Cancer Immunology Research

Hallmarks of T-cell Exit from Quiescence

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Abstract

The appropriate activation of the adaptive immune system relies upon the reprogramming of naïve T cells into specialized effector T cells that can combat pathogens and tumors. Naïve T cells are actively maintained in a state of hyporesponsiveness termed quiescence, which is characterized by small cell size, low proliferative rate, and low basal metabolism. Engagement of antigen and costimulatory receptors drives T cells to exit quiescence to promote subsequent clonal expansion and functional differentiation. The exit from quiescence, which precedes activation-induced proliferation, is associated with extensive remodeling of cellular morphology and metabolism. Here, we define and discuss the implications of the six key features of the exit of naïve T cells from quiescence: (i) cell-cycle entry, (ii) cell growth, (iii) autocrine or paracrine interleukin-2 signaling, (iv) anabolic metabolism, (v) nutrient uptake, and (vi) remodeling of mitochondrial function. Ultimately, understanding how naïve T cells meet each of these requirements for quiescence exit will allow for the tuning of T-cell responses to treat infectious diseases, autoimmunity, and cancer. *Cancer Immunol Res; 6(5); 502–8. ©2018 AACR.*

Introduction

T cells are crucial regulators of adaptive immune responses against pathogens and tumors. After developing in the thymus, mature T cells recirculate through secondary lymphoid organs in a naïve, quiescent state characterized by small cell size, low proliferative capacity, and low basal metabolic programs. These naïve T cells become activated upon receiving stimulation through the T-cell antigen receptor (TCR) and costimulatory receptor (e.g., CD28) signals, which ultimately leads to their clonal expansion and differentiation into distinct subsets. Clonal expansion of activated T cells is characterized by rapid cycling, with cell division occurring every 5 to 6 hours *in vitro*. For naïve $CD4^+$ T cells to enter the first cycle *in vitro*, the transition from the G_0 phase through the G_1 phase to the S phase of the cell cycle takes 25 to 30 hours (1), with cells subsequently undergoing multiple rounds of division within 48 hours (2). Unlike $CD4^+$ T cells *in vitro*, the initial entry of $CD8^+$ T cells into the cell cycle is not fixed *in vivo* and is instead controlled by the antigen stimulation from antigen presenting cells, where strong antigenic signals promote more rapid entry into G_1 phase and progression through the cell cycle (3). The transitional state that occurs during T-cell activation, between receiving antigen and costimulatory signals and undergoing active proliferation, is termed "quiescence exit."

It has long been recognized that T cells exiting from quiescence activate the cell-cycle machinery, dramatically increase in size, and increase their production and responsiveness to the key cytokine, interleukin-2 (IL2). These features are crucial for naïve T cells to clonally expand following their activation. However, recent studies have also highlighted that metabolic reprogramming is a key driving force for T cells to escape from quiescence by allowing cells to synthesize the appropriate macromolecules necessary for driving cellular division and differentiation (4, 5). Quiescence exit therefore will ultimately influence the proliferative capacity, metabolic fitness, differentiation, and effector functions of activated T cells. Here, we define, describe, and discuss the possible implications of six key hallmarks of mature, naïve T-cell exit from quiescence: (i) cell-cycle entry, (ii) cell growth, (iii) autocrine or paracrine IL2 signaling, (iv) anabolic metabolism, (v) nutrient uptake, and (vi) remodeling of mitochondrial function (summarized in Fig. 1). Understanding the molecular requirements of quiescence exit may greatly enhance our capacity to tune T-cell responses for various therapeutic interventions, including in autoimmune and infectious diseases and cancer.

Cell-Cycle Entry

Similar to other quiescent cell types, naïve T cells are maintained in the G_0 phase of the cell cycle. Naïve T cells can undergo massive clonal expansion following antigen recognition, which activates multiple signaling pathways, including the Src family kinases and the PI3K–Akt–mTOR pathway. Clonal expansion is preceded by entry into the cell cycle, which is divided into three periods: interphase, mitosis, and cytokinesis. Quiescent cells exit G_0 to enter interphase, which is further separated into the sequential G_1, S, and G_2 phases. The entry and progression through G_1 and these interphase phases define the period in which T cells are exiting from quiescence. When cells transition out of interphase they complete their exit from quiescence and are considered activated when they go through mitosis and cytokinesis to complete cell division. The cyclin-dependent kinases (CDKs) and cyclins, whose expression is regulated by various mitogenic growth factors, drive entry into the cell cycle and progression through interphase. Cyclins bind to CDKs to promote their activity, leading to the phosphorylation and inhibition of cell-cycle inhibitors, such as retinoblastoma (Rb) and p130. In contrast, binding of the CDK–cyclin complexes by members of the INK4 (e.g., p16) and KIP (e.g., p27) families inhibits CDK function (5, 6). Within 6 hours after antigen stimulation, naïve $CD4^+$ and $CD8^+$ T cells transition from G_0 to G_1, and this commitment can be inhibited by overexpression of p16, which

