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T cell metabolism in homeostasis and cancer immunity

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Abstract

T cells shape immune responses in cancer, autoimmunity and infection, in which $CD4^+$ T helper (Th) and $CD8^+$ T cells mediate effector responses that are suppressed by regulatory T (T_{reg}) cells. The balance between effector T cell and T_{reg} cell function orchestrates immune homeostasis and functional programming, with important contributions to the onset and progression of cancer. Cellular metabolism is dynamically rewired in T cells in response to environmental cues and dictates various aspects of T cell function. In this review, we summarize recent findings on how cellular metabolism modulates effector T cell and T_{reg} cell functional fitness in homeostasis and cancer immunity, and highlight the therapeutic implications of targeting immunometabolic pathways for cancer and other diseases.

Keywords

immunometabolism; cancer; Treg; effector T cell; homeostasis

Introduction

Conventional $CD4^+$ or $CD8^+$ αβ T cells that express T cell receptors (TCRs) recognizing tumor- and self-antigens play pivotal roles in shaping immune responses in cancer and autoimmune diseases. Upon cognate antigen stimulation, T cells are activated, proliferate, and undergo functional specialization in response to environmental cues. Antigen-inexperienced naïve $CD8^+$ T cells differentiate into cytotoxic effector cells and long-lived memory cells. Naïve $CD4^+$ T cells differentiate into Th1, Th2, Th17, and Tfh effector cells, which can also form long-term memory cells, as well as Foxp3-expressing immune-suppressive T_{reg} cells [1].

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One long standing goal of cancer immunotherapy is to identify factors that stimulate T cell responses to tumor antigens. Tumor antigens may be unique to tumors (tumor-specific antigens) or self-antigens expressed with temporally and spatially distinct patterns (tumor-associated antigens). Cancer development is frequently associated with an immunosuppressive tumor microenvironment (TME) wherein tumor-specific cytolytic $CD8^+$ T cells are often underrepresented among T cells and T cells are frequently dysfunctional and unable to eradicate malignant cells. In addition, T_{reg} cells accumulate and undergo functional maturation in tumors, supporting an immunosuppressive TME [2]. As a consequence, tumor antigens are often unable to elicit an effective antitumor response. While targeting immune checkpoint pathways has shown remarkable clinical success by reinvigorating tumor-specific T cell responses, one of the major challenges is the development of autoimmune-like immune-related adverse events (irAEs). Moreover, although T_{reg} cell ablation can rapidly eradicate tumors, loss of T_{reg} cell function promotes development of severe autoimmune and inflammatory complications [3,4]. Therefore, successful immunotherapies require an in-depth understanding of the mechanisms underlying immune homeostasis under steady state and antitumor immunity.

Although immune receptors, signaling proteins, and transcription factors dictate T cell responses, emerging data has identified cellular metabolism as a central regulator of T cell survival, proliferation, and function [5]. How metabolic rewiring impacts T cell functional adaptation in situ remains underexplored. Recently, extensive efforts have been made to fill this gap, by exploring immunometabolic changes underlying effector T cell and T_{reg} cell functional fitness in the TME and other disorders, with important therapeutic implications. Given the availability of excellent reviews [6–9], we mainly discuss the recent progress, with a particular focus on immunometabolism in effector T cells and T_{reg} cells in the TME.

