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Review Article

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Metabolic Signaling as a Driver of T Cell Aging

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The authors declare no potential conflicts of interest.

Abbreviations
A2AR, A2A receptor; AMP, adenosine monophosphate; AP-1, activating protein-1;

ABSTRACT

Aging significantly diminishes T cell immunity, increasing susceptibility to infections and reducing vaccine efficacy in older individuals. Metabolism plays a key role in T cell function, shaping their energy requirements, activation, and differentiation. Recent studies highlight altered metabolic signaling as a pivotal factor in T cell aging, influencing the ability of T cells to maintain quiescence, respond to activation, and differentiate into functional subsets. Aberrant metabolic pathways disrupt the quiescence of aged T cells and skew their differentiation toward short-lived, pro-inflammatory effector T cells while hindering the generation of long-lived memory and T follicular helper cells. These changes contribute to a hyper-inflammatory state, exacerbate chronic low-grade inflammation, and compromise immune homeostasis. In this review, we explore how metabolic signaling is altered during T cell aging and the resulting functional impacts. We also discuss therapeutic approaches aimed at restoring proper T cell differentiation, improving vaccine responses, and rejuvenating immune function in older populations.

Keywords: T cell aging; Metabolic signaling; T cell differentiation; Memory T cells; Vaccine; Inflammaging

INTRODUCTION

As individuals age, the immune system's ability to combat infectious pathogens progressively declines, rendering older adults more susceptible to severe illnesses caused by infections such as influenza, varicella-zoster virus (VZV), respiratory syncytial virus, and severe acute respiratory syndrome coronavirus 2 (1). While vaccines are highly effective in preventing infectious diseases in children and younger adults, their efficacy diminishes significantly with age. For instance, over 90% of influenza-related deaths occur in individuals aged 65 and older, despite higher rates of annual vaccination in this age group (2). Similarly, herpes zoster (shingles), caused by the reactivation of VZV, frequently occurs in older individuals as vaccine-induced immune memory wanes with age (3,4). Therefore, understanding the age-associated changes in the immune system is essential for devising strategies to enhance immune defenses and mitigate the impact of infectious diseases in older populations (5).

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FOXO1, forkhead box protein O1; GSK3β, glycogen synthase kinase 3β; HK-II, hexokinase II; IL-2Rα, IL-2 receptor alpha; IL-7R, IL-7 receptor; miRNA, microRNA; mTORC1, mTOR complex 1; MVB, multivesicular body; NRF1, nuclear respiratory factor 1; OXPHOS, oxidative phosphorylation; SIRT1, sirtuin 1; TEC, thymic epithelial cell; TFEB, transcription factor EB; Tfh, T follicular helper; TRM, tissue-resident memory; VZV, varicella-zoster virus.

Author Contributions

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Recent studies have revealed significant age-related alterations in the T cell compartment, which impair the ability to mount effective T cell responses and increase susceptibility to infectious diseases (6-9). Intriguingly, metabolic signaling pathways have emerged as critical regulators of these age-associated defects in T cell responses (10-12). Therefore, understanding the interplay between metabolic signaling and T cell aging offers promising opportunities for developing strategies to mitigate age-related immune decline. In this review, we explore the age-associated changes in metabolic signaling that influence T cell immunity. Additionally, we discuss underlying mechanisms and potential therapeutic strategies aimed at targeting these pathways to rejuvenate T cell responses and enhance vaccine efficacy in older adults.

T CELL RESPONSE AND METABOLIC SIGNALING

At steady state, naïve T cells circulate through secondary lymphoid organs in a quiescent state. Upon Ag encounter, they are primed and undergo massive expansion during the immune response. During this proliferation, naïve T cells differentiate into heterogeneous populations acquiring diverse effector functions, such as cytokine production and cytolytic activity. Following Ag clearance, most effector T cells are short-lived and undergo apoptosis. However, a small subset of less differentiated effector T cells, often referred to as memory precursor T cells, preferentially survive and retain the potential to differentiate into memory T cells. These precursors exhibit characteristics that favor their development into memory subsets, such as central memory or effector memory T cells. Once established, memory T cells provide rapid protection upon subsequent encounters with the same Ag (13-15). Memory T cells can persist without cognate Ags, maintaining their population through self-renewal driven by homeostatic cytokines such as IL-7 and IL-15, thereby remaining at stable levels for years (16).

The ability of T cells to transition from quiescence to activation and differentiation is governed by their metabolic state (17). In their quiescent state, naïve T cells rely on oxidative phosphorylation (OXPHOS) in mitochondria to meet minimal energy demands. However, upon Ag stimulation, quiescent T cells undergo rapid metabolic reprogramming, shifting from OXPHOS to aerobic glycolysis and glutaminolysis. This metabolic shift generates ATP and biosynthetic precursors required for cell growth, proliferation, and differentiation (17,18).

Central to this metabolic regulation is the PI3K-AKT-mTOR complex 1 (mTORC1) pathway, which integrates signals from the TCR, costimulatory molecules, and cytokines (19). This pathway drives anabolic metabolism, which is essential for T cell activation, growth, and proliferation. In quiescent naïve T cells, AKT-mTORC1 activity is actively suppressed to maintain metabolic dormancy and preserve the quiescent state (17). Upon activation, however, the strength and duration of PI3K-AKT-mTORC1 signaling become critical determinants of T cell fate. Excessive mTORC1 activation skews the differentiation of activated naïve T cells toward terminally differentiated effector T cells, often at the expense of memory T cell formation. Conversely, pharmaceutical attenuation or genetic inhibition of mTORC1 signaling has been shown to promote the development of effector T cells with memory potential, which exhibit enhanced self-renewal capacity and longevity, as well as T follicular helper (Tfh) cells, which are critical for B cell-mediated Ab responses (20-22). The transition from effector to memory T cells also requires a metabolic shift back to OXPHOS and fatty acid oxidation, processes also governed by mTORC1 activity. Thus, dynamic regulation of mTORC1 signaling is crucial for balanced T cell responses, a process that becomes increasingly dysregulated with age.

