs and tissues

The aging process of T cells is intricately linked to the aging of immune-related organs and tissues. The development, differentiation, homeostasis, and immune responses of T cells occur within various immune organs and tissues. In this section, we will provide a description of the characteristic changes observed in the aging process of the thymus, spleen, lymph nodes, tonsils and blood (Figure 1).

Changes in the thymus during aging

The thymus is enveloped by a thin layer of dense connective tissue called the capsule, which extends into the thymus to form interlobular septa, dividing the parenchyma into incomplete thymic lobes. Each lobe comprises a cortex and a medulla, with the medulla of adjacent lobes being continuous (Hale et al., 2020; Rodewald, 1998). The cortex is supported by thymic epithelial cells (cTECs) and contains a large number of thymocytes and a small number of other stromal cells (Nitta, 2022). The medulla contains more thymic epithelial cells (mTECs), as well as a few immature T cells (Kishimoto and Sprent, 1997), macrophages (Zhou et al., 2022b), and dendritic cells (Li et al., 2021b). The thymus serves as the site of T-cell differentiation, development, and maturation. Lymphoid hematopoietic stem cells from the bone marrow enter the thymus through high endothelial venules at the corticomedullary junction and migrate from the cortex to the medulla for development (Raviola and Karnovsky, 1972). Positive selection occurs in the outer cortex, granting T cells the ability to recognize antigens presented by MHC molecules. Negative selection occurs in the deep cortex and medulla, eliminating T cells that react with self-antigens (Klein et al., 2009). Over 95% of thymic cells undergo apoptosis and are cleared by macrophages (Surh and Sprent, 1994). Mature naïve T cells exit the thymus through blood and lymphatic vessels to reach thymus-dependent regions of peripheral lymphoid organs and lymphoid tissues, where they participate in cellular immune responses (Matloubian et al., 2004).

The thymus plays a crucial role in the immune system, including in T-cell development, immune tolerance, and immune regulation. It is vital for maintaining normal immune function and preventing the occurrence of autoimmune diseases. The thymus begins developing during embryonic stages, around the sixth week, and originates from the third pharyngeal pouch (Farley et al., 2013). Subsequently, it starts to atrophy during puberty (Singh and Singh, 1979). During thymic involution, the thymus tissue gradually atrophies, perivascular spaces increase, and fat tissue accumulates (Lynch et al., 2009). Simultaneously, the thymus tissue undergoes deterioration, altering the distribution ratio of the cortex and medulla and resulting in a decrease in thymic cell count (Li et al., 2021b). Thymus degeneration leads to (i) a decrease in the output of thymus naïve T cells and a reduction in the number of peripheral naïve T cells (Sandstedt et al., 2023); (ii) a compensatory increase in memory T cells (Nasi et al., 2006); (iii) a decrease in TCR diversity (Yang et al., 2009), resulting in a diminished ability to resist external pathogens; and (iv) disruption of negative selection, leading to an increase in self-reactive T cells and an elevated risk of developing autoimmune diseases (Coder et al., 2015).

The causes of thymic atrophy include hormonal changes, infection, malnutrition, obesity, pregnancy, and antitumor treatment. Increased levels of sex hormones such as testosterone and estrogen promote thymic degeneration by affecting the function of TECs (Taves and Ashwell, 2022). An increase in steroid hormones such as cortisol and a decrease in growth factors (such as growth hormone, insulin-like growth factor-1 (IGF1), and keratinocyte growth factor (KGF)) also contribute to thymic degeneration (Min et al., 2006). Exogenous administration of IL-6 or injection of poly (I:C) to simulate viral infection can induce thymus degeneration in young mice (Sempowski et al., 2000). Recent studies have revealed that IL-33 causes naïve T-cell aging mediated by thymus degeneration and impairs host control of severe infections. It has also been shown that IL-33 induces the overproduction of mTEC IV and disrupts mTEC/cTEC lacunae, thus leading to thymic degeneration. Additionally, targeting IL-33 or growth stimulation expressed gene 2 (ST2) may be a promising intervention route to restore T-cell immunity for better control of severe infections (Xu et al., 2022). Older individuals are more prone to tumors, chronic diseases, and severe infections than are young individuals, partially due to thymus atrophy. Research on thymic involution is crucial for the prevention and treatment of these conditions.

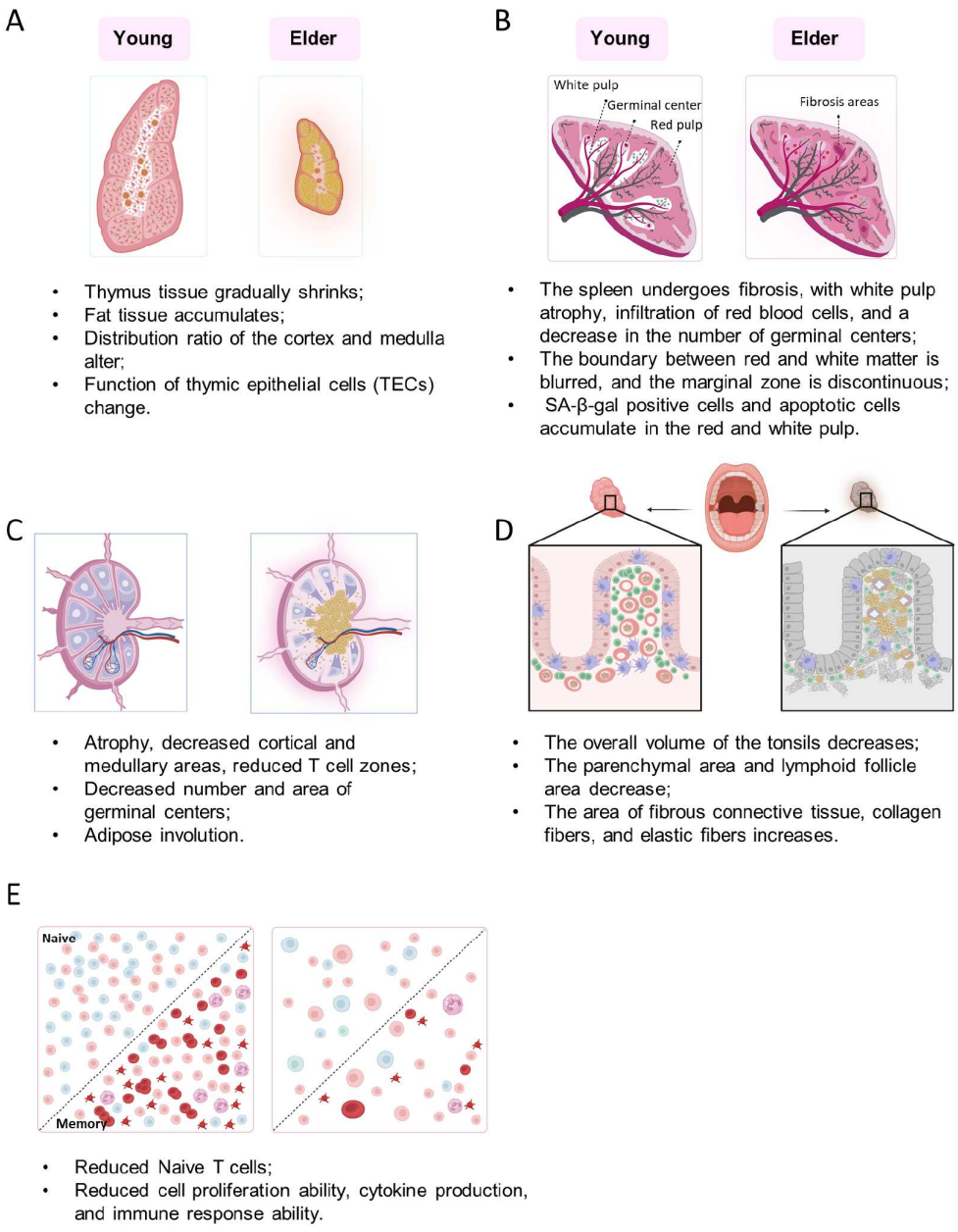

Figure 1. Age-related changes in the thymus (A), spleen (B), lymph nodes (C), tonsils (D) and peripheral venous blood (E).

Changes in the spleen during aging

The spleen is the largest lymphatic organ in the human body and serves various functions, including blood storage, hematopoiesis, removal of senescent red blood cells, and immune response. It consists of red and white pulp surrounded by a fibrous capsule. The red pulp contains stromal cells, macrophages, plasmablasts, and plasma cells. Stromal cells provide structural support, while macrophages remove harmful substances and senescent red blood cells while recycling iron. Plasmablasts and plasma cells ensure efficient secretion of antibodies into the blood (Mebius and Kraal, 2005; Nolte et al., 2000; Toellner et al., 1996; van Krieken and te Velde, 1988).

The structure of the white pulp in the spleen differs between mice and humans. Humans have an inner and outer marginal zone surrounding the white pulp, along with a large peri-follicular area. The periarterial lymphatic sheath surrounding the central artery contains T cells, macrophages (El-Naseery et al., 2020), fibroblast reticular cells (Bajénoff et al., 2008), and conventional dendritic cells (Zanna et al., 2021). B-cell follicles, which consist of B lymphocytes with germinal centers (GCs), are located adjacent to the lymphatic sheath (Mebius and Kraal, 2005). The marginal zone of the spleen plays a crucial role in capturing and removing blood-borne pathogens and antigens. It contains specialized populations of macrophages and B cells that act as a bridge between innate and adaptive immunity (Mebius and Kraal, 2005).

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During development, the spleen starts to form approximately 30 days after fertilization. As the stomach rotates in the third month, the spleen separates and moves upward, forming the splenic ligament that connects the mesentery and the stomach. Hematopoietic stem cells migrate to the spleen, initiating red blood cell production, and a dark center appears, eventually merging within the spleen (Weinzirl et al., 2020). The infant spleen has a thin membrane with uniform elastin fibers. With age, the capsule thickens and forms a layer of collagen (Higginson et al., 2020). Studies have shown that spleen stiffness is not influenced by age, sex, or spleen size, but spleen size is significantly smaller in females than in males. There is also a negative correlation between longitudinal spleen size and age (Albayrak and Server, 2019).

In aging mice, the spleen undergoes changes such as increased volume, fibrotic areas, blurred boundaries between red and white pulp, discontinuity in the marginal zone, and increased macrophages in the marginal zone. The red pulp accumulates senescence-associated β-galactosidase (SA-β-gal)-positive cells earlier and more frequently than does the white pulp. In the white pulp, SA-β-gal-positive cells initially accumulate in small amounts in the center and gradually spread throughout the entire white pulp with age. p21-positive proteins are primarily expressed in stromal cells, while no p16-positive proteins are detected in the spleen (Jin et al., 2023). Moreover, the number of mitochondrial DNA (mtDNA) copies increases in the spleen of aging C57 mice, which may lead to nuclear enlargement and mitochondrial dysfunction (Baek et al., 2019).

Similar changes are observed in aged rats, including a blurred boundary between the red pulp and white pulp, atrophy of the white pulp area, infiltration of red blood cells, and a reduced number of GCs. The antioxidant capacity decreases, and spleen damage increases in aged rats. The proportion of T cells and the number of IL-1β- and IL-6-immunopositive cells were significantly lower in the spleens of aged rats than in those of young rats. However, there is an increase in ssDNA- and caspase-3-positive apoptotic cells in the spleen of aged rats (El-Naseery et al., 2020). In elderly mice, overall cytosine-phosphate-guanine (CpG) methylation levels in spleen tissue decrease with age, with high methylation observed in promoter regions and low methylation in gene body and intergenic regions (Jeong et al., 2023).

Factors contributing to splenic senescence include age, infection, circadian dysregulation, and iron homeostasis. Infection with *Toxoplasma gondii* can lead to white pulp atrophy and premature aging of the spleen in mice (Pereira et al., 2019). Chronic circadian dysregulation accelerates splenic aging (Inokawa et al., 2020). Iron homeostasis promotes anti-immune senescence in the spleen (He et al., 2023). Various interventions, such as voluntary exercise, vitamin E supplementation, and the use of specific probiotics or extracts, have shown potential in restoring spleen function and preventing spleen damage and aging (Gao et al., 2022a; Lee et al., 2019; Li et al., 2021a; Li et al., 2020; Qian et al., 2018; Tao et al., 2021).

Changes in the lymph node during aging

Lymph nodes serve crucial functions in immune surveillance, antigen presentation, lymphocyte activation and proliferation, and lymphocyte migration. They play a vital role in maintaining the normal function of the immune system and defending against pathogen invasion. Three compartments—the cortex, paracortex, and medulla—of lymph nodes house distinct regions occupied by B cells, T cells, fibroblastic reticular cells, macrophages, dendritic cells, and follicular dendritic cells (D'Rozario et al., 2023; Willard-Mack, 2006).