T cell metabolism in immunity and homeostasis

Cell-intrinsic metabolic pathways direct the activation state of T cells (Figure 1a). In particular, aerobic glycolysis, glutaminolysis and mitochondria-associated functions, such as oxidative phosphorylation (OXPHOS) and one-carbon metabolism, support effector T cell responses by regulating their activation and differentiation. Overall, these pathways serve as bioenergenetic, biosynthetic, and signaling hubs to allow for the proliferative expansion and effector differentiation of T cells [10]. Aside from cell-intrinsic metabolic factors, metabolic rewiring in response to extracellular nutrients, metabolites, and growth factors also modulates effector T cell functional fitness. Indeed, glucose transport into cells is important for supporting aerobic glycolysis, while glucose, glutamine or fatty acid catabolism can drive flux via the tricarboxylic acid (TCA) cycle to support biosynthetic reactions and mitochondrial OXPHOS, both of which are essential for regulating T cell functionality [10,11]. Aside from glutamine, other amino acids have also been implicated in supporting T cell activation and immune responses [12]. For instance, extracellular methionine regulates epigenetic programming to tune $CD8^+$ T cell fate decisions and cooperates with serine (which can be synthesized de novo from glucose or derived from extracellular sources) to promote one-carbon metabolism [13–15]. Further, serine metabolism is also essential for regulating cellular redox state through synthesis of glutathione (GSH), an important regulator of $CD4^+$ and $CD8^+$ T cell responses [16,17]. By integrating cell-intrinsic and

extrinsic metabolic programs, T cells play a critical role for antitumor immunity and represent the cornerstone for successful immunotherapies.

T_{reg} cells exert potent immunosuppressive function and thereby maintain self-tolerance and control autoimmunity and tissue inflammation [3]. Recent results reveal novel roles for cellular metabolic processes in regulating T_{reg} cell functional integrity (Figure 1b). T_{reg} cells have distinct glycolytic and mitochondrial metabolism from effector $CD4^+$ T cells [18,19]. Moreover, mitochondrial metabolism is crucial for supporting T_{reg} cell function, self-tolerance, and immune homeostasis, as evidenced by the development of autoimmune diseases in T_{reg}-specific deletion of mitochondrial respiratory chain components or mitochondrial transcription factor A (Tfam), which is important for mitochondrial respiratory chain activity [20–23]. T_{reg} cells also require anabolic processes, such as lipid synthesis, for their activation and function [10]; however, excessive aerobic glycolysis or mitochondrial respiration that produces ROS is detrimental to T_{reg} cell lineage stability [24–27]. Recent studies have uncovered important roles of nutrient availability in modulating T_{reg} cell functional fitness. Specifically, amino acids, especially arginine and leucine, signal through RagA/B and Rheb1/2 to license TCR-induced mTORC1 activation and subsequent mitochondrial metabolic changes in T_{reg} cells [28,29]. Additionally, aberrant serine uptake and metabolism caused by GSH loss in T_{reg} cells leads to increased mTORC1 activation, proliferation, impaired Foxp3 expression, and suppressive function, resulting in the development of lethal autoimmune inflammation that can be rescued by a serine/glycine-deficient diet [30]. Lastly, intestinal immune homeostasis is maintained by T_{reg} cells, and microbial bile acid metabolites are essential for colonic T_{reg} cell generation and suppression of intestinal inflammation [31–33]. These studies collectively indicate that T_{reg} cell functional integrity and suppression of autoimmune responses requires proper cellular metabolic programming.

Metabolic activation of tumor-specific T cells

The immunosuppressive TME is one of the hallmarks of cancer and underlies the basis for tumor immune evasion [4]. Effector T cells play a pivotal role in controlling cancer; conversely, T_{reg} cells promote immunosuppression in the TME that is often associated with tumor progression. Therefore, the functional balance between effector T cells and T_{reg} cells is a key determinant of the effectiveness of immune control of tumor progression. Recent studies have made significant progress in elucidating the roles of immunometabolism in dictating the functional fitness of effector T cells (Figure 2) and T_{reg} cells (Figure 3) in the TME, and hence this effector-regulatory balance.