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NAÏVE T CELL MAINTENANCE IN AGING

T cell aging is characterized by a decline in both the number and repertoire diversity of naïve T cells (1,23). Reduced frequencies of naïve CD4 and CD8 T cells are associated with diminished T cell responses to the live-attenuated yellow fever vaccine in older adults (24). This decline is also closely linked to increased susceptibility to newly emerging infectious pathogens, as observed during the COVID-19 pandemic, where advanced age emerged as the most significant risk factor for adverse disease outcomes (25). These observations suggest that a diminished naïve T cell compartment compromises the ability to mount optimal T cell responses to new Ags (26).

Thymic involution and reduced naïve T cell output

The decline in the naïve T cell compartment primarily results from thymic involution in humans, a process in which the thymus gradually loses its capacity to produce new T cells as individuals age (27,28). While thymic involution is a major contributor to the age-related decline in the naïve T cell compartment, the metabolic factors governing this process remain underappreciated. With age, the thymus undergoes gradual atrophy, characterized by increased adipose tissue deposition, fibrosis, and reduced thymic epithelial cell (TEC) integrity, ultimately impairing thymopoiesis and diminishing the production of naïve T cells. Key metabolic pathways implicated in thymic atrophy include mTORC1 signaling, oxidative stress, and lipid metabolism dysregulation. Dysregulated mTORC1 activity in TECs disrupts thymic architecture and contributes to cellular senescence and functional decline (29,30). Meanwhile, chronic oxidative stress, driven by mitochondrial dysfunction and elevated ROS, further exacerbates TEC apoptosis and dysfunction. Additionally, lipid accumulation in the aging thymus impairs TEC function and restricts thymocyte development (31). These metabolic changes collectively lead to reduced thymic output, compounding the loss of naïve T cells. Targeting these metabolic pathways through mTORC1 modulation, antioxidant interventions, caloric restriction, or lipid metabolism regulation may offer promising strategies to restore thymic function and preserve T cell homeostasis in aging populations (31,32).

The TRIB2-AKT axis in maintaining naïve T cell quiescence

With age-related decline in the naïve T cell compartment, the maintenance of naïve T cells in adults relies on homeostatic proliferation driven by IL-7 signaling and TCR recognition of self-Ags presented on MHC molecules. Although this mechanism effectively sustains the naïve T cell pool, a gradual decline still occurs over time (33,34). Notably, this reduction is more pronounced in the CD8 T cell compartment compared to CD4 T cells, suggesting distinct homeostatic mechanisms for these subsets (33).

A recent study identified TRIB2, a negative regulator of AKT signaling, as a key factor in maintaining the naïve T cell compartment (35). Naïve CD8 T cells express lower levels of TRIB2 compared to naïve CD4 T cells, resulting in enhanced basal AKT activation and a greater propensity to exit quiescence upon stimulation. This finding is consistent with the observation that CD8 T cells exhibit higher frequencies of $Ki67^+$ cycling cells under steady-state conditions (36). IL-7-driven AKT activation is particularly pronounced in naïve CD8 T cells, driving robust homeostatic proliferation. Consequently, this leads to a loss of the naïve T cell phenotype and the acquisition of effector-like features, such as the production of IFN-γ and Granzyme B (35). These findings highlight the role of TRIB2 in maintaining quiescence by raising the activation threshold for AKT, which is intrinsically lower in naïve CD8 T cells (**Fig. 1**). This mechanism may also account for the preferential accumulation of

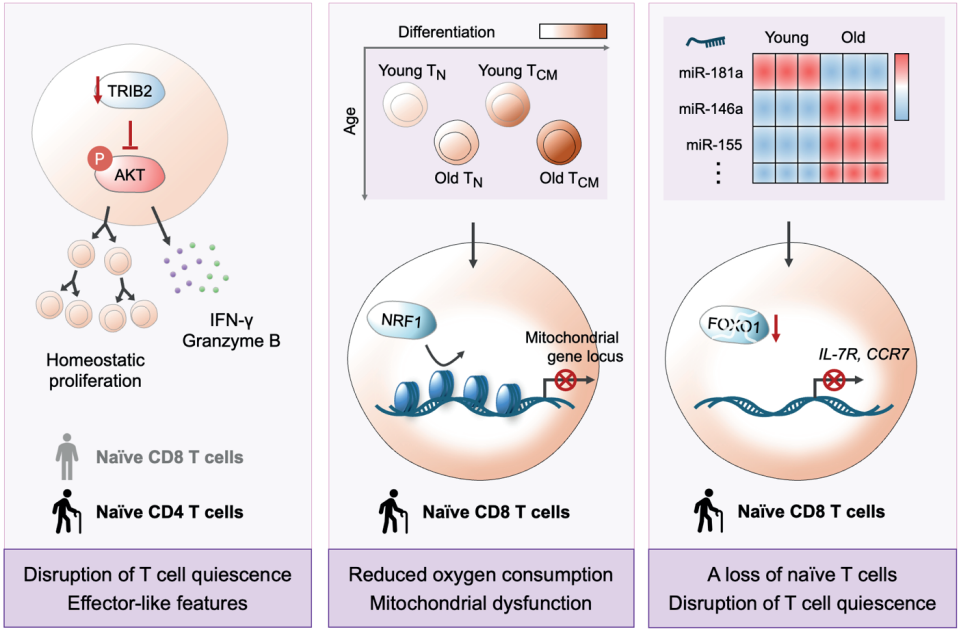

Figure 1. Mechanisms underlying compromised T cell homeostasis in older individuals.
This schematic illustrates key mechanisms driving impaired T cell homeostasis during aging. Compared to naïve CD4 T cells, naïve CD8 T cells exhibit an intrinsically lower activation threshold for AKT, leading to excessive homeostatic proliferation and increased production of effector molecule, accelerating the loss of naïve CD8 T cells with age. The aged naïve CD8 T cell epigenetic landscape shows reduced chromatin accessibility at NRF1 binding sites, resulting in decreased expression of mitochondrial respiratory chain genes and subsequent mitochondrial dysfunction. Concurrently, age-related dysregulation of miRNA expression decreases FOXO1 activity, reducing the expression of IL-7R and CCR7, both crucial for T cell survival and lymphoid homing. Together, these alterations disrupt T cell quiescence and homeostatic maintenance, exacerbate the loss of naïve T cells, and promote the acquisition of effector-like features.