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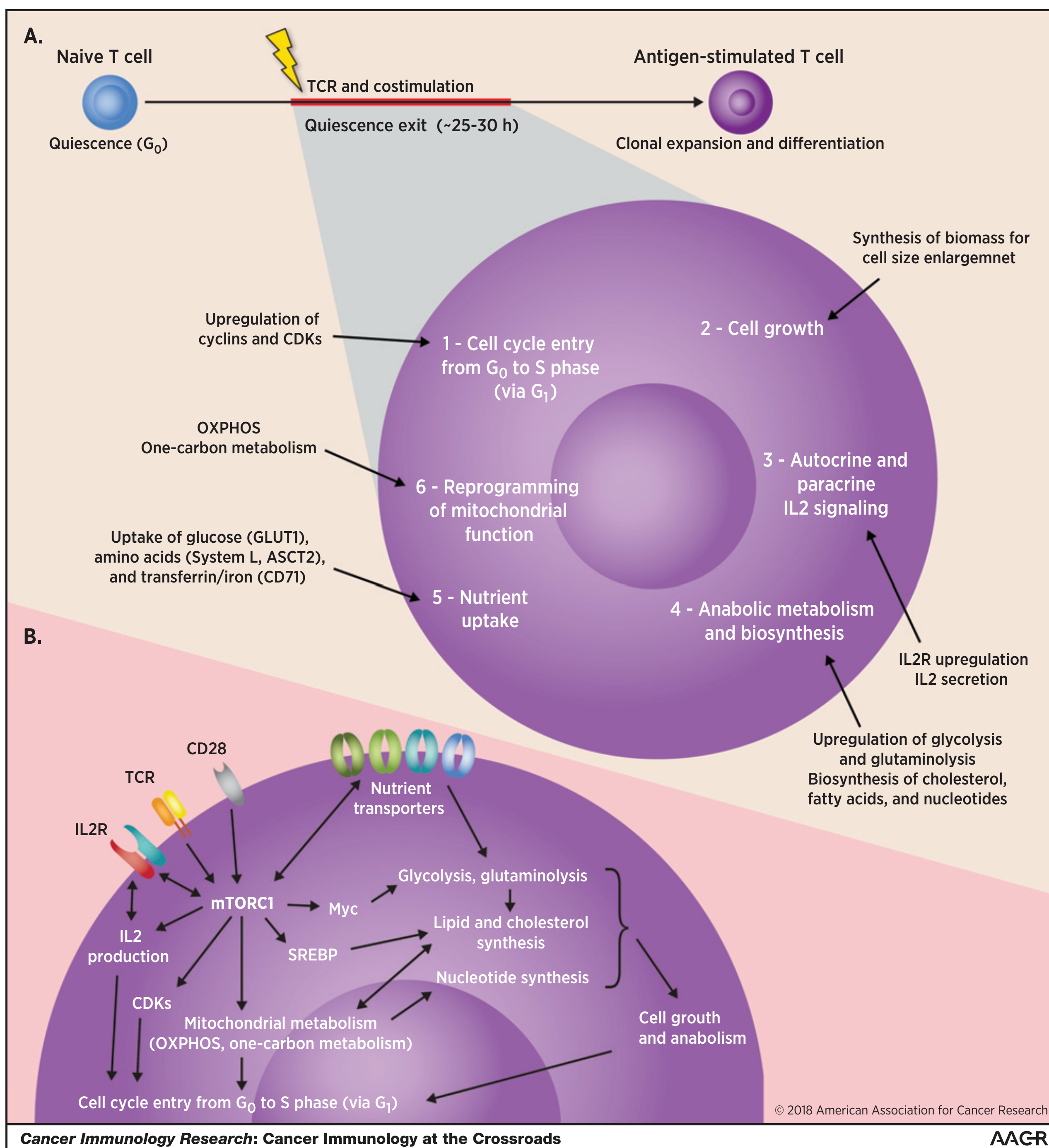