Aging of lymph nodes is characterized by atrophy, decreased cortical and medullary areas, reduced T-cell zones, diminished number and size of GCs, fibrosis, and increased adipose tissue (Dempsey, 2022; Luscieti et al., 1980; Silva-Cayetano et al., 2023). Research has revealed significant structural differences in lymph nodes among different age groups and anatomical locations. The formation of GCs is most prominent in infants and children, less common in young adults, and typically absent in older adults, resulting in weakened immune responses (Luscieti et al., 1980). Denton et al. (2022) reported that this age-related defect is associated with lymphoid stromal cells expressing MAdCAM1. Immunization of heterozygous mice demonstrated that the GCs in older mice were smaller and that the expansion of MAdCAM1$^+$ stromal cells was reduced. Transcriptomic analysis revealed changes in these stromal cells after immunization, but this response was absent in older mice. TLR4 agonist immunization enhanced the GC response in older mice, albeit with only slight improvement in humoral immunity (Dempsey, 2022). Moreover, the number and size of GCs in the lymph nodes of aged mice decreased. This is due to dysregulated CXCR4 expression in aging Tfh cells, leading to their misplacement within GCs and impairing their ability to support B cells and promote antibody production (Silva-Cayetano et al., 2023).

Adipose tissue replacement (adipose involution) is a characteristic of many peripheral lymph nodes, especially those subjected to less antigenic stimulation, such as the elbow, axillary, and popliteal lymph nodes (Chen et al., 2022; Luscieti et al., 1980). Lymph node adiposis is common in older adults, and one possible mechanism involves the infiltration of surrounding adipocytes into the lymph nodes (Leborgne et al., 1965). However, research data also suggest that adiposis originates from the deeper parts of the medulla and involves cells expressing markers of fibroblast and adipocyte lineages, exhibiting transitional phenotypes. These changes are associated with the downregulation of lymphoid protein β (LTB), which inhibits the differentiation of SC precursor cells into adipocytes during early lymph node development. Additionally, medullary reticular cells (MedRCs) are more prone to transdifferentiate into adipocytes, while T-cell zone reticular cells (TRCs) are less likely to do so. Lymph node adiposis leads to the loss of medullary stromal matrix and extensive vascular remodeling of high endothelial venules (HEVs) and lymphatic vessels, thereby altering the immune environment of human lymph nodes (Bekkhus et al., 2023). Aging of lymph nodes exacerbates inflammatory responses. In the draining lymph nodes of aged mice, effector T cells exhibit characteristics of cellular senescence and proinflammatory effects, with strong production of IFN-γ being a prominent feature (Ashour et al., 2023).

Changes in the tonsils during aging

The tonsils, which are situated at the base of the tongue and pharynx, comprise specialized compartments that contribute to immune functions, such as the reticular crypt epithelium, the extrafollicular area, the mantle zones of lymphoid follicles, and the GCs (Korsrud and Brandtzaeg, 1980; Nave et al., 2001).

During embryological development, lymphocytes and lymphoid stem cells invade the lamina propria and begin to form follicles and eventually GCs after approximately 16–17 weeks. The formation of tonsillar GCs signifies the activation of B cells induced by exogenous antigens, which typically occurs shortly after birth. The differentiation of effector B cells into extrafollicular plasma cells can be observed approximately 2 weeks after birth (Korsrud and Brandtzaeg, 1980). The pharyngeal and palatine tonsils usually reach their maximum size at approximately 6 years of age and during puberty, respectively. Subsequently, they undergo involution, characterized by increased production of fibrous tissue and eventual fatty atrophy, which typically occurs at approximately 8–10 years of age and in adulthood, respectively (Arambula et al., 2021). Unlike lymph nodes, tonsils are not fully encapsulated and lack incoming lymphatics. The surface of the tonsils forms crypts to increase the contact surface area with pathogens, and abundant dendritic cells are present. Dendritic cells take up exogenous antigens and transport them to the T-cell zone outside the follicles and B-cell follicles (Brandtzaeg, 2015; Perry and Whyte, 1998).

Tonsil volume significantly diminishes with age, primarily due to a reduction in lymphoid tissue and an increase in fibrous connective tissue (Isaacson and Parikh, 2008). Children exhibit larger palatine tonsils, which decrease in size as they mature (Akcay et al., 2006; Nave et al., 2001). The T-cell population, particularly the $CD4^+$ cell population, increases until the age of 35, after which it stabilizes. Conversely, the proportion of B cells decreased until 35 days of age and then stabilized. The number of natural killer cells remains consistently low across all age groups (Bergler et al., 1999; Harada, 1989). The age-related increase in T follicular regulatory (Tfr) cells suggests a potential role in IgG4-related disease (IgG4-RD) pathogenesis. However, the inhibitory function of Tfr cells declines in elderly individuals, which may contribute to the development of IgG4-RD (Ito et al., 2019). As individuals age, the tonsils undergo structural changes, with a decrease in lymphoid tissue and an increase in fibrous tissue. This is accompanied by shifts in immune cell populations. The increase in Tfr cells with age could theoretically enhance immune regulation. However, the decline in their inhibitory function in older individuals may lead to a reduced ability to control immune responses, potentially contributing to the development of IgG4-RD. This suggests that the balance between regulatory and effector immune responses in the tonsils is crucial and can be disrupted by age-related changes.

The aging process in tonsils is associated with alterations in both immune cell composition and metabolic profiles. The increase in eosinophils and mast cells may reflect an altered immune response, potentially contributing to chronic inflammation. Metabolic changes can affect tonsil function and the local immune environment, impacting both innate and adaptive immune responses. Epigenetic alterations may regulate gene expression related to immune function and inflammation, influencing tonsil aging and the progression of chronic inflammatory conditions. These changes collectively contribute to an age-dependent shift in tonsil physiology and immune capacity.

Changes in the blood during aging

The peripheral blood is the body's largest fluid tissue, circulating throughout and composed mainly of red blood cells, white blood cells, and platelets. Red blood cells, which are abundant in peripheral blood, contain hemoglobin for oxygen transport to tissues and carbon dioxide for transport to the lungs (Ahmed et al., 2020). White blood cells, including lymphocytes, granulocytes, and monocytes, play crucial roles in immune defense by identifying and clearing pathogens and foreign substances (Chaplin, 2010). Platelets, which are cell fragments, play a role in hemostasis and wound healing at sites of injury (Koupenova et al., 2018). Peripheral blood indicators can reflect an individual's health status, and its composition and function undergo age-related changes.

Older adults often experience a gradual decline in red blood cell count and hemoglobin levels, a condition known as anemia during aging. This is attributed to decreased production of erythropoietin, the hormone that stimulates red blood cell production, as well as decreased bone marrow function (Halawi et al., 2017). Red blood cells from older adults also tend to have decreased flexibility and increased rigidity, which can impair their ability to effectively transport oxygen (Wink, 1992). The lifespan of individual red blood cells may also be shortened in older adults, further contributing to anemia (Halawi et al., 2017). Platelet count and function can decline with age. Older adults often exhibit lower platelet counts than younger individuals (Le Blanc and Lordkipanidzé, 2019). Platelet aggregation and adhesion may be impaired in older adults, leading to an increased risk of bleeding and impaired wound healing (Gawaz and Vogel, 2013). Reduced platelet function in older adults is associated with changes in platelet signaling pathways, decreased expression of adhesion receptors, and alterations in platelet-endothelial cell interactions (Gawaz and Vogel, 2013).

With age, there is a decrease in conventional $CD8^+$ T cells, leading to an increase in the $CD4^+/CD8^+$ T-cell ratio, while the total $CD4^+$ T-cell count remains stable. Mucosal-associated invariant T (MAIT) cells decrease after 55 years of age. Naïve $CD4^+$ T cells undergo transcriptional remodeling, metabolic changes and active cytokine signaling, particularly upregulation of the IL-2-STAT5 pathway. This results in increased CD25 expression and enhanced homeostatic proliferation in elderly individuals. Th2 and $HLA\text{-}DR^+$ memory T cells accumulate with age, but cytotoxic $CD4^+$ T cells remain unchanged. There was a decrease in naïve Treg cells and an increase in memory Treg cells, with no overall change in Treg proportions. The number of naïve $CD8^+$ T cells significantly decreased, while the number of $GZMK^+$ effector memory and central memory $CD8^+$ T cells increased. In γδ T cells, naïve and Vδ1 $GZMB^+$ subsets show age-related changes. B cells and NK cells show limited or no age-related changes, and myeloid cells remain stable (Terekhova et al., 2023). Aging affects T-cell populations by altering their proportions and functions. The decrease in $CD8^+$ T cells and increase in the $CD4^+/CD8^+$ T-cell ratio reflect a shift in T-cell homeostasis. The transcriptional remodeling of naïve $CD4^+$ T cells, which is driven by metabolic changes and cytokine signaling, suggests an adaptation to maintain immune function despite age-related decline. The upregulation of the IL-2-STAT5 pathway and the consequent increase in CD25 expression promote homeostatic proliferation of naïve $CD4^+$ T cells, compensating for their reduced numbers. The selective accumulation of certain memory and effector T-cell subsets indicates a shift toward a memory-dominated immune system, which may be a response to cumulative antigen exposure over a lifetime. The stability of B cells, NK cells, and myeloid cells suggested that these

populations are less affected by age-related changes in the immune system. Overall, these changes reflect an attempt to maintain immune surveillance and response capacity in the face of aging.

Characteristics of T-cell aging

The complexities of T-cell aging are multifaceted. Aging leads to a reduction in TCR diversity and a decrease in naïve T-cell numbers. Moreover, aging triggers intricate modifications in memory T cells, marked by an increased proportion of effector T cells, central memory T cells, and terminally differentiated effector memory T cells re-expressing CD45RA (TEMRA) cells. Various subsets of effector T cells exhibit distinct behaviors as aging progresses, including an imbalanced Th1/Th2 ratio, heightened differentiation of Th9 cells, increased pathogenicity of Th17 cells, and compromised Treg cell function. Additionally, the ratio of Tfh/Tfr cells changes. These alterations may contribute to an elevated susceptibility to age-related diseases and a decline in immune function. In this context, we elucidated the characteristics and changes occurring within different T-cell subsets during the process of T-cell aging (Figure 2).

Reduction in the TCR repertoire diversity and naïve T cells during aging

The TCR is a crucial receptor on the surface of T cells and is composed of two polypeptide chains, α and β. These proteins activate T cells by recognizing and binding to specific peptide-MHC antigens. This recognition function of the TCR relies on its high diversity, which is produced by the gene recombination mechanism during the development of T cells (Kuhns et al., 2006). Specifically, the TCRα chain is composed of variable (V) and joining (J) gene segments, while the TCRβ chain is composed of V, diverse (D), and J gene segments. A small fraction of T cells express γδ TCRs, which directly bind to pathogen-derived glycoproteins or nonclassical MHC molecules. The random rearrangement of these gene segments, coupled with mechanisms such as the insertion and deletion of nucleotides, enables the extremely rich diversity of TCRs, which are theoretically capable of producing up to 10^{14}–10^{19} distinct TCR sequences (Weng, 2023). The unique combinations of various TCRs together construct the diversity of the TCR repertoire. The diversity of the TCR repertoire is crucial for the immune system's ability to recognize and respond to a wide range of different pathogens (Mao et al., 2024).

In immunological research, single-cell immune repertoire sequencing technology can provide paired sequence information on TCRs, while bulk-TCR sequencing can obtain data by analyzing TCRα or TCRβ (Pai and Satpathy, 2021). The algorithms for calculating the diversity of TCR repertoires include the GLIPH algorithm, which is based on sequence similarity and identifies specific groups by assessing features such as shared V gene usage and CDR3 length. The TCRdist algorithm enables clustering and visualization of TCR sequences by defining a new measure of distance. In addition, diversity metrics such as the Hill number, Rényi entropy, Shannon entropy, and Gini-Simpson index are important tools for quantifying and analyzing the complexity of TCR repertoires (Friedlander et al., 1985; Katayama et al., 2022). These methods are crucial for understanding immune responses and developing treatment strategies for immune-related diseases.