Ag-inexperienced virtual memory T cells, which are likely generated by cytokine signaling, in the CD8 T cell compartment (37-39).

Importantly, naïve CD4 T cells lose TRIB2 expression with age, accompanied by heightened IL-7-driven AKT activation (35). While the precise impact of TRIB2 loss on naïve CD4 T cell maintenance remains to be addressed, the substantial reduction in the naïve CD4 T cell pool observed after the seventh decade of life suggests a critical role for TRIB2 in preserving this compartment during aging (36).

Nuclear respiratory factor 1 (NRF1)-driven mitochondrial dysfunction in aged T cells

Aging induces significant changes in the epigenetic landscape that regulates transcriptional programs (40). Recent findings indicate that T cell epigenetic clocks reflect proliferative history, with DNA methylation changes accumulating at cell cycle regulators (41). Chromatin accessibility studies of immune cell subsets in PBMCs across age groups reveal that CD8 T cells undergo more pronounced chromatin remodeling with age compared to other immune subsets (42). Specifically, naïve CD8 T cells in older adults acquire epigenetic features resembling central memory T cells in young adults (43). CD4 T cells also display similar age-associated epigenetic changes, albeit to a lesser extent (44).

A notable feature of aged naïve CD8 T cells is the reduced chromatin accessibility at promoter regions enriched for NRF1 binding sites (43). NRF1 is a transcription factor critical for

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mitochondrial biogenesis and function (45). It drives the expression of mitochondrial genes, including those encoding components of the mitochondrial respiratory chain (46). Reduced chromatin accessibility at NRF1 binding sites is accompanied by decreased NRF1 expression and reduced mitochondrial respiratory chain gene expression, resulting in mitochondrial dysfunction, as evidenced by reduced oxygen consumption rates (43). This mitochondrial impairment likely compromises the homeostatic maintenance of the naïve CD8 T cell compartment with age (**Fig. 1**). Given the heterogeneity of the naïve CD8 T cell compartment, which includes subpopulations such as stem-like memory T cells and naïve-phenotype cells capable of producing IFN-γ and granzyme B, further single-cell analyses are necessary to better understand these changes (37,47-49). Nevertheless, these findings highlight the profound epigenetic remodeling in CD8 T cells with age and its association with mitochondrial dysfunction.

Forkhead box protein O1 (FOXO1) activity and its role in T cell survival and maintenance

MicroRNAs (miRNAs) are critical regulators of cellular function, primarily by repressing the expression of genes that are often involved in related pathways (50). Dysregulation of miRNA expression affects various aspects of T cell immunity, including development, survival, and function (50,51). Several miRNAs, including miR-181a, miR-146a, miR-155, and let-7f, are differentially expressed in young and aged T cell subsets, implicating their role in age-associated T cell dysfunction (52,53). Pathway analysis of the targets of these miRNAs identified reduced FOXO1 activity as a major age-related change in naïve CD8 T cells (52).

FOXO1 is a key transcription factor that regulates genes critical for T cell survival and quiescence, including IL-7 receptor (IL-7R) and lymph node homing molecules such as CD62L and CCR7 (54). In aged naïve CD8 T cells, reduced FOXO1 activity diminishes the expression of IL-7R and CCR7, correlating with the loss of naïve CD8 T cells (52). This highlights a critical link between FOXO1 signaling defects and impaired T cell maintenance during aging (**Fig. 1**) (52). Additionally, aged naïve CD8 T cells exhibit reduced chromatin accessibility at regulatory regions of the *IL7R* gene, implicating epigenetic modifications in the age-related decline in IL-7R expression (42). These findings emphasize the therapeutic potential of targeting miRNA networks or FOXO1-regulated pathways to counteract T cell aging and preserve T cell homeostasis.

T CELL ACTIVATION AND EFFECTOR DIFFERENTIATION IN AGING

Features of activation and differentiation in aged T cells

Upon Ag encounter, signals from the TCR and costimulatory molecules activate multiple signaling pathways, including PI3K-AKT-mTORC1, ERK, and NFAT pathways. These signaling cascades integrate external cues to regulate transcription factor networks that drive the transcriptional programs required for T cell activation and differentiation (14). Aging significantly impacts CD4 T cell differentiation by altering the dynamics of these signaling pathways, particularly through sustained activation of the AKT-mTORC1 and ERK pathways (55). This dysregulation skews transcription factor networks, leading to the upregulation of transcription factors associated with effector T cell differentiation, such as BLIMP1 and RUNX3, and the suppression of transcription factors, such as TCF1 and LEF1, critical for memory T cells and Tfh cells (56). As a result, aged CD4 T cells exhibit features characteristic

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of short-lived effector T cells, including increased expression of IL-2 receptor alpha (IL-2Rα), inhibitory molecules like TIM3, and cytotoxic mediators such as granzyme B. In contrast, molecules associated with memory T cells, such as IL-7R, CD62L, CD27, and IL-2, are downregulated (55,56).