Figure 1.
The hallmarks of T-cell exit from quiescence. **A,** Naïve T cells are actively maintained in a quiescent state defined by residing in stage G_0 of the cell cycle. During the ~25–30 hours window following TCR and costimulatory receptor activation, T cells undergo quiescence exit, which is defined by six key hallmarks shown in white text within the large cell in the center. Distinguishing features of each hallmark of quiescence exit are depicted surrounding this cell. The escape from quiescence is complete when the antigen-stimulated T cells enter into the mitosis and cytokinesis periods of the cell cycle. After these periods, antigen-stimulated T cells can continue to proliferate and differentiate into specialized effector cells. **B,** mTORC1 activates many transcriptional, translational, and metabolic pathways that act in concert to enforce T cell exit from quiescence. The pathways indicated in white are identifiable features of T-cell quiescence exit. CDKs = cyclin-dependent kinases; OXPHOS = oxidative phosphorylation.

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suppresses the activity of the CDK4/6–cyclin D complex (3, 5, 7). Mechanistically, p16-mediated inhibition of CDK4/6 impairs TCR and CD28-induced cell survival, as p16-deficient T cells accumulate owing to increased cell survival, not proliferation (8). In contrast, p18-deficient T cells have enhanced proliferation following concanavalin A stimulation (9), suggesting that distinct CDK4/6 complex inhibitors can differentially sense mitogenic signals to support T-cell survival versus progression through the cell cycle during quiescence exit.

As cells progress through G_1, CDK4/6–cyclin D activity is no longer required and the activity of the CDK2–cyclin E complex is upregulated to promote entry into S phase (5, 6), which is indicated by increased phosphorylation of Rb protein (3). The CDK2–cyclin E complex is inhibited by p27, but signals initiated by the TCR and CD28, transduced through the Src kinases and Akt, promote p27 degradation and cyclin E expression, resulting in CDK2 activity and the proliferation of T cells (5, 10–12). Although p27-deficient T cells are hyperproliferative even in the absence of costimulation (10–12), CDK2-deficient T cells do not have impaired proliferation (13), indicating that other interphase CDKs might compensate for CDK2 to ensure progression through the cell cycle.

Cell Growth

Naïve T cells nearly double in size during the first 24 hours after antigen stimulation. The transition into the cell cycle and increased cell growth are coordinated processes during quiescence exit. Indeed, blocking the G_0 to G_1 transition via inhibition of CDK4/6 inhibits activation-induced human T-cell growth (7), indicating that the G_0 to G_1 transition is a *bona fide* checkpoint for T-cell exit from quiescence. Cell growth begins during quiescence exit and is marked by the increased RNA and protein synthesis that is necessary for the housekeeping functions of cells. Included among these synthesized proteins are those necessary for the DNA replication that occurs during S phase. The increase in RNA and protein synthesis allows cells to meet a "critical mass" (also called the restriction point) necessary to enter into S phase. In addition to proteins, various lipid molecules are synthesized during cell growth to allow for proper cell division (5, 6). The mechanisms driving biosynthesis during cell growth are discussed in more details below.

Genetic studies show that cell growth plays a crucial role in mediating T-cell exit from quiescence. We have demonstrated that inhibition of the nutrient sensor mTORC1 decreases $CD4^+$ T-cell growth in response to antigen stimulation (14). Consequently, $CD4^+$ T-cell proliferation and differentiation are impaired upon genetic deletion of *Rptor* (encodes Raptor, the obligate adaptor for mTORC1 assembly). Conversely, loss of Tsc1, an upstream inhibitor of mTORC1, drives spontaneous exit from quiescence of naïve $CD4^+$ and $CD8^+$ T cells (15). mTORC1 activity is essential for the G_0 to G_1 transition, whereas cells that have already began active cycling are less dependent upon mTORC1 for their entry into S phase or proliferation (14). Mechanistically, mTORC1 induces ribosome biogenesis and mediates protein translation by activating $p70^{S6K}$ and inhibiting the 4E-BP translational repressors (16). mTORC1 also supports the upregulation of the interphase CDKs and cyclins following TCR and CD28 costimulation (14), thus ensuring that both cell growth and cell-cycle progression are coordinated upon T-cell activation. In addition, mTORC1 activation promotes c-Myc expression (14, 17), and c-Myc–deficient T cells also display cell growth and proliferation defects (17), in part, because c-Myc can induce the expression of the interphase CDKs and cyclins (6). Thus, the mTORC1–c-Myc axis is a key mitogenic signaling pathway supporting T-cell growth during quiescence exit.