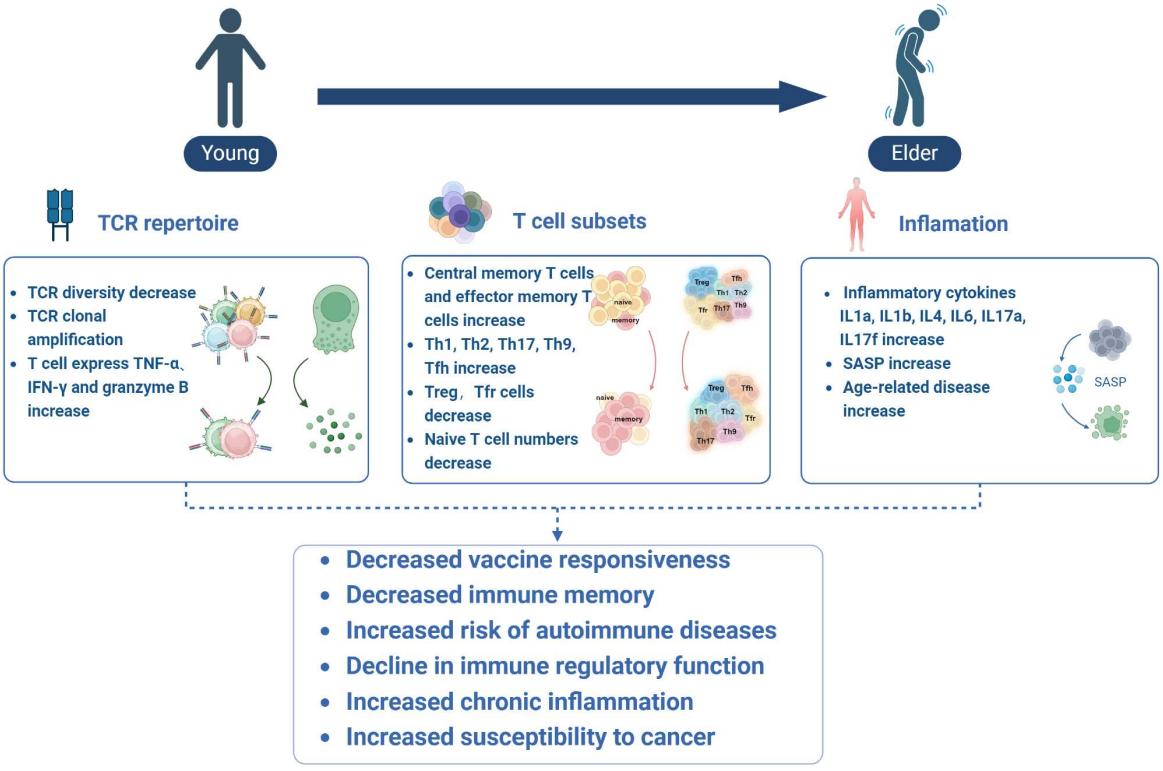

Figure 2. Characteristics of T-cell aging.

Mature naïve SPs exit the thymus and enter peripheral lymphoid organs. During pathogenic infections, T cells encounter foreign peptides presented by antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B cells. Engagement of the TCR with the antigenic peptide activates T cells, leading to clonal expansion and differentiation to perform effector functions through complex molecular changes in the plasma membrane, cytoplasm, and nucleus. TCR signaling is crucial for T-cell activation and the immune response, and dysregulation of TCR signaling can result in T-cell dysfunction or autoimmunity (Shah et al., 2021).

A reduction in TCR repertoire diversity may lead to a decline in the immune system's ability to recognize and respond to a variety of pathogens, weaken immune memory and the preventive effects of vaccines (Xiao et al., 2022; Xiao et al., 2023), increase the risk of autoimmune diseases (He et al., 2022), diminish the surveillance and clearance capacity against tumors (Schreiber et al., 2020; Tichet et al., 2023), and accelerate the process of immunological aging with advancing age (Foth et al., 2020), thereby affecting overall immune health and defense functions. The decline in TCR repertoire diversity with age is closely associated with a decrease in the number of naïve T cells. This reduction in peripheral naïve T cells is observed in both mice and humans, with a more pronounced decrease in $CD8^+$ naïve T cells than in $CD4^+$ naïve T cells in humans. This difference may be attributed to the greater abundance of Tribbles homolog 2 (TRIB2) in naïve $CD4^+$ T cells, which suppresses AKT activation and counteracts quiescence exit (Cao et al., 2023).

There are two main reasons for the decrease in naïve T-cell numbers during aging. First, thymic involution leads to reduced thymic output. Second, antigen stimulation of peripheral naïve T cells results in the accumulation of memory T cells over time and a decrease in the proportion of naïve T cells. In mice, the maintenance of peripheral naïve T cells primarily relies on thymic output throughout life rather than self-renewal and proliferation of peripheral naïve T cells. In humans, the maintenance of peripheral naïve T cells depends on thymic output to varying degrees at different stages of life. During childhood, the maintenance of peripheral naïve T cells relies on both thymic output and peripheral T-cell division. However, thymic involution becomes primarily dependent on peripheral T-cell division (de Boer et al., 2023). In elderly individuals, the self-renewal of naïve T cells through homeostatic proliferation often fails (Goronzy and Weyand, 2019). The diversity of the TCR repertoire in the human body decreases with age and is strongly associated with a decrease in naïve T cells. TCRβ diversity is significantly reduced in both $CD4^+$ and $CD8^+$ T cells, while TCRα expression remains relatively unchanged. These changes primarily occur in naïve T cells, with minimal alterations observed in memory T cells. Analysis of complementarity determining region 3 of the T-cell receptor β chain (CDR3β) region of the TCR revealed age-related decreases in CDR3 length, nontemplated diversification nucleotide (NDN) insertions, and nontemplate-added N nucleotide numbers. The physicochemical properties of the central region of the CDR3β loop also undergo changes (Weng, 2023). The reduced diversity in the TCR repertoire, which provides specific high-affinity TCRs, affects responses to newly encountered antigens in older adults (Čičin-Šain et al., 2010; Gustafson et al., 2020). The age-related decline in naïve T-cell numbers and TCR repertoire diversity has significant implications for immune function, leading to a diminished capacity to respond to new infections and a reduced efficacy of vaccines in elderly individuals, thereby highlighting the importance of maintaining a robust and diverse immune system throughout life.

Changes in memory T cells during aging

When naïve T cells interact with APCs, they become activated, proliferate, and differentiate into effector T cells and memory T cells. Effector T cells rapidly expand and release cytokines to directly eliminate pathogens. On the other hand, memory T cells enter a dormant state, awaiting a signal to encounter the same antigen again. Memory T cells possess long-term survival capabilities and can persist in the body for years or even a lifetime. When the body encounters the same antigen again, memory T cells are quickly activated and differentiate into effector T cells. These effector T cells rapidly expand and release a large amount of cytokines to counteract the reinvasion of pathogens (Künzli and Masopust, 2023).

Central memory T cells primarily reside in lymphoid tissues and provide long-term immune memory and persistent immune protection. Effector memory T cells mainly exist in nonlymphoid tissues, enabling them to rapidly respond to reinfection and clear pathogens swiftly. Tissue-resident memory T cells, on the other hand, are found in specific tissues and provide rapid and localized immune responses (Künzli and Masopust, 2023). Immunological memory plays a significant role in resisting foreign pathogens. However, achieving the same level of effectiveness as in young elderly individuals is extremely challenging. With age, varicella-zoster virus (VZV), which was originally in a latent state, can reactivate and manifest as a shingle. By the age of 80, approximately 50% of the population has experienced shingles at least once (Ciabattini et al., 2018; Goronzy and Weyand, 2019). Additionally, older adults who received the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine showed poor expansion of preexisting memory T cells (Saggau et al., 2022).

A study revealed that the proportion of total T cells in peripheral blood did not significantly differ among healthy individuals aged 20 to 70 years, while the percentage of $CD4^+$ T cells tended to increase and that of $CD8^+$ T cells tended to decrease with advancing age. However, significant changes were observed in the proportions of memory T-cell subgroups within $CD4^+$ T cells and $CD8^+$ T cells in peripheral blood, with more prominent changes in $CD8^+$ T cells (Jia et al., 2023).

For $CD4^+$ T cells in peripheral blood, the proportion of TEMRA cells did not significantly change with age (20–24 age group: 9.5%±5.96%, 70 age group: 9.05%±7.21%). However, the percentages of effector memory $CD4^+$ T cells, $CD4^+$ TEMRA T cells, and mature NK cells in peripheral blood were significantly greater in women aged 35 years and older than in younger women. Age-related dysregulation of $CD4^+$ T and NK cells may be involved in pregnancy loss in older women (Muyayalo et al., 2023). The proportions of $CD4^+$ T cells among central memory T cells (20–24 age group: 19.57%±6.34%, 70 age group: 24.32%±8.79%) and effector memory T cells (20–24 age group: 33.16%±11.42%, 70 age group: 37.09%±13.60%) increased with age. On the other hand, $CD8^+$ T cells exhibited more pronounced changes in memory T-cell subgroups in peripheral blood. Among $CD8^+$ T cells, the proportions of TEMRA (20–24 age group: 33.48%±16.92%, 70 age group: 44.97%±17.3%), central

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memory T cells (20–24 age group: 3.47%±2.46%, 70 age group: 5.32%±3.86%), and effector memory T cells (20–24 age group: 33.3%±16.69%, 70 age group: 37.75%±16.71%) increased with age, with the increase in TEMRA cells being more significant (Jia et al., 2023).

TEMRA cells represent a population of senescent cells that accumulate with age, often due to specific infections such as cytomegalovirus. Compared with effector memory T cells, $CD8^+$ T cells exhibit greater expression of genes related to cytotoxicity and depletion, especially in $CD8^+$ T cells, where high levels of the cytotoxic cytokines TNF-α, IFN-γ, perforin, and GZMB are expressed. Approximately 60% of TEMRA cells express high levels of markers of aging, including killer cell lectin-like receptor G1 (KLRG1), CD57, and programmed cell death receptor 1 (PD-1), in contrast to only 10% of naïve cells and central memory T cells. Furthermore, TEMRA cells have a lower proliferation capacity and lower telomerase activity (Strickland et al., 2023). $CD8^+$ TEMRA cells are increased in the lungs of individuals with mild to moderate chronic obstructive pulmonary disease and may contribute to inflammation preceding severe disease (Villaseñor-Altamirano et al., 2023). Age-related high heterogeneity in $CD8^+$ TEMRA cell accumulation and disruption of the kynurenine pathway are associated with the development of chronic inflammation and insulin resistance (IR). Comprehensive strength and endurance exercise attenuates $CD8^+$ TEMRA cell differentiation and impacts the kynurenine pathway in older individuals (Boßlau et al., 2023).

Changes in the effector T-cell subset

Effector $CD4^+$ T cells encompass various subpopulations, including Th1, Th2, Th17, Th9, and Tfh cells, while Treg and Tfr cells serve as regulatory immune cells. Each of these T-cell subpopulations plays a distinct role in immunity, contributes to the development of different immune-related diseases, and undergoes specific dynamic changes during aging. Consequently, they exhibit diverse manifestations of diseases that are more prevalent among elderly individuals.

Th1 cells

Th1 cells primarily combat intracellular pathogens such as parasites, viruses, and intracellular bacteria by mediating cellular immunity and delayed hypersensitivity (Szabo et al., 2000). The differentiation of naïve T cells into Th1 cells requires IL12 and involves the activation of macrophages and dendritic cells. Th1 cells also produce TNF, lymphotoxin-α, and IL-2, which actively participate in anti-infection immunity (Abbas et al., 1996). A study analyzing peripheral blood samples from healthy individuals across different age groups (30–69 years old) revealed that the proportion of Th1 cells increases between the ages of 30 and 59 but declines after the age of 50 (Aragon et al., 2023). Moreover, the spleens of older mice exhibit a greater proportion of Th1 cells than those of younger mice (Kawata et al., 2021).

Th2 cells

Th2 cells are crucial for B cells to execute humoral immunity, eliminate extracellular microorganisms, and combat intestinal worms (Szabo et al., 2000). Additionally, they contribute to antibody class switching, resulting in the production of IgE, which can induce or sustain allergic reactions (Kemter and Nagler, 2019). Unlike those of Th1 and Th17 cells, the proportion of Th2 cells in the peripheral blood of individuals aged 40–49 years increases from 19.72% to 23.36% and remains stable until the age of 69 years (Aragon et al., 2023). Similarly, the proportion of Th2 cells in the spleens of older mice is greater than that in the spleens of younger mice (Kawata et al., 2021). In rats, Th2 cell abundance continues to increase during aging (Ye et al., 2022). The age-related increase in Th2 cells impacts immune responses associated with aging (Mansfield et al., 2012) and contributes to an increased frequency of food allergies among elderly individuals (De Martinis et al., 2019).

Th1/Th2 balance

During the aging process in humans and mice, there is a decline in the Th1 response and an exacerbation of the Th2 response (Shearer, 1997). The decreased expression of CD28 with age disrupts the balance between Th1 and Th2 cells, impairing T-cell-mediated immunity (Shimizu et al., 2008). The consumption of probiotic *Lactobacillus rhamnosus* fermented milk has been shown to improve Th1/Th2 immune homeostasis, antioxidant status, and resistance to pathogenic *Escherichia coli* in aging mice and to enhance anti-infection immunity (Sharma et al., 2014).

Th9 cells

Th9 cells play a role in preventing intestinal worm infections, and their IL-9 production stimulates the proliferation of hematopoietic cells, inhibits their apoptosis, and activates proinflammatory Th17 cells (Angkasekwinai, 2019). Naïve $CD4^+$ T cells from elderly individuals tend to differentiate into Th9 cells through two main mechanisms. First, there is increased responsiveness to transforming growth factor β (TGFβ) stimulation as age advances, which is attributed to the upregulation of the TGFbR3 receptor and increased expression of the PU.1 transcription factor. Second, aged immature $CD4^+$ T cells display altered transcription factor profiles upon TCR stimulation, including increased expression of BATF and IRF4 and decreased expression of ID3 and BCL6. These transcription factors contribute to Th9 differentiation and IL9 transcription (Hu et al., 2019).