This shift toward effector differentiation at the expense of effector T cells with memory potential and Tfh cells is particularly evident in clinical settings. For example, in VZV-specific T cell responses after vaccination, the initial activation and proliferation of VZV-specific T cells are comparable between young and older individuals. However, older adults experience a more pronounced contraction phase, leading to reduced generation of long-lived VZV-specific memory T cells (57). Similarly, after influenza vaccination, older individuals exhibit lower frequencies and impaired functionality of circulating Tfh cells compared to younger adults (58). Unlike in younger populations, the Tfh cell response in older individuals does not correlate with the vaccination-induced increase in Ab titers, highlighting the diminished Tfh cell contribution to vaccine efficacy in aging populations (58). This preferential differentiation into short-lived effector T cells contributes to the reduced efficacy of vaccines in older adults.

Dampened TCR signaling and enhanced IL-2 signaling

Aged T cells exhibit diminished TCR signaling due to attenuated ERK activation downstream of TCR engagement (59). This reduction is attributed to the age-associated decline in miR-181a expression, which leads to increased levels of its target, the phosphatase DUSP6 (51,53). DUSP6 dephosphorylates ERK, raising the activation threshold for TCR signaling and dampening early T cell responses. This impairment in TCR signaling contributes to reduced Ag sensitivity and impaired activation in older individuals (**Fig. 2**) (59).

Despite this dampened TCR signal, aged T cells undergo accelerated chromatin remodeling after activation, enabling transcriptional programs favoring effector T cell differentiation (60). This phenomenon is driven in part by heightened IL-2 signaling, resulting from elevated IL-2Rα expression in aged T cells. The increase in IL-2Rα is due to the age-related loss of the transcriptional repressor HELIOS (60). Upon activation, the enhanced IL-2 signaling activates the STAT5 pathway, promoting chromatin remodeling and upregulating transcription factors like BLIMP1 and BATF, which are critical for effector T cell differentiation (**Fig. 2**) (60). Simultaneously, IL-2-STAT5 signaling suppresses FOXO1 activity, further reducing the expression of genes essential for memory T cell maintenance.

In parallel, IL-2 signaling engages the PI3K-AKT-mTORC1 pathway, further boosting AKT-mTORC1 activity in IL-2Rα$^+$ T cells (20). This pathway enhances mitochondrial function and glucose uptake, facilitating a shift toward glycolytic metabolism (61). This metabolic reprogramming further supports effector T cell differentiation and function but limits the flexibility required for memory T cell formation and Tfh cell generation (20). Consequently, aged T cells exhibit a strong propensity for differentiation into Th1 cells with effector-like features, often at the expense of long-lived memory T cells (**Fig. 2**).

miR-21 upregulation and sustained AKT-mTORC1 and ERK pathways

Excessive activation of the AKT-mTORC1 pathway in activated CD4 T cells of older individuals is also driven, in part, by elevated expression of miR-21, a microRNA that is significantly upregulated upon T cell activation and further elevated with age (55). miR-21 directly represses the expression of PTEN, a critical inhibitor of the AKT pathway, thereby sustaining