Autocrine and Paracrine IL2 Signaling

Besides antigenic signals, growth factors are also crucial regulators of cell growth and cell-cycle progression (5, 6). IL2 is a key growth factor for T cells, and its signaling is mediated by the IL2 receptor (IL2R), which is comprised of α (CD25), β (CD122), and common γ (γ_c, CD132) chains. Naïve T cells constitutively express CD132 and little CD122, which interact and form an intermediate affinity IL2R complex. Upon TCR and CD28 costimulation, the transcription factors NF-κB, NFAT, and AP-1 induce *Il2* transcription and promote *Il2ra* (gene for CD25) upregulation via the transcriptional activity of STAT5. Then, autocrine or paracrine IL2 signaling further boosts CD25 and CD122 expression to maintain high-affinity IL2 binding and sustain IL2 signaling (18).

In addition to the conventional STAT5 pathway, IL2 signaling activates the PI3K–Akt–mTOR pathway to promote and sustain T-cell growth and drive their proliferation (18). Indeed, Raptor-deficient $CD4^+$ T cells have defective IL2 production, CD25 expression, and STAT5 activation after antigen stimulation (14), suggesting that the mTORC1 axis promotes autocrine/paracrine IL2 signaling during quiescence exit. Intriguingly, cell-cycle regulators can also control IL2 production during quiescence exit. The inhibition of CDK2 in $CD4^+$ T cells severely attenuates TCR and CD28-induced IL2 production (13). Thus, the ability to produce IL2 also appears to be coupled to the CD28-dependent regulation of CDK2 activity at the G_1–S checkpoint.

Anabolic Metabolism

T cells rapidly accumulate biomass during quiescence exit, which requires an increase in amino acid, lipid, and cholesterol biosynthesis to allow for augmented protein and membrane synthesis. Like cancer cells, the increased demand for biosynthetic intermediates is met by metabolic adaptation from a catabolic state to an anabolic state mediated by an increase of aerobic glycolysis, also called Warburg metabolism. The classical features of Warburg metabolism are an increase in glucose consumption and lactate production and a concomitant reduction in oxidative phosphorylation (OXPHOS) driven by the mitochondrial electron transport chain (ETC; ref. 19). T cells strongly upregulate aerobic glycolysis upon TCR and CD28 costimulation, and T-cell proliferation and differentiation can be impaired when glycolysis is limiting (4, 20–23). Glycolytic reprogramming is linked to mTORC1-dependent upregulation of the transcription factor c-Myc and glycolytic enzymes such as HK2 and lactate dehydrogenase (LDH; refs. 14, 17, 24), demonstrating that mTORC1 is a key regulator of glucose anabolism in T cells.

Glucose can serve as an energy source for proliferating cells and provide biosynthetic intermediates necessary for promoting cell growth and cellular programming (19). Glycolytic intermediates, such as phosphoenolpyruvate (PEP), serve as precursors for amino acid synthesis that is necessary to support increased protein synthesis that drives cell growth and cell-cycle progression. The synthesis of PEP is also crucial to sustain intracellular Ca^{2+} concentrations that drive NFAT activation (20), which in turn

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regulates metabolic reprogramming and activation of $CD8^+$ T cells, in part, by augmenting mTORC1 activity (25). Additionally, entry of glucose-derived glucose-6-phosphate into the pentose phosphate pathway (PPP) is crucial for producing five carbon sugars that couple with purines and pyrimidines to form nucleotides that support $CD4^+$ and $CD8^+$ T-cell proliferation (26, 27).