Th17 cells

Th17 cells provide protection against bacteria and fungi at mucosal surfaces (Wang et al., 2024), targeting certain microorganisms that Th1 or Th2 cells cannot effectively combat, such as *Mycobacterium tuberculosis*, *Bacillus fragilis*, and *Klebsiella pneumoniae* (Bedoya et al., 2013). The proportion of Th17 cells increases between the ages of 30 and 49, followed by a decrease after the age of 49 (Aragon et al., 2023). Furthermore, the spleens of older mice exhibit a greater proportion of Th17 cells than those of younger mice (Kawata et al., 2021). Elevated Th17 expression in $CD4^+$ T cells of elderly individuals promotes age-related chronic inflammation and inflammatory processes. In elderly mice infected with *Listeria monocytogenes*, the differentiation of proinflammatory Th17 cells is enhanced, exacerbating the pathological response during listeriosis (Alam et al., 2020). However, another study revealed that Th17 cell pathogenicity decreases in aging mice, as indicated by reduced levels of the IL-23R transcript and protein and downregulated secretion of GM-CSF in aging Th17 cells.

Th1/Th17 cell ratio

The ratio of Th1 to Th17 cells significantly increases before the

age of 59 and then decreases (Aragon et al., 2023). Additionally, a study on T cells in women before and after menopause revealed that after menopause, the proportion of Th1 cells decreases, while the proportion of Th17 cells increases. This shift has been associated with osteoporosis and is influenced by estrogen levels (Bhadricha et al., 2023). Another study revealed that testosterone inhibits the differentiation of Th1 and Th17 cells (Kissick et al., 2014). These findings suggest that age-related changes in sex hormones play a significant role in T-cell aging and that the effects of estrogen and testosterone differ, indicating potential gender-specific susceptibilities to different diseases in aging individuals. Furthermore, the differentiation of Th1 and Th17 cells has been implicated in other autoimmune diseases, such as psoriasis and Crohn's disease (Gao et al., 2022b).

Treg cells

Treg cells can suppress immune responses and maintain peripheral immune tolerance (Caza and Landas, 2015). FOXP3 is the master transcription factor for Treg cells (Jia et al., 2024). Insufficient expression of CD4, CD25, and FOXP3 in Treg cells leads to severe autoimmune responses in experimental and clinical models (Buckner, 2010). Studies have shown that in aged BALB/c mice, the percentage of $CD4^+CD25^+$ Treg cells increases, but their function significantly changes (Zhao et al., 2007). Moreover, the proportion of Treg cells in the spleens of older C57BL/6J mice is greater than that in the spleens of younger mice (Kawata et al., 2021). During the aging process in humans and mice, the number of naïve Treg cells decreases, while the number of memory Treg cells increases. This dual effect may lead to a decline in immune function in elderly individuals, although aged Treg cells may exhibit an enhanced ability to regulate immune responses. These changes are closely linked to immune aging and the development of related diseases (Rocamora-Reverte et al., 2020). Aging Treg cells exhibit a defective proliferative capacity and display high levels of SA-β-gal activity. Additionally, aging-related genes, including *p16Ink4a*, *p19Arf*, and *p21Cip1*, were upregulated. Compared with young Treg cells, aged Treg cells fail to protect mice from colitis induced by immature T cells. Aged Treg cells express characteristic Treg genes (*Foxp3*, *Tnfrsf18* encoding GITR, *Ikzf2*, *Il2ra*, *Capg*) at normal levels but exhibit increased expression of key inflammatory cytokines (Il1a, Il1b, Il4, Il6, Il17a, Il17f) (Guo et al., 2020).

Tfh and Tfr cells

Tfh cells reside in the lymphoid follicular region of peripheral immune organs. Tfr cells have immunomodulatory functions within GCs, inhibiting GC reactions and interacting with Tfh and B cells to suppress the production of high-affinity antibodies (Ding et al., 2019). The main role of B cells is to assist in the survival, proliferation, and differentiation of B cells in the GCs of lymphoid follicles (Crotty, 2014). In a study on aging in BALB/c mice, it was observed that the number of Tfh cells in the spleens of older mice was lower than that in younger mice, while the number of Tfr cells remained unchanged. Consequently, the proportion of Tfr to Tfh cells significantly increased, resulting in a decrease in the number of splenic B cells. This change was more pronounced in females (Arsenović-Ranin et al., 2019). Similar changes were observed in aging C57BL/6 mice (Bufan et al., 2020). Another study revealed that older mice had a greater proportion of Tfh cells than younger mice, but Tfh cell populations from older mice exhibited increased PD-1 expression and contained more CD153-positive cells. These markers are described as age-related features of T cells. Additionally, the ability of Tfh cells to aid in the production of IgG antibodies by B cells was decreased in older mice (Kawata et al., 2021). In humans, the abundances of Tfh1 and Tfh2 cells largely remain unchanged with age (Huang et al., 2020).

Mechanisms of T-cell aging

Many mechanisms contribute to T-cell aging, including epigenetic inheritance, telomeres, metabolism, oxidative stress, mitochondria, and autophagy. A comprehensive understanding of the regulation and interrelationships among these factors is crucial for elucidating the molecular mechanisms of T-cell aging and establishing a theoretical foundation for preventing and treating related diseases. In this context, we aimed to elucidate the roles of these factors in T-cell aging (Figure 3).

Epigenetics

Epigenetics refers to changes in gene expression or cellular phenotype that can be preserved and inherited through mechanisms other than alterations in DNA sequence. Epigenetic phenomena involve various mechanisms, such as DNA methylation, RNA methylation, RNA interference, nucleosome positioning, chromatin conformational changes, chromatin remodeling, histone modifications, and long noncoding RNA sequences. Epigenetic research primarily focuses on two categories: gene-selective transcriptional regulation, including DNA methylation, genomic imprinting, histone covalent modifications, and chromatin remodeling; and posttranscriptional regulation, including noncoding RNA, microRNA, antisense RNA, introns, and riboswitches in the genome.

Chromatin accessibility

The highly folded chromatin structure plays a crucial role in exposing DNA sequences for replication and transcription. This region, known as the chromatin development region, is closely associated with transcriptional regulation because it allows for the binding of transcription factors and other regulatory elements. When the dense nucleosome structure is disrupted, it creates an accessible region known as open chromatin or chromatin accessibility. Open chromatin encompasses cis-regulatory elements such as promoters, enhancers, insulators, and silencers, as well as trans-acting factors.

The epigenetic state of naïve T cells enables them to remain in a quiescent and viable state while retaining the capacity to proliferate and differentiate upon stimulation (Weng et al., 2012). On the other hand, the chromatin structure provides stability to memory states after antigen clearance. The epigenetic landscape of accessible sites formed in effector T cells is maintained in memory cells for extended periods, serving as a crucial mechanism for immunological memory (Akondy et al., 2017).

In a study, the authors investigated differentially open chromatin sites between TCR-stimulated and unstimulated T cells. The number of differentially active open sites increased over time. Genes associated with T-cell activation, such as TNF, IL2RA, and GZMB, gained chromatin accessibility following TCR stimulation, while quiescent genes such as TCF7 lost accessibility. Changes in chromatin accessibility are closely correlated

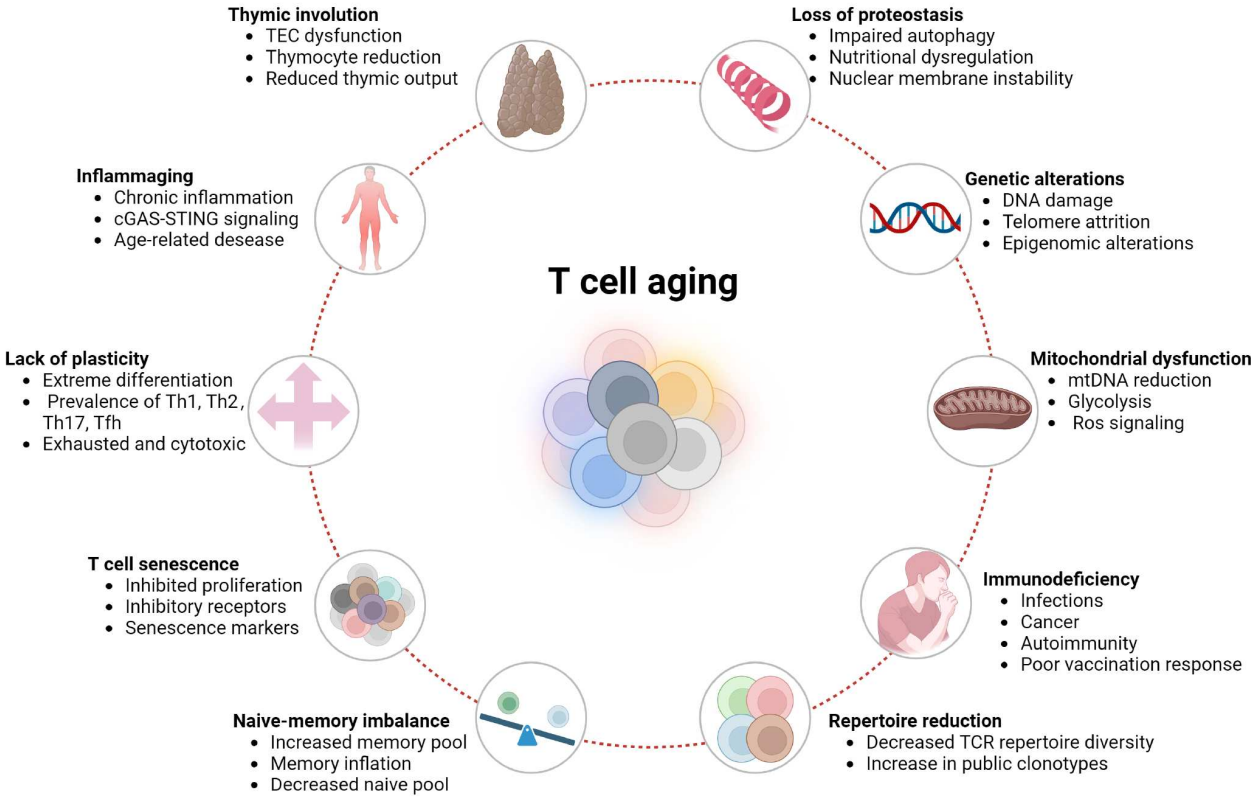

Figure 3. The mechanism of T-cell aging.

with alterations in transcription. However, T cells from elderly individuals exhibited weaker TCR signaling during TCR stimulation, yet they displayed similar temporal patterns in chromatin changes as those observed in younger adults, even with excessive accessibility to bZIP family members after 48 h of stimulation (Zhang et al., 2023).

Significant changes in chromatin accessibility occur during the aging process in $CD4^+$ and $CD8^+$ T cells. These changes in $CD4^+$ T cells are relatively minor compared with those in $CD8^+$ T cells, which undergo extensive chromatin remodeling during aging. This discrepancy is closely associated with the differential rate of aging between $CD4^+$ and $CD8^+$ T cells, with $CD8^+$ T cells experiencing more pronounced changes due to a reduced initial T-cell population after aging (Ucar et al., 2017).

Histone modification

Histone modification is a cellular process that plays a crucial role in regulating gene expression by modifying the structure and function of histones. These modifications encompass a range of chemical reactions, including methylation, acetylation, and phosphorylation, which can impact DNA accessibility and regulate the transcription and posttranscriptional modifications of genes. As a result, histone modifications have significant implications for cellular function and development.

Researchers have compared immune organs in aged and young rats and observed histone modification changes in lymphocytes associated with gene expression and epigenetic regulation. For instance, in aged rats, Suv39h1, a histone methyltransferase, is downregulated in the spleen and thymus, leading to reduced levels of H3K9me3 overall (Sidler et al., 2013).

During acute lymphocytic choriomeningitis virus (LCMV) infection in mice, individual $CD8^+$ T cells were analyzed, revealing that the differentiation of terminal effector cells was initiated by an early burst of transcriptional activity. Subsequently, the epigenetic silencing of transcripts associated with memory lymphocytes is fine-tuned through the histone modification H3K27me3 and the enzyme Ezh2 (Gray et al., 2017).

At the single-cell level, older T cells exhibit increased heterogeneity in histone acetylation, indicating diverse states of activation and differentiation (Goronzy and Weyand, 2019). This suggests that histone acetylation patterns contribute to the variability in T-cell function and differentiation observed in aging individuals.

DNA methylation

DNA methylation refers to the addition of a methyl group to DNA molecules, primarily occurring on cytosine residues in CpG dinucleotides. This modification has a significant impact on gene accessibility, gene transcription activity, and consequently, cellular function and development.

During $CD4^+$ T-cell senescence, there are CpG methylation changes at more than 10,000 sites, while in $CD8^+$ T cells, the changes are even more extensive, affecting more than 40,000 sites (Goronzy and Weyand, 2019). The changes in DNA methylation in senescent $CD4^+$ T cells partially overlap with those observed in senescent $CD8^+$ T cells (Zhu et al., 2018). In both $CD4^+$ and $CD8^+$ T cells, changes in DNA methylation at each specific site are inconsistent. Some sites show increased DNA methylation levels (upregulation), while others exhibit

decreased levels (downregulation) (Roy et al., 2023).