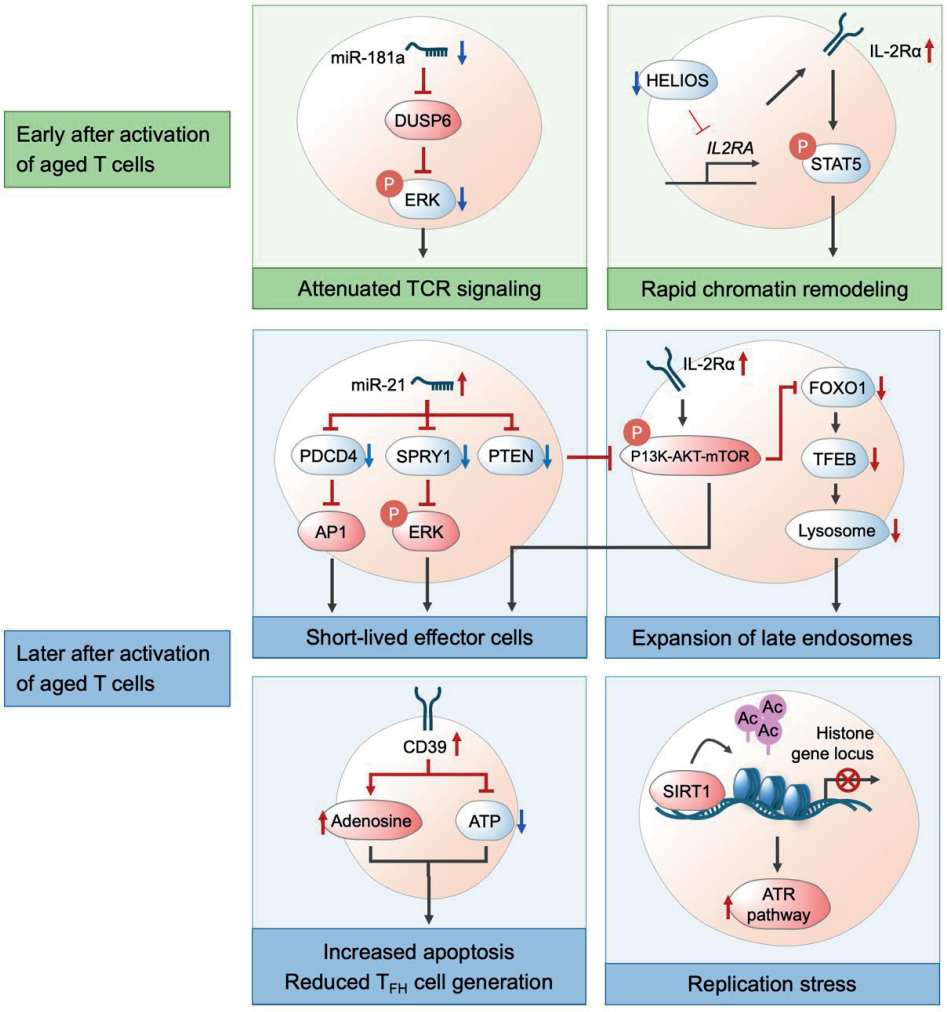

Figure 2. Molecular mechanisms of aged T cell responses.
This schematic outlines early and late molecular events following the activation of aged T cells, highlighting critical pathways contributing to impaired T cell responses with age. Early after activation, increased DUSP6 expression due to reduced miR-181a levels inhibits ERK activation and attenuates TCR signaling. Reduced HELIOS levels elevate IL-2Rα expression, leading to faster STAT5 activation and rapid chromatin remodeling. Later after activation, increased miR-21 expression sustains ERK and PI3K-AKT-mTOR activation, promoting short-lived effector T cell differentiation. Sustained AKT activation reduces FOXO1 activity, which in turn downregulates TFEB expression and impairs lysosomal activity. Lysosomal dysfunction drives the expansion of late endosomes, further contributing to metabolic dysregulation and impaired autophagy. Increased CD39 expression in aged T cells reduces ATP levels and elevates adenosine, promoting apoptosis of activated T cells and impairing Tfh cell generation. Elevated SIRT1 expression causes replication stress through reduced histone production and ATR activation, leading to cell cycle arrest and the secretion of pro-inflammatory mediators.

AKT-mTORC1 activation and promoting effector T cell differentiation (55,62). In addition to its effects on the AKT pathway, miR-21 suppresses negative regulators of other signaling pathways. For example, it represses PDCD4, a key inhibitor of activating protein-1 (AP-1) signaling, and SPRY1, a regulator of ERK signaling (63,64). This regulatory role contributes to sustained activation of the AKT-mTORC1, AP-1, and ERK pathways in aged T cells, driving their differentiation toward effector phenotypes (**Fig. 2**).

Targeting miR-21 has shown potential in reversing these effects. Inhibition of miR-21 using antisense oligonucleotides curtails AKT-mTORC1 and ERK signaling, restoring balance and promoting the differentiation of activated T cells into effector T cells with memory potential

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(55). Collectively, these findings demonstrate the critical role of miR-21 dysregulation and sustained AKT-mTORC1 signaling in shaping the impaired T cell responses observed in older individuals. Therapeutic strategies aimed at modulating miR-21 activity or its downstream pathways could improve vaccine responses by enhancing Tfh cell and memory T cell differentiation while reducing effector bias in older adults.

The AKT-FOXO1 axis and lysosomal dysfunction

One of the functional consequences of AKT activation is FOXO1 phosphorylation and subsequent proteasomal degradation (65). FOXO1 levels are dynamically regulated during T cell responses, partly through the AKT pathway. It is highly expressed in naïve T cells, downregulated after activation, and re-expressed in memory T cells (66). However, in the CD4 T cell response of older adults, prolonged AKT activity prevents the re-expression of FOXO1 following its initial downregulation (66). This sustained suppression of FOXO1 not only reduces the expression of genes critical for memory T cell maintenance but also reinforces the metabolic shift toward glycolysis, favoring terminal effector T cell differentiation over memory formation. Additionally, IL-2-STAT5 signaling, which is enhanced in aged T cells, further suppresses FOXO1 activity, compounding the defects in memory T cell generation. Consistent with these findings, in a mouse model of acute viral infection, FOXO1 deficiency skewed T cell differentiation toward terminally differentiated effector T cells, with a marked failure to generate long-lived memory T cells, resembling the impaired memory formation observed in aged T cell responses (67-69). These interactions between AKT-mTORC1, IL-2-STAT5, and FOXO1 create a feedforward loop that promotes effector T cell bias while limiting the plasticity required for memory and Tfh cell differentiation in older adults.

One of the transcriptional targets of FOXO1 is transcription factor EB (TFEB), a master regulator of lysosomal biogenesis that controls the expression of key lysosomal genes (70,71). Impaired FOXO1 re-expression in activated aged T cells significantly reduces TFEB expression, leading to decreased lysosomal gene expression and diminished lysosomal activity (66). Lysosomes are the primary degradative organelles essential for cellular quality control. During this process, nutrients, cellular waste, and damaged organelles are captured either by endocytosis into early and late endosomes or via autophagy into autophagosomes, which subsequently fuse with lysosomes for degradation and recycling (72,73). Consequently, impaired lysosomal activity in activated T cells from older adults disrupts these degradation pathways, redirecting cellular components toward the expansion of multivesicular bodies (MVBs, late endosomes) and subsequent exosomal release into the extracellular environment (66). Consistent with defective lysosomal activity, CD4 T cells from older adults accumulate autophagosomes containing undegraded mitochondria, indicating impaired mitochondrial recycling (**Fig. 2**) (74).

mTORC1 dysregulation on late endosomes

Lysosomes play a central role in regulating metabolic signaling. mTORC1 activation is initiated upon its recruitment to the lysosomal membrane, where cellular degradation products, including leucine and arginine, sustain mTORC1 activation (75). Once activated, mTORC1 phosphorylates its downstream targets, such as S6K and 4E-BP1, driving anabolic metabolism. Interestingly, mTORC1 also phosphorylates TFEB, retaining it in the cytosol and preventing its nuclear translocation. Cytosolic retention of TFEB downregulates lysosome biogenesis, creating a negative feedback loop that limits mTORC1 activity (76).

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Notably, in aged T cells, mTORC1 activation occurs predominantly on multivesicular late endosomes, which aberrantly expand due to lysosomal dysfunction (77). This shift bypasses the lysosomal negative feedback loop and relies on extracellular amino acids by increasing the expression of plasma membrane amino acid transporters, such as the leucine transporter SLC7A5 (78). This compensatory mechanism sustains mTORC1 activity despite lysosomal impairment, contributing to metabolic dysregulation in aged T cells (77).