Glucose also serves as a precursor for acetyl coenzyme A (CoA), NADH, and NADPH, metabolites crucial for amino acid, fatty acid, and cholesterol biosynthesis (4, 28). Consistent with a role for fatty acid or cholesterol synthesis in the exit of T cells from quiescence and their activation, mTORC1 increases the expression of the sterol regulatory binding protein (SREBP) transcription factors upon $CD4^+$ T-cell activation (14). Both mTORC1 and SREBP cleavage-activating protein (SCAP), which promotes SREBP function, are essential for $CD8^+$ T-cell growth and proliferation (14, 29). Owing to the high biosynthesis demands of the tricarboxylic acid (TCA) cycle flux that promotes acetyl–CoA synthesis, glucose flux alone is insufficient. Therefore, T cells also increase c-Myc–dependent glutaminolysis, which generates α-ketoglutarate (α-KG) and replenishes the TCA cycle (17). Culture media contain high concentrations of glutamine, which may help explain how T cells can overcome restriction of glucose metabolism for their proliferation *in vitro* (21, 24). Thus, mTORC1-induced anabolic metabolism supports biosynthesis to enable T-cell growth during quiescence exit.

Nutrient Uptake

Nutrient uptake also increases during T-cell activation to meet the increased biosynthetic demands. Initial observations demonstrated that T cells exiting from quiescence increase their uptake of glucose, which is facilitated by glucose transporter 1 (GLUT1). Quiescent T cells express little extracellular GLUT1. However, the activation of PI3K–Akt signaling in response to strong TCR signals, or weak or intermediate TCR stimulation combined with CD28 costimulation, induces GLUT1 expression and trafficking to the plasma membrane to facilitate glucose uptake (30, 31). In line with a role for GLUT1 in T-cell activation, genetic deletion of GLUT1 diminishes antigen-induced T-cell proliferation *in vitro* and *in vivo* (23). Conversely, overexpression of GLUT1 enhances $CD4^+$ T-cell growth and IL2 production, which are important for subsequent T-cell proliferation (31), and follicular helper T (T_{FH}) cell differentiation (32). Thus, glucose uptake is a key step for promoting the exit of T cells from quiescence.

Other nutrient transporters are also upregulated during T-cell quiescence exit. T cells upregulate the System L amino-acid transporter (composed of CD98 and LAT1) to facilitate large neutral amino-acid (e.g., leucine) uptake into cells, which is crucial for their proliferation and effector differentiation (33). The expression of glutamine transporters, especially ASCT2, also increases upon antigen stimulation; however, ASCT2-deficient $CD4^+$ T cells do not have proliferation defects despite having reduced glutamine uptake (34), suggesting a functional redundancy between pathways that feed into the TCA cycle during T-cell exit from quiescence. In addition to serving as nutrient sources for metabolic pathways, the uptake of nutrients induces mTORC1 activation. Indeed, glucose and several amino acids (leucine, isoleucine, valine, arginine, and glutamine) activate mTORC1 (16, 22, 33, 34). Thus, mTORC1 activation and nutrient uptake act in a feed-forward loop to ensure that cells exiting from quiescence maintain the appropriate levels of mitogenic signals and nutrient concentrations for cell growth and cell-cycle progression. Finally, mTORC1 activity increases the expression of transferrin receptor (CD71) during T-cell exit from quiescence (14), and human T cells that bear a missense mutation in CD71 are not efficiently activated upon antigen stimulation (35). Thus, mTORC1 is a crucial regulator of nutrient uptake to support anabolic metabolism during quiescence exit.

Remodeling of Mitochondrial Function

Mitochondria are key signaling organelles. In addition to producing ATP via the ETC-OXPHOS, mitochondria regulate cell survival, epigenetic modifications, and biosynthesis (36). The mitochondrial proteome is rapidly remodeled and mitochondrial biogenesis is induced during T-cell quiescence exit (24, 27). Mechanistically, these events are driven, in part, by mTORC1 activation (24). The increase in mitochondrial biogenesis supports two key functions in T cells escaping from quiescence: it increases OXPHOS and augments one-carbon metabolism. Indeed, mTORC1 activity enhances mitochondrial gene expression and protein translation to augment OXPHOS after T-cell activation (14, 24), and inhibition of mitochondrial ETC activity impairs $CD4^+$ and $CD8^+$ T-cell proliferation (24, 37, 38). Mechanistically, mitochondria-derived reactive oxygen species (ROS) generated by complex III of the ETC induces Ca^{2+} signaling, which in turn activates NFAT-dependent *Il2* transcription in T cells (37). In addition to being essential for T-cell proliferation, OXPHOS is protective against cell death, as we and others observed increased apoptosis in $CD4^+$ and $CD8^+$ T cells lacking the ETC complex IV subunit, Cox10 (24, 39). Finally, mitochondrial respiration is essential for generating NAD^+ from NADH, which among other functions limits lysosome biogenesis that can impair T-cell proliferation and differentiation (38).