In aging CD8$^+$ TEMRA cells, there are significant alterations in DNA methylation levels. Genome-wide methylation analysis of CD8$^+$ TEMRA cells revealed numerous methylation sites associated with immunosenescence. The methylation levels of these sites are positively correlated with the degree of immunosenescence (Salumets et al., 2022). With increasing age, C57BL mice exhibit hypomethylation of CpG sites on *Foxp3*, accompanied by increased Foxp3 expression and an increased number of Treg cells. Furthermore, Treg cells in older mice exhibit stronger inhibitory effects, as indicated by higher levels of IL-10 production, while dendritic cells express lower levels of CD86 (Garg et al., 2014). Additionally, the DNA methylation levels of certain inflammation-related genes, such as *IL-6* and *IFN-γ*, are influenced by age, potentially leading to an enhanced inflammatory response (Stevenson et al., 2021).

Overall, DNA methylation plays a crucial role in T-cell aging by regulating gene expression and function, thereby influencing the immune response and function of T cells. Analyzing the methylation levels of the ELOVL2 gene and quantifying sjTREC levels in blood samples from individuals of varying ages has proven useful for predicting actual age. These markers provide valuable insights into age prediction (Paparazzo et al., 2022).

MicroRNAs

MicroRNAs (miRNAs) are a class of small noncoding RNA molecules consisting of approximately 20–22 nucleotides. They play a crucial role in posttranscriptional gene regulation by binding to messenger RNA (mRNA) molecules, either inhibiting their translation or promoting their degradation. In the context of T-cell aging, miRNAs have emerged as important regulators of immune function. Studies have revealed that changes in specific miRNAs during T-cell aging contribute to the regulation of immune responses.

One extensively studied miRNA is miR-155, which is upregulated in T cells with age. This upregulation is associated with enhanced inflammatory responses and immune activation. miR-155 is involved in the age-related increase in Toll-like receptor 5 (TLR5) expression, leading to heightened inflammatory responses in aged T cells (Qian et al., 2012).

Another miRNA of interest is miR-181a, which plays a significant role in T-cell development and function. Downregulation of miR-181a in aged T cells contributes to T-cell dysfunction and impaired immune responses (Li et al., 2012). Decreased expression of miR-181a leads to increased activity of bispecific phosphatase 6, which impairs TCR sensitivity.

Overall, miRNAs are key players in the regulatory networks involved in T-cell aging. Changes in miRNA expression, such as the upregulation of miR-155 and downregulation of miR-181a, contribute to altered immune function and the age-associated decline in T-cell responses. Understanding the roles of specific miRNAs in T-cell aging can provide insights into potential therapeutic targets for immune-related disorders associated with aging.

Telomere

As individuals age, the length of telomeres in T cells gradually decreases, which is associated with immunosenescence and an increased risk of disease (Ucar et al., 2017). Telomerase is an enzyme that plays a role in protecting and repairing shortened or damaged telomeres (Cech, 2004). The activity of telomerase in T cells from peripheral blood decreases with age (between 23 and 83 years). However, telomerase activity in centenarians is significantly greater than that in individuals aged 67 to 83 and is comparable to that in individuals aged 50 to 66 (Tedone et al., 2019). Peripheral blood mononuclear cells isolated from healthy individuals show an increasing number of cells with age-related β-galactosidase activity. Among these cells, the CD8$^+$ T-cell population exhibited the greatest age-related increase, with an average proportion of 64% of cells showing high SA-β-Gal activity in donors over 60 years old. CD8$^+$ T cells with high SA-β-Gal activity exhibit senescence induced by telomere dysfunction and p16-mediated senescence, resulting in impaired proliferative capacity (Martínez-Zamudio et al., 2021). In a recent study, it was found that certain APCs deliver telomeres to T lymphocytes through small particles called extracellular vesicles. After telomere transfer, recipient T cells become long-lived and possess memory and stem cell properties, enabling them to provide long-term protection against deadly infections (Lanna et al., 2022).

Metabolism

Naïve T cells are characterized by low metabolic activity and preferentially utilize oxidative phosphorylation (OXPHOS) to generate ATP, maintaining a resting state and homeostasis (Han et al., 2023). However, with age, the failure of NRF1 to maintain promoter opening results in decreased oxygen consumption in senescent CD8$^+$ T cells, impairing their metabolic status and leading to increased cell loss. This metabolic dysfunction hinders vigorous and energy-demanding clonal expansion during immune responses (Moskowitz et al., 2017). Upon antigen stimulation, initial T cells rapidly shift their metabolic mode from OXPHOS to aerobic glycolysis (Chang et al., 2013). During acute infection, the primary metabolic mode of CD8$^+$ T cells transitions from mitochondrial OXPHOS to glycolysis, meeting the bioenergy demands necessary for the activation of initial T cells into effector T cells (Buck et al., 2015). The activation defects observed in aging CD4$^+$ T cells are associated with decreased glycolysis and carbon metabolism. The addition of metabolites to one-carbon metabolism partially restores the activation defect in aging CD4$^+$ T cells (Ron-Harel et al., 2018). It remains to be studied whether naïve CD8$^+$ T cells also experience impaired glycolysis during aging. Fatty acid oxidation (FAO) and OXPHOS are crucial for maintaining the survival and energy requirements of differentiating memory T cells (Corrado and Pearce, 2022). After reaching peak effector differentiation, memory precursor cells shift back to OXPHOS while also gaining the ability to utilize FAO (O'Sullivan et al., 2014; van der Windt et al., 2012). Compared with effector T cells, memory T cells possess greater mitochondrial mass and greater mitochondrial spare respiratory capacity (SRC) (van der Windt et al., 2012). Additionally, in contrast to the small, distinct mitochondria observed in effector T cells, memory T cells maintain a network of fused mitochondria (Buck et al., 2016). Aging memory T cells exhibit lower levels of OXPHOS, decreased proliferative capacity, and impaired cytokine production (Han et al., 2023).

Oxidative stress

Under normal conditions, reactive oxygen species (ROS) are primarily produced by mitochondria at low concentrations and

serve as key signaling molecules in various cellular processes, including cell cycle regulation, survival, and the immune response (Ray et al., 2012). However, excessive production of ROS can lead to oxidative damage to DNA, proteins, and lipids, resulting in cellular dysfunction and aging (Schieber and Chandel, 2014). Telomere shortening is a characteristic feature of T-cell senescence (Ucar et al., 2017). *In vitro* treatment with ROS scavengers prevents telomere shortening in $CD8^+$ T cells (Sanderson and Simon, 2017). Downregulation of DCAF1 in aging Treg cells and decreased ability to control ROS accumulation via GSTP1 leads to abnormal activation of ERK, resulting in deficiencies in proliferative capacity and function. Treatment with ROS scavengers effectively restores the immunosuppressive function of aging and DCAF1-deficient Treg cells (Guo et al., 2020).

Mitochondria and autophagy

Mitochondria play a crucial role in cellular energy production through metabolic pathways such as OXPHOS and FAO. Additionally, mitochondria are involved in various cellular processes, including lipid synthesis, apoptosis, and calcium (Ca^{2+}) homeostasis. Dysfunction of mitochondria is observed in multiple cell types across organisms (Escrig-Larena et al., 2023). Previous studies have demonstrated significant changes in mitochondrial morphology in aging lymphocytes (Beregi et al., 1980). *In vitro* stimulation of naïve $CD4^+$ T cells from young and old mice for 24 h followed by electron microscopy imaging revealed that while the number of mitochondria was similar, the stimulated T cells from older mice exhibited smaller mitochondria with reduced activation and function in response to the stimulus (Ron-Harel et al., 2018). A deficiency in TFAM leads to a substantial decrease in mtDNA content in T cells, impairing the expression of critical components of the electron transport chain and resulting in mitochondrial dysfunction and accelerated aging (Desdín-Micó et al., 2020). Recent research has shown that spermidine can enhance FAO activity in $CD8^+$ T cells by binding to mitochondrial translocating protein (MTP), thereby activating mitochondrial metabolism, improving the antitumor response to PD-L1 in mice, and significantly extending the lifespan of aging mice (Al-Habsi et al., 2022).

T-cell senescence is closely associated with autophagy. A study conducted as part of the Baltimore Longitudinal Study of Aging (BLSA) revealed dysregulation of OXPHOS and energy metabolism-related molecular pathways in $CD4^+$ T cells of older adults, along with impaired mitochondrial respiratory function. Despite similar numbers of mitochondria in the naïve and memory cells of older and younger participants, older individuals exhibited significantly greater quantities of autophagosomes, many of which contained undegraded mitochondria. These findings suggest that the persistence of mitochondrial dysfunction in $CD4^+$ T lymphocytes during aging is linked to defects in mitochondrial turnover caused by autophagy (Bektas et al., 2019). Another recent study demonstrated that age-related ceramide stress in 8-month-old mouse T cells induces mitochondrial dysfunction through PKA inhibition, leading to Drp1 activation and mitochondrial autophagy, which is not observed in young (2-month-old) mice. This impaired mitochondrial autophagy restricts antitumor function. Moreover, inhibition of ceramide synthesis and activation of PKA attenuated mitochondrial autophagy, restored effector T-cell function, and suppressed tumor growth following adoptive transfer of $CD8^+$ T cells isolated from 8-month-old mice (Vaena et al., 2021).

The role of T cells in age-related diseases

The process of human aging is primarily characterized by cumulative cellular aging. T cells, a vital component of the immune system, are responsible for regulating and coordinating immune responses. However, as the body ages, the immune system gradually enters a state of aging, resulting in functional impairments, a decline in immune responses, and the occurrence of induced inflammation (Akbar and Fletcher, 2005). Major changes include a decrease in the number and function of hematopoietic stem cells, a decrease in the proportion of immature T cells, an increase in the proportion of memory T cells, and elevated levels of proinflammatory cytokines (ElyaHu et al., 2019; Mogilenko et al., 2021). Notably, the diminished ability of $CD8^+$ T cells to mount a response to infection is a significant age-related immune change (Blank et al., 2019; Czesnikiewicz-Guzik et al., 2008), which has been observed in humans (Goodwin et al., 2006), mice (Effros and Walford, 1984; Yager et al., 2008), and monkeys (Čičin-Šain et al., 2010). In humans, aging T cells are terminally differentiated T cells known as TEMRA cells. These cells undergo extreme differentiation of memory T cells, lose the expression of the costimulatory molecules CD27 and CD28, and experience T-cell aging and exhaustion (Callender et al., 2018). Furthermore, aging T cells possess a preferential homing ability to peripheral tissues and often accompany the occurrence of induced inflammatory reactions, leading to their classification as pathogenic (Rodriguez et al., 2021).

Recent research reports have highlighted significant changes in chromatin modifications of human immune cell epigenetic phenotypes (Goronzy et al., 2018). Genetic changes have been found to exert a substantial impact on the function of immune cells. For instance, the expression of the IL-7 receptor (IL-7R) and age-dependent IL-8 signals in $CD4^+$ T cells have been observed, and these changes are typically associated with immune cell dysfunction, particularly age-related dysfunction in T cells (Ucar et al., 2017). Experimental studies further revealed that the loss or abnormality of certain genes can result in impaired immune cell function, resembling the characteristics of cellular aging. In mouse experiments, the deletion of menin leads to reduced antigen reactivity in $CD4^+$ T cells and the emergence of a senescence-associated secretory phenotype (SASP) (Kuwahara et al., 2014). The SASP promotes inflammation, drives the differentiation of Th17 and Th1 cells, and ultimately leads to tissue damage (Faust et al., 2020; Mogilenko et al., 2021). Additionally, Carrasco et al. (2022) demonstrated that mice with a specific deficiency in TFAM display several features of immune aging, including impaired TCR-dependent proliferation and the accumulation of highly differentiated T-cell phenotypes. They also found that immune aging is accompanied by premature inflammation, severe cardiovascular and metabolic dysfunction, and cognitive impairments, ultimately resulting in a reduced lifespan in mice (Ekiz et al., 2020). Moreover, senescent T cells primarily produce proinflammatory cytokines such as IFN-γ and TNFα (Kato et al., 2018), which can contribute to a chronic low-grade inflammatory state in elderly individuals even in the absence of infection. It has also been reported that mice subjected to dietary restriction treatment (previously shown to extend

lifespan) exhibit lower levels of TNFα, which may play a role in improving survival rates (Spaulding et al., 1997). These studies underscore the close relationship between inflammation and T-cell function, particularly in the context of T-cell aging. Age-related diseases often manifest as sustained inflammatory processes, and T cells play a crucial role in both initiating and terminating inflammation. They are key players in various age-related diseases, notably neurodegenerative diseases, cardiovascular diseases (CVDs), and diabetes. Therefore, analyzing the relationship between T cells and age-related diseases provides valuable insights. In the following sections, we delve into the specific roles of T cells in different age-related diseases (Table 1).