Glycogen synthase kinase 3β (GSK3β) sequestration, proteostasis, and metabolic reprogramming

A key consequence of lysosomal dysfunction and late endosome expansion in aged T cells is the sequestration of GSK3β into MVBs and its extracellular release via exosomes (66,79). GSK3β is a key regulator of proteostasis, controlling protein ubiquitination and proteasomal degradation. Loss of cytoplasmic GSK3β activity during T cell activation disrupts protein turnover, prolonging protein half-life and leading to increased cell size (66). Along with lysosomal defects, this disruption in proteostasis is accompanied by increased exosomal release of cytotoxic molecules, such as granzyme B and mitochondrial DNA, which exacerbate tissue damage and inflammatory responses, contributing to inflammaging (66,80).

GSK3β also regulates cellular metabolism and inhibits glycogen synthesis (81,82). In aged T cells, reduced intracellular GSK3β activity leads to excessive glycogen accumulation and increased mitochondrial hexokinase II (HK-II) (66). This upregulation of HK-II enhances glucose uptake and lactate production, indicating a shift toward glycolytic metabolism. While this metabolic reprogramming supports effector T cell differentiation, it also exacerbates the inflammatory phenotype by promoting the secretion of pro-inflammatory cytokines. These metabolic changes reduce the flexibility required for generating long-lived memory T cells (66).

Collectively, the loss of cytoplasmic GSK3β activity during activation of aged T cells extends protein stability, increases cell size, shifts metabolism toward glycolysis, and promotes the differentiation of effector T cells producing pro-inflammatory cytokines — all of which represent features of senescent cells (66,73). Together, the metabolic and functional disruptions in aged T cells highlight the critical role of the AKT-FOXO1-GSK3β axis in balancing T cell activation, proteostasis, and differentiation, which becomes increasingly dysregulated with age (**Fig. 2**).

PD-1 accumulation and proliferative defects

Impaired lysosomal activity in aged T cells prevents the degradation of inhibitory molecules like PD-1, leading to their accumulation on the T cell surface (77). PD-1 plays a critical role in dampening T cell activation and proliferation by engaging its ligands, PD-L1 and PD-L2, on Ag-presenting cells or tumor cells. T cells from older adults exhibit elevated surface expression of PD-1 after activation, which inhibits their proliferative capacity and cytokine production, thereby contributing to the impaired immune responses characteristic of aging populations (**Fig. 2**) (77).

Consistent with these findings, PD-1 blockade significantly improves T cell proliferation in older adults in response to pathogen-derived peptides presented by Ag-presenting cells, further emphasizing the critical role of PD-1 in limiting T cell responses during aging (77). Targeting PD-1 or its downstream signaling pathways offers a promising strategy to restore T cell proliferation and effector functions in the context of aging. Additionally, interventions aimed at enhancing lysosomal function may provide an alternative approach to reduce PD-1 accumulation, thereby improving T cell responses in older individuals (73).

Sirtuin 1 (SIRT1) dysregulation and replication stress

SIRT1, a NAD^+-dependent histone deacetylase, is a critical regulator of cellular metabolism, modulating key processes in response to nutrient availability and metabolic status (83). By deacetylating a broad range of targets, including histones, metabolic enzymes, and transcription factors, SIRT1 regulates diverse biological functions, such as chromatin remodeling, DNA repair, and cellular stress responses (84).

SIRT1 is involved in maintaining peripheral T cell tolerance by suppressing T cell activation through deacetylation of c-Jun, thereby inhibiting AP-1 activity (85). In terminally differentiated memory CD8 T cells lacking the costimulatory molecule CD28, reduced SIRT1 expression at steady state is closely linked to elevated glycolytic metabolism and a pro-inflammatory phenotype characterized by increased granzyme B production (86). In contrast, aged CD4 T cells show significantly elevated SIRT1 levels (53). One prominent consequence of this overexpression is increased histone deacetylation at histone gene promoters during the S-phase of the cell cycle (87). This deacetylation reduces histone gene transcription, resulting in insufficient histone production required for proper chromatin assembly during DNA replication. The resulting replication stress activates ATR signaling, which triggers downstream pathways involving p21, p53, and γH2AX, ultimately causing cell cycle arrest and limiting T cell expansion (87). In addition to impairing proliferation, replication stress in aged T cells promotes the secretion of pro-inflammatory mediators, such as CCL3 and colony-stimulating factors (CSF1/2). This secretory phenotype mirrors the senescence-associated secretory phenotype, exacerbating local inflammation in aging (**Fig. 2**) (87).

The dysregulation of SIRT1 in aged T cells is partly attributed to the age-related reduction in miR-181a levels, which suppress SIRT1 expression (53,87). The resulting hyperactivation of SIRT1 disrupts T cell proliferation and delays viral clearance, as demonstrated in mouse models of acute infection (88). Importantly, pharmacological or genetic inhibition of SIRT1 has been shown to restore T cell proliferation, alleviate replication stress, and improve viral control (87). These findings underscore the therapeutic potential of targeting SIRT1 or modulating miR-181a activity to rejuvenate T cell responses and improve immune function in older individuals.

MEMORY AND TFH CELL DIFFERENTIATION IN AGING

Purinergic signaling in aged T cell responses

Purinergic signaling, mediated by extracellular nucleotides such as ATP and their metabolites, plays a critical role in regulating immune responses (89). Extracellular ATP, released by stressed or dying cells, acts as a danger-associated molecular pattern, triggering inflammation through various purinergic receptors (90). Among these, signaling through the P2RX7 receptor is crucial for generating and maintaining tissue-resident memory (TRM) CD8 T cells, which are essential for localized immune defense (91).