Enzymes driving folate-one-carbon metabolism, a serine-dependent metabolic pathway that regulates purine and pyrimidine biosynthesis (28), are upregulated in T cells in an mTORC1-dependent manner during quiescence exit (24, 26, 27). These metabolites are precursors for nucleotides, which must be synthesized to promote entry into and progression through S phase of the cell cycle. Consistent with this requirement, inhibition of one-carbon metabolism impairs pyrimidine and purine synthesis and reduces T-cell proliferation without altering their activation, as indicated by the upregulation of the activation markers CD25, CD69, and CD44 (26, 27). The observations that *in vitro*–activated T cells do not synthesize serine but can rather acquire it from extracellular sources could account for why T cells are still able to proliferate when glycolysis is limited *in vitro* (21, 24, 26). Additionally, glutathione produced downstream of one-carbon metabolism neutralizes ROS and protects T cells from activation-induced cell death (27, 28, 40). Thus, the rapid induction of mitochondrial one-carbon metabolism during quiescence exit balances activation-induced apoptosis and proliferation.

Epigenetic modifications regulate T-cell responses (41). Mitochondria can tune epigenetic programs through multiple mechanisms. First, the generation of α-KG via the mitochondria-coupled TCA cycle is important for controlling methylation reactions. Indeed, α-KG is a cofactor for DNA and histone demethylases, and modulation of α-KG and related metabolites can impact $CD4^+$ and $CD8^+$ T-cell fate decisions (42, 43). When

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$NADH/NAD^+$ ratios are high, α-KG is converted into *S*-2-hydroxyglutarate via the activity of LDH, which impedes the activity of these demethylases and increases methylation. Second, acetyl-CoA generated via the TCA cycle can also modify histones and promote active gene transcription (36). Finally, one-carbon metabolism generates *S*-adenosylmethionine, which is a key methyl donor used by histone or DNA methyltransferases to induce methylation (28). It is unclear how the mitochondrial network balances OXPHOS and biosynthetic-related processes that facilitate epigenetic modifications during T-cell exit from quiescence. Mitochondrial fission and fusion determine how efficiently mitochondria induce OXPHOS in activated $CD8^+$ T cells and the inhibition of the ETC alters epigenetic programs (44–46). Thus, it is possible that temporal or spatial regulation of mitochondrial dynamics, in parallel with mitochondrial biogenesis, coordinates the metabolic and epigenetic programs necessary for T cells to exit quiescence.

Quiescence exit is a checkpoint for naïve T-cell activation

Quiescence exit is a key feature of T-cell activation, but what is the function of quiescence exit as it relates to T-cell activation? To investigate this question, we explored the functional importance of mTORC1-related signaling for T-cell activation, as measured by cellular proliferation and differentiation into $CD4^+$ T_H2 cells. Completion of the first cell division defines the point at which cells have officially escaped quiescence, which occurs within 30 hours of cell activation (1, 3). Therefore, we inhibited mTORC1 signaling and aerobic glycolysis at the onset, or after 24 hours of TCR and CD28 costimulation to determine how quiescence exit affects $CD4^+$ T-cell activation. When mTORC1 activity or glycolysis is inhibited at the time for naïve $CD4^+$ T cells to receive TCR and CD28 costimulation, they do not proliferate and fail to differentiate into T_H2 cells. However, inhibition of these pathways after 24 hours of stimulation leads to only a partial block in proliferation or T_H2 differentiation, compared with inhibition before activation. T cells that had exited from quiescence (i.e., were no longer in G_0) and had been activated for 48 hours no longer require mTORC1 activity or glycolysis for proliferation or T_H2 differentiation (14). Together, these studies emphasize that T-cell proliferation and differentiation into effector T cells is determined, at least partially, during the period defined as quiescence exit, demonstrating that quiescence exit is a checkpoint for $CD4^+$ T-cell activation.