T cells in autoimmune diseases

The aging process leads to significant dysregulation of the immune system, characterized by immune senescence and chronic inflammation. Immune senescence weakens the body's immune defense against pathogens and tumors, while chronic inflammation increases the risk of autoimmune diseases. Autoimmune diseases are a group of conditions in which the immune system mistakenly attacks its own tissues and organs (Weyand and Goronzy, 2021). Older individuals are more susceptible to developing autoimmune disorders (Yung and Julius, 2008), and previous research has shown that the aging of T cells contributes to the risk of autoimmune diseases (Gray et al., 2006). In the context of autoimmune diseases, the improper activation and differentiation of naïve T cells can lead to the breakdown of immune tolerance and the generation of autoreactive T cells. The differentiation of naïve T cells into Th1 cells can lead to the production of IFN-γ, a cytokine that can exacerbate autoimmune inflammation. Similarly, the Th17 subset, characterized by the production of IL-17, has been implicated in several autoimmune diseases, including psoriasis and multiple sclerosis (van den Broek et al., 2018). On the other hand, the development of Treg cells from naïve T cells is crucial for maintaining immune homeostasis and preventing autoimmunity, as Treg cells suppress the activation and proliferation of other T cells (Lee, 2018).

As individuals age, the recognition and killing abilities of T cells decline, making them more prone to attack their own tissues and increasing susceptibility to autoimmune diseases ('t Hart et al., 2013). The accumulation of $CD28^{-}CD4^{+}$ and $CD28^{-}CD8^{+}$ T cells displaying an aging phenotype has been observed in the peripheral blood of patients with rheumatoid arthritis (RA) (Fasth et al., 2007). Compared with normal $CD4^{+}$ $CD28^{+}$ T cells, $CD4^{+}$ CD28- T cells produce higher levels of IFN-γ and TNF-α, which may play a key role in triggering autoimmune diseases. The authors also observed an enrichment of KLRG1 in the synovial fluid of patients with spondyloarthritis (SPA) and RA. KLRG1-positive T cells were shown to be effective producers of IFN-γ and TNF-α in previous studies (ElyaHu et al., 2019; Hashimoto et al., 2019; Pieper et al., 2014). Furthermore, decreased glycolytic activity has been observed in immature $CD4^{+}$ T cells of RA patients, leading to the accumulation of NADPH and the consumption of ROS, ultimately resulting in abnormal TCA cycle function (Wen et al., 2017; Yang et al., 2013). $CD4^{+}$ T cells accumulate damaged DNA throughout their lifespan, and research has confirmed that the rate of DNA damage accumulation in $CD4^{+}$ T cells is significantly accelerated in patients with RA (Li et al., 2018). This is due to the transcriptional inhibition of DNA repair kinases in patients with mutations associated with endothelial dysfunction-related vascular diseases, which is also a hallmark of T-cell senescence in

Table 1. Summary of T-cell aging-related diseases

Diseases	Changes of T cells	Clinical features	References
Rheumatoid arthritis	$CD4^{+}$ $CD28^{-}$, $CD8^{+}$ $CD28^{-}$ and $KLRG1^{+}$ T cells have increased.	Joint pain, swelling, morning stiffness, and deformity. This condition can lead to complications such as pleurisy and valvular heart disease.	ElyaHu et al., 2019
Multiple sclerosis	Increased expression of PD-1 in $CD57^{+}$ $CD8^{+}$ T cells.	Visual impairment, motor impairment, fatigue, cognitive and emotional impairment.	Bjornevik et al., 2022; Kuchroo and Weiner, 2022; López et al., 2016
IBD	Decreased ratio of $CD8^{+}$ $CD28^{+}$ T cells to $CD8^{+}$ $CD28^{-}$ T cells.	Symptoms such as bloating, abdominal pain, and rectal bleeding.	Dai et al., 2013; De Tena et al., 2004; Schramm-Luc et al., 2018
Cardiovascular diseases	It leads to high levels of TNF-α, IL-6, IFN-γ, and IL-17, accompanied by a decrease in Treg cells that secrete IL-10 and TGF-β.	Chest tightness, shortness of breath, palpitations, sitting upright to breathe, difficulty breathing, rapid heartbeat.	Desdín-Micó et al., 2020; Libby et al., 1995; Wang et al., 2019
Alzheimer's disease	Increased $CD8^{+}$ T cell inflammatory infiltration in the brain, increased TEMRA cell population, and increased secretion of TH17 T cells.	Memory impairment, loss of speech ability, emotional blunting, and labile affect.	Gate et al., 2020; Jorfi et al., 2023; Mietelska-Porowska and Wojda, 2017
Parkinson's disease	Dopamine neurotoxicity mediated by T cells is mainly produced by $CD4^{+}$ T cells, with an increased ratio of Th1 and Th17 cells and a decreased ratio of Th2 and Treg cells.	Bradykinesia, muscle rigidity, resting tremor, and abnormal posture and gait.	Kustrimovic et al., 2018; Mount et al., 2007; Reynolds et al., 2010; Sommer et al., 2018
Obesity	Increased $CD8^{+}$ T cells in adipose tissue, increased IFN-γ^{+} expressing T cells, Th2 cells, and $CD153^{+}$ $PD\text{-}1^{+}$ $CD44^{+}$ $CD4^{+}$ T cells.	The body fat percentage has exceeded the diagnostic criteria (male body fat percentage >25%, female >30%).	Ahnstedt et al., 2018; Bapat et al., 2015; Jiang et al., 2014; Lumeng et al., 2011
Diabetes/insulin resistance	Increased Th1 and Th17 cells, decreased Treg cells, increased TEMRA cells, increased TNF-α, IL-6, IL-1β in adipose tissue.	Drink more water, eat more, urinate more, and lose weight.	Coope et al., 2016; Galicia-Garcia et al., 2020; Hotamisligil et al., 1993; Lau et al., 2019; Zeng et al., 2012
Tumors Breast cancer/prostate cancer/ lung cancer	The T cells lose CD28, but show increased expression of KLRG1, CD57, PD-1 and CTLA-4, and secrete more immunosuppressive cytokines.	Presence of a lump or mass in the breast/ difficulty urinating, decreased urine flow/ cough, coughing up blood-tinged sputum.	Chen and Mellman, 2017; Grosso and Jure-Kunkel, 2013; Hurez et al., 2012; Klebanoff et al., 2006; Pereira et al., 2020

RA patients (Shao et al., 2010). Increased expression of PD-1 has also been detected in $CD57^+CD8^+$ T cells in another autoimmune disease, multiple sclerosis (Cencioni et al., 2017). Similarly, these cells with evident aging phenotypes are unable to control the replication of EBV, which is considered a definitive trigger for multiple sclerosis (MS) (Bjornevik et al., 2022; Kuchroo and Weiner, 2022). In $CD4^+$ T cells from aged humans and mice, the regulatory subunit KU complex of the DNA-dependent protein kinase (DNA-PK) is able to recognize the accumulation of cytosolic DNA. This process enhances T cell activation and pathology in experimental autoimmune encephalomyelitis (EAE) in aged mice (Wang et al., 2021). A significant increase in $CD4^+$ $CD28^-$ T cells displaying an aging phenotype has also been observed in patients with systemic lupus erythematosus (SLE) (Kalim et al., 2021; López et al., 2016), and the percentage of aging T cells is significantly correlated with SLE activity and disease severity (Kalim et al., 2021; Ugarte-Gil et al., 2016). Finally, an increase in $CD4^+$ $CD28^-$ and $CD8^+$ $CD28^-$ T cells has been observed in patients with inflammatory bowel disease (IBD) (De Tena et al., 2004; Kobayashi et al., 2007). The ratio of $CD8^+CD28^+$ T cells to $CD8^+CD28^-$ T cells is often used as an important indicator for assessing the severity of IBD in clinical evaluations, indicating that aging T cells can impact the progression of IBD (Dai et al., 2017; Dai et al., 2013). Additionally, the size and function of the naïve T-cell pool are also critical factors in autoimmune diseases (Jia et al., 2023). With aging, the ability of the thymus to produce new naïve T cells declines, leading to a reduced naïve T-cell repertoire. This reduction can impair the immune system's capacity to respond to new antigens and may contribute to the increased incidence of autoimmune diseases in older individuals (Jia et al., 2023; Mao et al., 2024). A reduction in naïve T cells may lead to a decrease in immune system tolerance to self-tissues, increasing the activity of autoreactive T cells, which can trigger or exacerbate the disease. Aging T cells have been found to be associated with the severity of other autoimmune inflammatory diseases, including ankylosing spondylitis, juvenile idiopathic arthritis, and psoriasis (Lima et al., 2015; Schramm-Luc et al., 2018). In conclusion, there is a close relationship between aging T cells and autoimmune diseases. A decrease in function, a decrease in quantity, and a disturbance in immune tolerance in aging T cells all contribute to an increased risk of developing autoimmune diseases. However, further research is needed to elucidate and confirm the specific underlying mechanisms and impacts involved.

T cells in cardiovascular disorders

T-cell aging has been implicated in chronic inflammation, which, in turn, can contribute to vascular wall damage and the formation of plaques. As such, aging T cells may play a significant role in the development of CVD. CVD is a leading cause of death and disability worldwide, with the number of affected individuals increasing from 271 million in 1990 to 523 million in 2019 (Song et al., 2020). Inflammation has emerged as a key driver and primary therapeutic target in CVD over the past few decades (Lusis, 2000; Tardif et al., 2019). The disease involves complex interactions between vascular endothelial cells and the immune system, ultimately leading to cardiac and arterial pathology. The primary cause of CVD is typically the excessive accumulation of lipids and cholesterol on the arterial wall (Lusis, 2000).

Recent studies have indicated a correlation between naïve T cells and CVD (Kose et al., 2018). CVDs are often associated with chronic inflammation, and naïve T cells play a crucial role in initiating and regulating inflammatory responses. Naïve T cells can differentiate into Th1 cells that produce IFN-γ, a cytokine that is associated with the development of atherosclerosis. Additionally, naïve T cells may also differentiate into Treg cells, which help maintain immune tolerance and prevent excessive immune responses from damaging the cardiovascular system (Lee, 2018). Aging T cells can secrete proinflammatory cytokines such as TNFα and IL-6 and enhance macrophage recruitment, thereby promoting foam cell formation in atherosclerotic lesions (Galkina and Ley, 2009). Previous studies have confirmed the involvement of T cells in the progression of atherosclerotic lesions. For instance, T cells infiltrating the affected area can promote the production of inflammatory molecules (e.g., IFN-γ) and inflammatory cytokines (e.g., IL-10) (Libby et al., 1995; Seko et al., 1997). In aged mice, the accumulation of $CD4^+IFN\gamma^+$ T cells in the heart and lymph nodes induces inflammation, leading to myocardial damage (Ramos et al., 2017). The peripheral blood of elderly individuals also contains an increased number of $CD4^+$ T cells that produce high levels of IL-17 and IFN-γ, along with clear signs of aging (Wang et al., 2019). Age-related cardiovascular changes have also been observed in mice with premature T-cell aging caused by mitochondrial dysfunction (Desdín-Micó et al., 2020). As age increases, thymic function declines, leading to a reduced production of naïve T cells. This can weaken the immune system's ability to respond to new antigens and simultaneously decrease the protective effect on the cardiovascular system (Mao et al., 2024). Therefore, maintaining a healthy pool of naïve T cells is important for preventing CVD.

Studies have shown that Treg cells can secrete cytokines such as IL-10 and TGF-β, thereby inducing macrophages to differentiate into the M2 type. The enrichment of reparative M2 macrophages in plaques is a hallmark of atherosclerosis regression (Ait-Oufella et al., 2006; Feng et al., 2009). The overexpression of autophagy-related protein 14 (ATG14) can inhibit the accumulation of p62, promote Treg differentiation, and increase the quantity of Treg cells, thereby reducing inflammation and lesions in atherosclerosis. Conversely, weakened autophagy has been observed in aging T cells, which may contribute to the reduced number of Treg cells in elderly individuals (Zhang et al., 2021). Simiao Yong'an decoction, a traditional Chinese herbal medicine, has also been shown to improve atherosclerotic lesions by reducing the infiltration of inflammatory macrophages and increasing the number of Treg cells (Chen et al., 2021). Furthermore, a significant positive correlation has been reported between a reduction in CD69 levels in T cells, the emergence of inflammatory cytokines, and the risk of human clinical atherosclerosis (Tsilingiri et al., 2019). Recent research has further revealed that in the angiotensin II model, transferring aged T cells from old mice to young mice results in damage to the heart and kidneys through increased secretion of IFN-γ, thereby promoting inflammation and fibrosis (Pan et al., 2021).

In summary, these studies clearly demonstrated that T-cell-mediated immune alterations and changes in T-cell subsets are major regulatory factors in the pathogenesis of atherosclerosis and CVD.

T cells in neurodegenerative disease

The blood-brain barrier (BBB) plays a crucial role in maintaining homeostasis in the brain. As a highly sensitive organ, the brain is susceptible to irreversible damage from foreign substances or immune reactions. Under normal circumstances, the BBB acts as a protective barrier, preventing the entry of peripheral immune cells, including T cells, into the brain and safeguarding it from potential threats from the external environment (Da Mesquita et al., 2018). Due to the robust defense provided by the BBB, the brain is considered one of the most isolated organs from the external environment.