CD39, a cell membrane ectonucleotidase encoded by *ENTPD1*, hydrolyzes extracellular ATP into adenosine diphosphate, and adenosine monophosphate (AMP). CD73, another ectonucleotidase expressed on the cell surface, subsequently converts AMP into adenosine, which exerts potent immunosuppressive effects by engaging P1 receptors such as the A2A receptor (A2AR) (89). This adenosine-mediated signaling pathway elevates intracellular cAMP levels, inhibiting T cell activation, proliferation, and cytokine production (92). CD39 is

highly expressed on Tregs, which utilize adenosine to suppress effector T cell responses (93). It is also recognized as a marker of exhausted T cells (94,95).

In addition to its role in Tregs, CD39 is induced in subsets of effector and memory T cells following activation, with increased frequencies observed in older individuals (92). Compared to $CD39^-$ T cells, $CD39^+$ T cells exhibit terminally differentiated effector phenotypes, characterized by elevated expression of T-BET, IL-2Rα, HLA-DR, and PD-1, and reduced IL-7R expression (92). The ATPase activity of CD39 contributes to this process, as adenosine signaling via A2AR in $CD39^+$ effector T cells activates AMP-activated protein kinase and its downstream target, p53. This pathway induces the expression of the cell cycle inhibitor p21 and promotes apoptosis. Consequently, T cell responses in older adults are dominated by $CD39^+$ short-lived effector T cells that fail to transition into long-lived memory T cells (**Fig. 2**) (92). In contrast, $CD73^+$ T cells exhibit characteristics of long-lived memory T cells capable of differentiating into TRM cells; however, their frequencies decline with age (96). CD39 and CD73 expression on activated T cells are mutually exclusive, and this age-related shift contributes to impaired vaccine efficacy (96). Supporting this, individuals with genetic polymorphisms reducing CD39 expression exhibit enhanced T cell responses after VZV or influenza vaccination (92). Whether these individuals also have improved Tfh cell responses, increased Ab production, or better long-lived memory T cell generation remains to be determined.

Purinergic signaling and Tfh cell generation in older adults

CD39 and purinergic signaling also influence Tfh cell differentiation (97). Tfh cells lack CD39 expression due to transcriptional repression by BCL6, the master transcription factor for Tfh development. Adenosine generated by CD39 and CD73 activates the cAMP-PKA-pCREB pathway via A2AR, interfering with BCL6 activity and inducing *ENTPD1* transcription, thereby suppressing Tfh differentiation (**Fig. 2**) (97). Consistently, individuals with genetic polymorphisms resulting in reduced CD39 expression exhibit higher frequencies of circulating Tfh cells *ex vivo* and preferential Tfh differentiation after activation *in vitro* (97). Additionally, age-associated increases in transcription factors such as BLIMP1 and RUNX3 promote CD39 expression, reinforcing a shift away from Tfh cell differentiation (97). Furthermore, elevated IL-2Rα expression in aged T cells amplifies STAT5 signaling, which suppresses BCL6 expression, further compromising Tfh and memory T cell generation in aging populations.

These findings highlight the potential for therapeutic strategies targeting purinergic signaling to enhance immune responses in older adults. Interventions aimed at inhibiting CD39 activity or modulating the purinergic signaling pathway could provide immune protection and improve vaccine efficacy in older individuals (6). For example, the temporal use of CD39 inhibitors could prevent ATP hydrolysis, reducing adenosine generation while preserving extracellular ATP levels, thereby supporting memory T cell differentiation (92). Blocking adenosine signaling through selective A2AR antagonists could counteract the immunosuppressive effects of adenosine and improve Tfh cell generation (97). Moreover, strategies to enhance $CD73^+$ TRM cell precursors, potentially through IL-7 supplementation, may bolster immune protection against localized infections (98).

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THERAPEUTIC STRATEGIES AND CHALLENGES IN RESTORING AGED T CELL RESPONSES

Based on the molecular mechanisms underlying T cell aging, targeted metabolic interventions offer promising approaches to restore aged T cell responses and enhance immune function in older adults. One potential strategy involves enhancing thymic function to promote the generation of new T cell clones. The prolongevity hormone fibroblast growth factor-21 or caloric restriction has been shown to support TEC integrity and delay thymic involution (99). Additionally, cytokine supplementation, such as IL-22 or IL-7, has demonstrated benefits in mitigating thymic atrophy and enhancing thymopoiesis (100,101). Exogenous IL-7 treatment in vivo has been shown to expand the naïve T cell pool and increase TCR repertoire diversity by promoting the homeostatic proliferation of naïve T cells (102).

Restoring activation and effector differentiation of aged T cells is another critical therapeutic goal, with mTORC1 emerging as a key target. Preclinical studies have demonstrated that transient, low-dose mTOR inhibition enhances memory T cell formation and improves antiviral T cell responses in a mouse model of viral infection (21). Clinical trials have further shown that mTOR inhibition enhances vaccine responses to influenza and reduce the incidence of viral infections in older individuals (103,104). These findings highlight the potential for mTOR-targeted interventions to mitigate age-related impairments in T cell activation, differentiation, and memory formation.

Beyond direct metabolic modulation, senolytic therapies aimed at targeting senescent cells have gained interest in immune rejuvenation strategies. Senescent cells contribute to chronic inflammation and immune dysfunction, and their selective elimination has been shown to improve immune responses and overall physical function in aged mice (105). Chimeric Ag receptor T cell therapy has recently emerged as a promising tool to selectively eliminate senescent cells, thereby ameliorating metabolic dysfunction and restoring immune homeostasis (106). Additionally, although the precise mechanisms remain unclear, lifestyle interventions such as caloric restriction and exercise have been associated with enhanced mitochondrial function, reduced oxidative stress, and improved immune function, providing a non-pharmacological avenue for enhancing aged T cell responses.