What happens if naïve T cells do not meet all the criteria for quiescence exit described here? An analysis of T cells deficient in the ETC complex IV subunit has begun to address this question. As noted earlier, Cox10-deficient T cells undergo activation-induced cell death and also have reduced proliferation. These cells also fail to become T_H1, T_H2, and T_H17 cells *in vitro* and have decreased effector $CD4^+$ T-cell responses *in vivo* (24, 39). Analysis of several of the hallmarks of quiescence exit showed that Cox10-deficient $CD4^+$ or $CD8^+$ T cells have impairments in cell-cycle entry/progression (hallmark 1) and mitochondrial respiration (component of hallmark 6), whereas paracrine and autocrine IL2 signaling (hallmark 3), glucose uptake and aerobic glycolysis (components of hallmark 4), and expression of GLUT1, CD71, and CD98 (components of hallmark 5) are not markedly affected (24, 39). Therefore, these results suggest that the failure to fulfill even a subset of the hallmarks for quiescence exit can profoundly impair T-cell responses. Future studies are needed to establish how hallmarks of quiescence exit are temporally regulated, to what extent they need to be upregulated, and how they intersect with the other hallmarks to influence both $CD4^+$ and $CD8^+$ T-cell responses. Overall, this information will help investigators gain a better understanding of the role of quiescence exit in T-cell activation.

Manipulation of quiescence exit and T cell–mediated therapies

Vaccinations strategies aim to increase the pool and function of memory T cells that recognize tumors or pathogens (47). Strategies to manipulate quiescence exit have been explored as a means to boost memory T-cell responses. For instance, mTORC1 signaling positively regulates effector $CD8^+$ T-cell effector responses, but suppresses the formation of memory $CD8^+$ T cells during viral infections (48, 49). Compared with effector $CD8^+$ T cells, memory $CD8^+$ T cells have enhanced mitochondrial fusion that leads to increased mitochondrial OXPHOS (44, 50). When mitochondrial metabolism is enforced, $CD8^+$ T cells preferentially differentiate into memory cells and have enhanced function against viruses and tumors (4, 44, 51). Thus, mTORC1 activity and mitochondrial metabolism balance $CD8^+$ effector and memory T-cell fate decisions and may be attractive targets to help promote more effective memory $CD8^+$ T-cell responses against pathogens or tumors. Effective vaccinations can also be developed by invoking antibody responses, which are facilitated by T_{FH} cells that promote B-cell differentiation into germinal center B cells and long-lived plasma cells (52). mTORC1 and GLUT1-dependent glycolysis are essential for promoting T_{FH} responses (32, 53). Therefore, targeting mTORC1 or glycolysis in $CD4^+$ T cells could diminish vaccination-induced neutralizing antibody responses. However, these pathways might be useful targets in autoimmune diseases where autoantibody responses are often elevated (52).

Adoptive T-cell and checkpoint blockade therapies are rapidly emerging as potent cancer treatments (47). Altering the quiescence exit hallmarks may also increase the efficacy of these therapies. Enforcing PEP production or OXPHOS enhances the antitumor responses of adoptively transferred $CD8^+$ T cells (4, 20, 51), suggesting that manipulating the metabolic hallmarks of quiescence exit can enhance adoptive T-cell therapies for cancer. Programmed death-1 (PD-1) and cytotoxic T-cell antigen-4 (CTLA-4) checkpoint blockade therapies can also augment endogenous T-cell accumulation or function with the tumor microenvironment (47). T cells rapidly upregulate the expression of PD-1 and CTLA-4 upon activation (54, 55), and PD-1 signaling in human $CD4^+$ T cells decreases activation-induced glycolysis and amino-acid catabolism, and increases the rate of OXPHOS induced by fatty acid catabolism (54). This observation was true even in cells that were activated for as little as 4 hours before PD-1 ligation. Likewise, CTLA-4 ligation combined with TCR and CD28 costimulatory signals inhibits glucose and glutamine metabolism within human $CD4^+$ T cells (54). These results indicate that PD-1 or CTLA-4 checkpoint blockade might boost antitumor responses, in part, by augmenting the glycolysis necessary for naïve $CD4^+$ T cells to differentiate into potent effector $CD4^+$ T cells. Whether these observations are similar in $CD8^+$ T cells remains unknown. Together, these studies provide exciting evidence that modulating the exit of naïve T cells from quiescence

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could have strong effects for tuning T-cell responses to treat various diseases.

Concluding Remarks

The exit of T cells from quiescence is now firmly established to depend upon the coordinated actions of transcriptional, translational, and metabolic programs. Activation of mTORC1 is essential for transcriptome, proteome, and metabolome remodeling during quiescence exit. Here, we have highlighted six key features of T cells escaping from quiescence. Understanding how naïve T cells meet each of these criteria will be crucial for the manipulation of T-cell responses in vaccines, cancer immunotherapy, and autoimmune diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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