The BBB is formed by specialized brain endothelial cells (BECs) that line the lumen of brain capillaries and tightly regulate the entry of molecules and cells into the central nervous system (CNS). BECs are blocked by tight junction proteins (such as claudins and occludin) and adherens junction proteins (such as VE-cadherin) (Castro Dias et al., 2019; Engelhardt et al., 2017). These proteins contribute to the barrier properties of the BBB and collectively form what is known as the neurovascular unit (Louveau et al., 2018). However, recent studies have suggested that the function of the BBB can be influenced by certain factors, resulting in a loss of strict control over peripheral immune cells. Aging is an important factor that contributes to BBB breakdown (Louveau et al., 2018). Research has also indicated that age-related neurodegenerative diseases may exacerbate BBB dysfunction (Ferretti et al., 2016).

As individuals age, the integrity of the BBB gradually deteriorates, allowing peripheral immune cells, including T cells, to enter the brain. This breakdown in BBB integrity leads to a decline in brain function and the onset of neurodegenerative diseases (Sweeney et al., 2018). Notable examples of such diseases include Alzheimer's disease (AD) (Berente et al., 2022) and Parkinson's disease (PD) (Thomas, 2009), among others. In addition, emerging evidence suggests that the immune system, including the activity of naïve T cells, may contribute to the pathogenesis of neurodegenerative diseases (Kanematsu et al., 2015). The relationship between naïve T cells and neurodegenerative diseases is multifaceted. Upon antigen exposure, naïve T cells can differentiate into various effector T cells, which can then traffic to the CNS, where they may influence neuroinflammation (Bödvarsson, 2007). For instance, some naïve T cells can differentiate into Th1 cells that produce proinflammatory cytokines, such as IFN-γ, which can exacerbate neuroinflammation and contribute to neuronal damage (Lee, 2018; Valldeperas et al., 2011).

AD is an age-related neurodegenerative brain disorder and the most common neurodegenerative disease among the elderly population (Bondi et al., 2017). Its primary features include intracellular neurofibrillary tangles (NFTs) and extracellular deposition of amyloid-beta (Aβ) plaques (DeTure and Dickson, 2019; dos Santos Picanco et al., 2018). Despite significant efforts to understand the pathogenesis of AD, most clinical trials related to this disease have failed, highlighting the urgent need to explore alternative potential mechanisms (Serpente et al., 2014).

Neuroinflammation in AD is generally believed to be mediated by microglia and astrocytes, but emerging evidence suggests that T cells also play a role in regulating the inflammatory response in AD (Togo et al., 2002). Chi et al. reported that Aβ plaques may induce the proliferation of proinflammatory microglia and that $CD8^+$ T cells accumulate in later stages, reducing microglial inflammation and preventing further formation of Aβ plaques (Su et al., 2023). However, another study conducted by a team at Massachusetts General Hospital in the United States using a 3D human neural-immune model revealed that under pathological conditions of AD, $CD8^+$ T cells infiltrate the brain and induce neuroinflammation mediated by astrocytes, resulting in more severe damage to neurons and astrocytes (Jorfi et al., 2023). Additionally, T-cell infiltration has been observed in postmortem brain tissues of AD patients (Togo et al., 2002).

Patients with AD exhibit increased levels of $CD8^+$ and $CD4^+$ effector memory and late-stage effector T cells in their cerebrospinal fluid, while central memory T cells are reduced. AD patients also show an increased presence of TEMRA cells, characterized by enhanced TCR signaling and a negative correlation with cognitive decline (Gate et al., 2020; Mietelska-Porowska and Wojda, 2017). Studies in mouse models have demonstrated that β-amyloid can promote T-cell infiltration and disrupt normal T-cell functions, including activation and antigen presentation, leading to an impaired ability of T cells to generate protective immune responses in AD (Ferretti et al., 2016). Furthermore, cytokines secreted by T cells can affect the functions of chemokines expressed by local astrocytes in inflammation and neurodegenerative diseases (Williams et al., 2020a). T cells in AD patients exhibit greater levels of activation than those in healthy controls, further promoting the release of proinflammatory cytokines that impact the pathological process of AD (Mietelska-Porowska and Wojda, 2017).

Mouse studies have shown that mice lacking T and B cells exhibit altered learning behavior while retaining motivation. Mice lacking T cells and B cells also exhibit changes in learning and memory abilities without altered exercise capabilities (Brynskikh et al., 2008; Kipnis et al., 2004). Additionally, the cognitive impairments observed in mice with IL-4 deficiency can be improved by the use of T cells from wild-type mice (Derecki et al., 2010). Moreover, T cells are associated with TAU protein pathology. In the brains of AD patients, particularly in the hippocampus, there is a strong association between T cells and Tau pathology (Merlini et al., 2018). Previous studies have also confirmed a positive correlation between T-cell infiltration and P-TAU levels in the superior temporal gyrus and middle temporal gyrus in AD patients (Laurent et al., 2017). This evidence collectively indicates the involvement of T cells in the disease progression of AD and their critical regulatory role.

PD is a neurodegenerative disorder characterized by the gradual loss of dopaminergic neurons in the brain (Thomas, 2009). Pathological studies have shown that patients with PD exhibit excessive activation of microglia in the brain and elevated levels of cytokines in the cerebrospinal fluid (Boka et al., 1994; Dobbs et al., 1999), suggesting the presence of chronic inflammation in the brains of PD patients. Previous studies have confirmed the early infiltration of $CD4^+$ and $CD8^+$ T cells in the brains of animal models overexpressing a-Syn (Sanchez-Guajardo et al., 2010). T cells from severe combined immunodeficiency (SCID) mice have also been shown to be relatively resistant to MPTP-induced substantia nigra (SN) degeneration (Benner et al., 2008), indicating that T cells can enhance cytotoxicity. Additionally, compared with normal mice, immune-deficient mice (RAG1 and TCRB mice) exhibited a significant decrease in dopamine neuron death after MPTP induction (Brochard et al., 2008). However, in MPTP-induced mice, the proportion of dopaminergic neuron cell death was not significantly reduced in

mice lacking $CD8^+$ T cells. These studies suggest that $CD4^+$ T cells may play a relatively important role in promoting neurodegeneration via the nigrostriatal pathway. Further research revealed that $CD4^+$ T cells predominantly contribute to T-cell-mediated dopaminergic neurotoxicity (Jorfi et al., 2023), a conclusion that has been validated in animal models (Reynolds et al., 2010) and clinical data (Sommer et al., 2018).

The specific $CD4^+$ T-cell subset that regulates MPTP-induced cytotoxicity in mice is still unclear. Th1 cells can exert cytotoxic effects on dopaminergic neurons by releasing IFN-γ, which activates and recruits other immune cells to amplify local inflammation (Mount et al., 2007). Additionally, Th17 cells can promote neurotoxicity by secreting IL-17 or releasing GZMB, a cell lytic enzyme (Kebir et al., 2007). The proinflammatory effects of Th1 and Th17 cells were further confirmed in the MPTP mouse model. When naïve $CD4^+$ T cells are treated with a-synuclein, they polarize toward Th1 or Th17, resulting in the degeneration and death of SN neurons and dopamine neurons (Reynolds et al., 2010). Chen et al. (2015) observed that PD patients have an increased ratio of Th1 and Th17 cells compared with healthy controls but a significant decrease in the absolute number and ratio of Th2 (Kustrimovic et al., 2018) and Treg cells (Reynolds et al., 2010). Reynolds et al. further demonstrated the neuroprotective effects of Treg cells in an MPTP-induced mouse model of PD. After transferring Treg cells into MPTP-induced mice, clear dose-dependent protection of dopamine neurons was observed (Chen et al., 2003), possibly through attenuation of the neurodegeneration mediated by Th17 or Th1 cells (Reynolds et al., 2010). These findings collectively indicate that T cells play important roles in mediating cytotoxicity and neuroprotective effects in PD models. Therefore, gaining a better understanding of the initiating signals and specific mechanisms by which T cells mediate PD may provide new therapeutic opportunities for PD patients.

T cells in metabolic dysfunction

During the aging process, the excessive accumulation of fat often leads to a chronic metabolic disease that is typically caused by energy intake exceeding energy expenditure (Hotamisligil, 2017). This condition is characterized by weight gain and fat accumulation in the abdomen, buttocks, thighs, and other areas and is accompanied by a series of health problems, such as IR (Mehta et al., 2015), diabetes (Nishimura et al., 2009; Rocha et al., 2008), and obesity (Jagannathan-Bogdan et al., 2011). Studies have shown that T cells in adipose tissue may play an important role in regulating energy metabolism and immune function (Grover et al., 2015; Lim and Meigs, 2014). In middle age, the ability of subcutaneous adipose tissue to store lipids decreases (Jensen, 2008), resulting in excess fat being transferred to visceral adipose tissue, leading to visceral obesity (Kuk et al., 2009; Mraz and Haluzik, 2014). Excessive lipid accumulation in visceral adipose tissue and the surrounding tissue microenvironment may increase the number of immune cells and play a critical role in immune-metabolic homeostasis (Nosalski and Guzik, 2017).

Obesity can lead to accelerated immune aging, a phenotype commonly observed in older individuals (Bektas et al., 2017; Yang et al., 2009), which has also been found in obese children (Spielmann et al., 2014). In addition, obesity can result in poor vaccine efficacy (Painter et al., 2015; Park et al., 2014), as studies have shown a correlation between increased body mass index (BMI) and decreased influenza-specific antibody titers one year after vaccination (Park et al., 2014). Xiao et al. (2023) reported that after vaccination with excess SARS-CoV-2 vaccine, it takes longer for elderly individuals to reach a neutralizing antibody level similar to that of young people. Recent reports indicate that a significant increase in T cells in adipose tissue is associated with aging. Aged mice show an increased ratio of $CD4^+$ T cells to $CD8^+$ T cells, with the increase in $CD8^+$ T cells being greater than that in $CD4^+$ T cells (Jiang et al., 2014; Lumeng et al., 2011). Additionally, an increase in $CD8^+$ T cells expressing IFN-γ and activated $CD4^+$ T cells is observed in aged mouse adipose tissue (Ahnstedt et al., 2018; Bapat et al., 2015), similar to the T-cell phenotype changes induced by obesity. Furthermore, obesity accelerates T-cell aging in the visceral adipose tissue of mice (Shirakawa et al., 2016), as evidenced by the accumulation of $CD153^+PD\text{-}1^+CD44^+CD4^+$ T cells in obese mice, resembling the phenotype of age-related T cells (Shirakawa et al., 2016). These changes in $CD4^+$ T cells resemble the alterations observed in senescence-associated T cells during the aging process.

Adipose tissue T (ATT) cells are present in visceral fat during normal aging (Lumeng et al., 2011). The role of ATT cells in obesity-induced inflammation has also been documented. Recent studies have reported that changes in T-cell homeostasis in individuals with obesity may be attributed to a decrease in Th2 cells and an increase in $CD8^+$ T cells (Feuerer et al., 2009; Winer et al., 2009). Additionally, the number of Treg cells decreases with obesity, which may contribute to excessive immune activation. Researchers have also observed a decrease in the proportion of naïve T cells and an increase in the number of memory T cells in the adipose tissue of aged mice (Mauro et al., 2017). Compared with those from lean mice, ATT cells from obese mice produce higher levels of proinflammatory mediators such as IFN-γ and GZMB (Lumeng et al., 2011). This finding is consistent with previous reports that T cells from healthy elderly individuals secrete higher levels of cytokines (TNF-α and IL-6) than those from young individuals.

With the increase in the prevalence of obesity, the worldwide incidence of diabetes has dramatically increased. Diabetes is one of the major health problems of the 21st century, with one in every 11 adults affected by the disease (Williams et al., 2020b). Type 2 diabetes (T2D) is the most common type of diabetes, accounting for approximately 90% of all cases globally (Khan et al., 2020). IR, often associated with obesity, increases susceptibility to T2D, which is characterized by impaired insulin secretion, glucose intolerance, and high blood sugar (Guzmán-Flores and López-Briones, 2012). There is increasing evidence that T cells play a pathological role in diabetes and IR. T2D can induce hyperglycemia and trigger IR, leading to compensatory overproduction of insulin in the body, ultimately resulting in β-cell exhaustion (Coope et al., 2016). A large body of data indicates a strong pathogenic link between obesity, IR, and T2D (Nikolajczyk et al., 2011; Roden and Shulman, 2019). In this process, T cells play a crucial role (McLaughlin et al., 2017), first by inducing a chronic state of low-grade systemic inflammation in response to obesity and, second, by excessive production of inflammatory mediators such as TNF-α, IL-6, MCP, and IL-1β in adipose tissue. Once released, these proinflammatory cytokines interfere with insulin signaling in insulin-responsive tissues (such as the liver and skeletal muscle) and impair pancreatic β-

cell function, ultimately leading to defective insulin secretion (Coope et al., 2016; Galicia-Garcia et al., 2020). Previous studies have demonstrated increased expression and production of TNF-α in the blood and adipose tissue of T2D patients (Hotamisligil et al., 1993), which can activate intracellular transduction cascades and interfere with insulin signaling by inhibiting insulin receptor substrate 1 (IRS-1) (Hotamisligil et al., 1996). Additionally, it has been reported that the levels of the proinflammatory cytokines Th1 (McLaughlin et al., 2014) and Th17 (Garidou et al., 2015) are increased in the adipose tissue and blood of T2D patients. In obese mouse models, Th1 cells can induce IR, while reducing the number of Th17 cells can improve glucose homeostasis (Sumarac-Dumanovic et al., 2013). In humans, Treg cells appear to be reduced in the blood of more obese subjects than in that of leaner subjects and are negatively correlated with BMI and plasma leptin levels (van der Weerd et al., 2012). The number of Treg cells in the blood of T2D patients is also lower than that in nondiabetic individuals, while the numbers of Th1 and Th17 cells are increased, indicating a proinflammatory shift in T cells in T2D patients (Zeng et al., 2012). Recent research has also shown that transferring T cells from the adipose tissue of obese mice to that of lean mice causes inflammation and IR. Conversely, removing senescent T cells from the adipose tissue of obese mice can significantly improve insulin sensitivity (Shirakawa et al., 2016; Yoshida et al., 2020). Additionally, the numbers of functionally impaired senescent $CD4^+$ and $CD8^+$ TEMRA cells are significantly increased in the circulation of T2D patients (Lau et al., 2019). In addition to changes in conventional T cells, studies have shown increased γδ T cells and decreased iNKT cells in the adipose tissue of obese patients, and both subsets play a role in the development of IR (Kohlgruber et al., 2018; Mehta et al., 2015).