Despite the promise of metabolic interventions, translating these therapeutic targets into clinical applications presents several challenges (11). One major obstacle is the heterogeneity of the human population, where genetic diversity, environmental influences, and lifestyle factors contribute to variable responses to interventions. Precision medicine approaches will be essential for optimizing therapeutic strategies tailored to individual aging profiles. Additionally, the clinical use of many metabolic inhibitors, including mTOR-targeted therapies, is often limited by potential side effects, particularly in older adults with comorbidities. Given the essential roles of mTOR signaling across multiple cell types, complete inhibition of mTOR may lead to undesirable systemic effects. Furthermore, prolonged use of small-molecule inhibitors can impose metabolic burdens and pose challenges for liver function in elderly individuals. Further research is needed to refine the specificity of these interventions while minimizing toxicity. Future studies should focus on optimizing treatment regimens, such as intermittent dosing strategies, to maximize efficacy while reducing adverse effects.

CONCLUSIONS AND FUTURE DIRECTIONS

Alterations in metabolic signaling are emerging as critical upstream regulators driving T cell aging. Age-associated dysregulation of key pathways, including PI3K-AKT-mTORC1, FOXO1, IL-2-STAT5, and SIRT1, triggers a cascade of downstream effects, such as rapid chromatin remodeling after activation and alterations in transcription factor networks. These changes not only disrupt T cell quiescence but also bias T cell differentiation toward inflammatory, short-lived effector T cells at the expense of memory and Tfh cell formation. The resulting hyper-inflammatory state, exacerbated by senescence-associated secretory phenotypes, contributes to chronic low-grade inflammation, known as inflammaging, which further compromises immune homeostasis (**Fig. 3**) (7,8,107).

These metabolic and functional shifts lead to diminished vaccine efficacy and a reduced ability to generate robust, long-lived immune memory. Older adults experience a loss of naïve T cells, impaired Tfh cell responses, a limited capacity to support Ab production, and failure to generate long-lived memory T cells. Addressing these deficits requires targeted therapeutic strategies to modulate metabolic signaling pathways and restore T cell balance and function. Encouragingly, clinical trials have shown that selective, low-dose TORC1 inhibition enhances immune responses to influenza vaccination and significantly

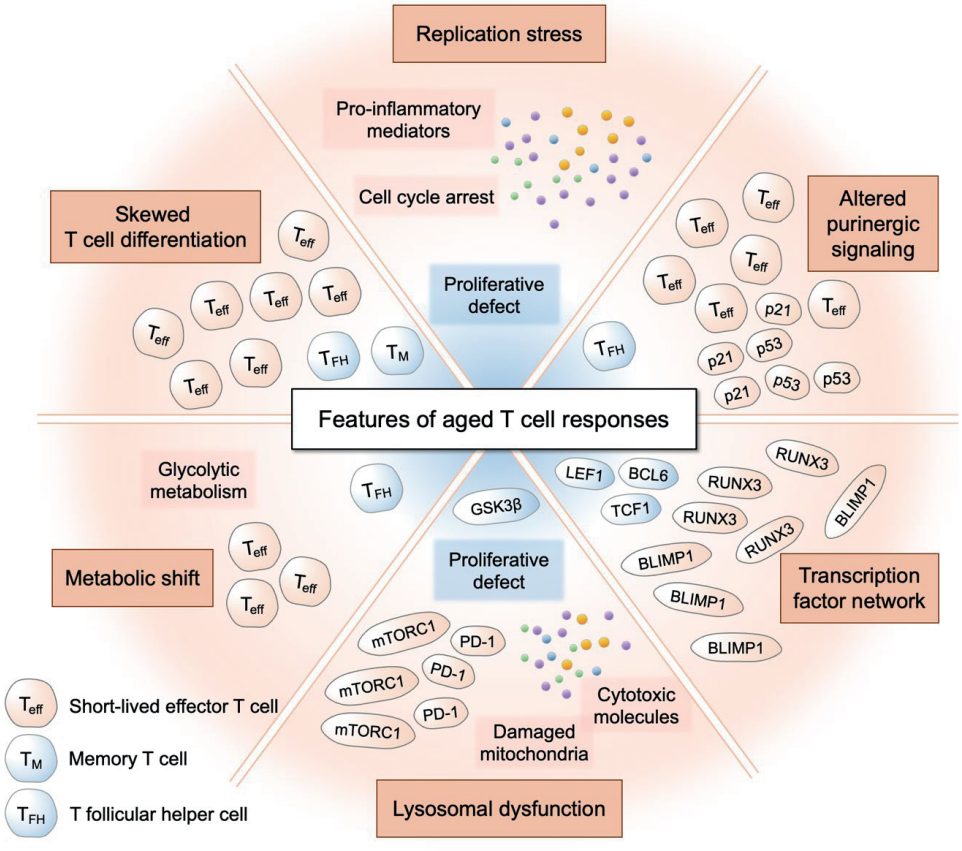

Figure 3. Key features of aged T cell responses.
This schematic summarizes key characteristics of activation and differentiation of aged T cells, including skewed T cell differentiation, lysosomal dysfunction, transcription factor and metabolic shifts, altered purinergic signaling, and replication stress—hallmark features of aged T cell responses. These age-associated changes contribute to diminished immune function and reduced vaccine efficacy.

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reduces infection rates in older adults (104). Additionally, targeting the FOXO1 pathway and purinergic signaling, such as inhibition of CD39 ATPase activity or blockade of adenosine receptors, offers potential to enhance the generation of long-lived memory and Tfh cells. Future research should focus on translating these molecular insights into clinical applications. Advanced single-cell technologies will also be critical in identifying precise molecular targets within the heterogeneous aged T cell subsets, paving the way for innovative approaches to rejuvenate the aging immune system.

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