T cells in tumors

With aging, the incidence of cancer increases significantly (López-Otín et al., 2023). Among the elderly population, cancer is not only more common but also often has a poorer prognosis. In recent years, an increasing number of studies have shown that aging of the immune system, particularly T-cell senescence, plays a key role in this process (Hong et al., 2019; Yang et al., 2022; Zhou et al., 2022a). A decrease in immune function due to T-cell senescence is a significant factor in tumor immune evasion and maintenance of a suppressive TME (Hasegawa et al., 2023; Staber et al., 2019; Wang et al., 2022). Meanwhile, the extracellular signals in the TME of the elderly drive the tumor-infiltrating age-related dysfunctional (T_{TAD}) cell state, and these cells may promote the progression of tumors in the elderly (Chen et al., 2024).

During the process of organismal aging, T cells undergo multiple divisions and activations and then enter a state of functional decline (Effros, 2005). Senescent T cells typically exhibit a loss of CD28, along with increased expression of KLRG1 and CD57 (Effros, 2005). These changes make it difficult for T cells to proliferate effectively and carry out immune functions. Moreover, the proliferative capacity of senescent T cells is significantly reduced, with diminished responsiveness to antigens and decreased cytotoxicity (Akbar and Henson, 2011). Additionally, the profile of cytokines secreted by these cells also changes, and these cells tend to secrete more inhibitory cytokines (Lages et al., 2008). Additionally, studies have reported that the metabolic functions of T cells from elderly individuals are significantly altered, characterized by mitochondrial dysfunction and changes in glucose metabolism, which further limit the functionality of T cells (Henson et al., 2014).

Due to their functional decline, aging T cells are unable to effectively recognize and kill tumor cells, leading to the evasion of tumor cells from immune surveillance (Pawelec et al., 2010). Moreover, the expression of immune checkpoint molecules such as PD-1 and CTLA-4 on senescent T cells is increased, further suppressing their antitumor activity (Pereira et al., 2020). Senescent T cells maintain a suppressive tumor microenvironment by secreting inhibitory cytokines (such as IL-10 and TGF-β) and expressing inhibitory receptors (such as PD-1 and CTLA-4) (Jiang et al., 2015). This environment not only hinders the antitumor functions of other immune cells but also promotes the growth and metastasis of tumor cells. Studies have shown that senescent T cells may promote tumor growth and metastasis by secreting proinflammatory cytokines (such as IL-6) (Campisi, 2013; Li et al., 2022). These proinflammatory factors not only directly stimulate tumor cells but also indirectly promote tumor progression by affecting other cell types in the tumor microenvironment, such as fibroblasts and endothelial cells (Freund et al., 2010).

In the elderly population, T-cell senescence is closely associated with the incidence and prognosis of various cancers. Studies have shown that T cells from elderly breast cancer patients exhibit significant signs of senescence, and these patients generally have a poorer prognosis (Pereira et al., 2020). High expression of PD-1 on senescent T cells is closely related to immune evasion and tumor progression (Klebanoff et al., 2006). T cells from elderly prostate cancer patients also show significant signs of senescence, including loss of CD28 and increased expression of KLRG1 (Hurez et al., 2012). These senescent T cells are unable to effectively kill prostate cancer cells, leading to accelerated disease progression. Furthermore, research has shown that the expression of PD-1 and CTLA-4 on senescent T cells from prostate cancer patients is significantly increased, which further inhibits their antitumor activity (Grosso and Jure-Kunkel, 2013). In elderly lung cancer patients, T-cell senescence is associated with high expression of immune checkpoint molecules, such as PD-1 (Pereira et al., 2020). These senescent T cells not only are functionally impaired but also maintain a suppressive tumor microenvironment by secreting inhibitory cytokines, such as IL-10 and TGF-β (Chen and Mellman, 2017). The combined effect of these factors leads to a poorer response to immunotherapy in elderly lung cancer patients (Dunn et al., 2002). In summary, T-cell senescence plays a crucial role in tumor immune evasion and the tumor microenvironment and is an important factor contributing to the increased incidence of cancer in elderly individuals. Future research should further explore the molecular mechanisms underlying T-cell senescence and work toward developing novel therapeutic strategies to counteract or decelerate the aging process of T cells.

T cells in anti-aging applications

As human life expectancy continues to increase, there is an urgent need to understand the mechanisms of aging and develop methods to delay it. Changes in the immune system can contribute to the aging of other tissues and can lead to increased disease and premature death. Research has demonstrated that

the knockout of the Ercc1 gene in hematopoietic cells of mice results in premature immune aging in adulthood. This aging process is characterized by the loss and aging of specific immune cell populations, as well as impaired immune function, similar to the changes observed in naturally aging mice (Yousefzadeh et al., 2021). These manifestations include a significant decrease in the number of immune cells, with the number continuing to decline with age. The spleen and thymus also experience reduced weight, and there is a significant increase in the expression of cell aging markers (p16, p21) and the SASP. It is important to note that the aging and oxidative stress observed in gene knockout mice also cause damage to other normal tissues, suggesting that aging immune cells can promote systemic aging. Targeting T cells and overcoming their exhaustion during aging are highly important because of their crucial role in driving organismal senescence and the aging of other organs. The prevailing view is that T cells delay aging by activating telomerase (Lanna et al., 2014). However, recent reports have revealed a new pathway independent of telomerase, in which some T cells (particularly naïve and central memory cells) can extend telomeres by acquiring telomere-containing vesicles from APCs (Lanna et al., 2022). The research team also confirmed that telomere-containing extracellular vesicles can be purified from blood and, when added to T cells, exhibit anti-aging activity in the immune system of humans and mice. The aging of immune cells can significantly accelerate the aging process, leading to adverse effects on both quality of life and lifespan. It can alter the entire physiological process of the human body, thus having a major impact on overall health. Researchers found that treating gene knockout mice with rapamycin reduced the expression of aging markers in immune cells, improved immune function, and enhanced the immune function of mice, demonstrating that immune aging can be regulated. Furthermore, when spleen cells from gene knockout mice or normally aged mice were transplanted into young mice, the aging process in the recipient mice accelerated. However, when spleen cells from normal young mice were transplanted into gene knockout mice, the aging process was found to slow (Yousefzadeh et al., 2021). This further illustrates that aging immune cells promote systemic aging, while transplanting young immune cells can delay aging. In a mouse model study conducted in Japan, mice with early reproductive ability and rapid apoptosis were found to undergo overall aging. Additionally, it was discovered that some supercentenarians (individuals over 100 years old) have a greater presence of T cells and greater expression of the CRELD1 gene, which is believed to be the main reason for their healthy state and longevity (Bonaguro et al., 2020). Another article provides detailed reports on how the absence of TFAM in mouse T cells leads to mitochondrial dysfunction, accelerates aging, and results in premature death in mice (Desdín-Micó et al., 2020). A decrease in this type of mitochondria is associated with the distortion of Th1 cells, characterized by the excessive secretion of the proinflammatory cytokines IFN-γ and TNF-α, as well as the expression of the Th1 cell regulator T-bet. In addition to this proinflammatory phenotype, these $CD4^{Cre}$ mice exhibit immune defects that normally only appear in normal mice at 22 months of age. Subsequently, researchers injected etanercept, a drug that can prevent T cells from releasing the cytokine TNF-α, into $Tfam^{fl/fl}CD4^{Cre}$ mice. After a few weeks, mouse muscle strength, cognitive function, and heart function improved (Desdín-Micó et al., 2020). These results indicate that defects in T cells accelerate the aging of T lymphocytes in the human body. The above findings indicate that the aging of immune cells plays a crucial role in overall aging and that maintaining the quantity and activity of immune cells in the body is of significant importance in combating aging. When immune cells in the body undergo aging, strategies such as telomerase activation, small molecule drugs, or cell therapy can be employed to reverse aging. If these methods can be successfully applied to T cells, they may provide new opportunities for restoring exhausted T cells. In conclusion, gaining a deeper understanding of T-cell exhaustion and aging processes will contribute to the development of more effective treatment strategies.

Despite the potential of the aforementioned regimens in certain cancer treatments, the application of such methods in the field of anti-aging is still in its infancy. Moreover, when considering the application of T cells for anti-aging purposes, it is essential to weigh the potential benefits against the risks. T-cell therapies may trigger a range of side effects, including cytokine release syndrome (CRS), autoimmune reactions, and a potential risk of carcinogenesis (Koppelman et al., 2004; Latner et al., 2004). Additionally, the long-term consequences of T-cell therapy are not yet fully understood, and long-term follow-up studies are needed to assess their safety and efficacy. Furthermore, due to genetic and phenotypic differences among individuals, anti-aging T-cell therapy may necessitate a personalized approach. This means that treatment strategies need to be tailored to an individual's immune status, health condition, and specific disease risks. The implementation of personalized medicine will face significant technical and economic challenges (Galderisi et al., 2018; Vogelsang et al., 1994). Finally, the application of T cells for anti-aging purposes may also involve a series of ethical issues (Ishida et al., 2014; Yu et al., 2018). For instance, who will have access to such treatments? How will the costs of treatment be distributed? Are there trade-offs between extending lifespan and improving quality of life? These questions require the collective discussion of policymakers, healthcare professionals, and the public at large.

Therefore, future research on the application of T cells for anti-aging purposes should focus on the following areas. First, more basic research is needed to elucidate the mechanisms by which T cells are involved in the aging process. Second, clinical trials are required to assess the safety and efficacy of T-cell therapies. Third, interdisciplinary collaboration is necessary to address the issues of personalized medicine and ethics. Finally, public education is needed to increase awareness of immunosenescence and T-cell treatments. Once these issues are resolved, it is believed that this discovery will drive another transformation in human medical technology.

Conclusion and perspectives

As the body ages, the immune system gradually erodes, and T-cell aging has emerged as a crucial issue with significant implications for immune function and human health. During development, T cells undergo differentiation from immature cells to mature cells. However, as age progresses, the thymus continues to shrink, resulting in the production of fewer immature T cells (Taams and Taylor, 2023). Additionally, other immune organs also undergo degenerative aging, leading to changes in the number and function of different T-cell subsets, ultimately culminating in immune senescence. Immunosenes-

cence is characterized by progressive functional decline and enhanced autoimmunity, which renders individuals more susceptible to infections and cancer and reduces vaccine efficacy (Akbar and Fletcher, 2005). Moreover, aging of $CD4^+$ T cells can trigger chronic inflammation and exacerbate systemic aging phenotypes, suggesting that T-cell aging can contribute to systemic aging and the development of age-related diseases, including CVD, neurodegenerative diseases, T2D, and autoimmune diseases. Therefore, current research on T-cell aging should primarily focus on understanding the relative importance of various changes occurring during the aging process of T cells, determining their interrelationships, and distinguishing primary from secondary changes. This will enable the identification of optimal molecular targets that can slow or interrupt the aging process.

Currently, several therapeutic approaches targeting T cells have shown initial efficacy in age-related diseases. One promising therapy, calledenolytics, induces the death of aging cells by targeting apoptosis and protein modification, thus selectively eliminating aging T cells in the body. These findings present a new avenue for the clinical treatment of CVD (Goronzy and Weyand, 2019). Recent studies have also highlighted age-related dysfunctional T cells as therapeutic targets for age-related diseases (Serrano, 2017). However, the current research is primarily focused on determining the associations between T cells and these diseases. The precise mechanisms through which T cells influence the processes of these age-related diseases or how changes in these diseases impact T-cell aging remain unknown. Addressing these questions will significantly enhance our understanding of the mechanisms underlying T-cell aging and may pave the way for the development of targeted drugs in this field.

Compliance and ethics

The authors declare that they have no conflict of interest.

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