Glucose metabolism is an essential regulator of T cell function in tumors, a site where competition for nutrients, including glucose, often occurs [5]. Accordingly, restriction of glucose or the glycolytic metabolite phosphoenolpyruvate (PEP) in effector $CD8^+$ T cells dampens antitumor responses [34–36]. However, it was recently reported that the antitumor activity of adoptively transferred $CD8^+$ T cells can be improved by acute glucose restriction, which enables them to more efficiently shuttle glucose-derived carbons into anabolic programs upon glucose refeeding [37]. $CD8^+$ T cells can also utilize inosine as a carbon source to support cell proliferation and effector function under glucose restriction conditions

in vitro [38], and inosine can promote effector T cell expansion and function in the TME [38,39]. How T cell adaptations to alternative nutrient sources impact effector function in the TME remains to be fully explored. PI3K-mTOR signaling has a well-established role in glucose metabolism [40], but its upstream regulators in primary T cells are less well understood. Recently, acylglycerol kinase (AGK), an enzyme involved in lipid and glycolipid metabolism, was identified as an upstream activator for mTORC1 and subsequent metabolic reprogramming by interacting with and inhibiting PTEN (the lipid phosphatase that antagonizes PI3K signaling) upon following antigen recognition, thereby promoting $CD8^+$ T cell proliferation and antitumor functions [41]. Thus, glucose metabolism regulates cellular signaling and anabolic programs to support tumor-specific T cell function.

T cells also require mitochondria to fulfill the metabolic requirements for rapid proliferation, activation, and function [5]. Accordingly, impaired mitochondrial fitness underlies effector $CD8^+$ T cell dysfunction in tumors [42–44], while restoring mitochondrial metabolism rescues tumor-infiltrating effector $CD8^+$ T cell function [45]. Recent studies have uncovered important factors supporting mitochondrial metabolism, thereby fueling effector T cell expansion and function in the TME. Transcription factors have well-established roles in shaping effector T cell responses [46], and transcription factor–mediated metabolic programming and its contribution to antitumor T cell responses is just beginning to be explored. The transcription factor BATF has been identified to be a limiting factor for tumor-specific $CD8^+$ T cell expansion and effector function in tumors, in part by supporting mitochondrial fitness [47]. Interestingly, unlike in tumors, BATF overexpression does not boost effector $CD8^+$ T cell expansion in a viral infection model [48], suggesting unexpected context specificity. Additionally, the transcription factor Bhlhe40 helps sustain mitochondrial metabolism that drives acetyl-coenzyme A (CoA) synthesis and acetyl-CoA-associated functional epigenetic programing in tumor-infiltrating $CD8^+$ T cells that promotes their accumulation and effector function [49]. $CD8^+$ T cell dysfunction in tumors is, in part, driven by downregulation of Bhlhe40 downstream of PD-1 signaling. Indeed, anti-PD-L1 blockade-dependent reinvigoration of tumor-infiltrating $CD8^+$ T cell requires Bhlhe40 re-expression [49]. Therefore, transcription factor control can act by modulating metabolic functions during antitumor immunity, and transcription factor activity intersects with key checkpoint blockade pathways, including PD-1–PD-L1.

Recent studies have uncovered additional metabolites that modulate effector T cell function in the TME. Specifically, mitochondrial respiration is supported by the intracellular metabolite BH4, which is generated by the rate-limiting enzyme GTP cyclohydrolase 1 (GCH1). Deleting GCH1 in T cells leads to defective proliferation and mitochondrial respiration; in contrast, enhancing production of BH4 by overexpressing GCH1 enhances the proliferation of both tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, thereby inhibiting tumor growth [50]. Furthermore, in the TME, methylglyoxal from myeloid-derived suppressor cells (MDSCs) dampens $CD8^+$ T cell mitochondrial respiration, activation, and proliferation, partially by depleting L-arginine [51]. This observation is in line with the crucial role of L-arginine in supporting antitumor effector $CD8^+$ T cell function [52]. These results highlight the indispensable roles of cellular metabolites in programming effector T cell mitochondrial metabolism and effector function in the TME.

Metabolic control of T cell differentiation state in the TME

The antitumor activity of tumor-specific $CD8^+$ T cells critically depends upon their differentiation state and longevity [53]. Recent findings have established the role of immunometabolism in controlling tumor-infiltrating effector T cell fate decisions. In the TME, most tumor-specific $CD8^+$ T cells express high levels of inhibitory receptors, possess limited effector function, and often acquire a dysfunctional differentiation state termed exhaustion [53]. Recent work has begun to illuminate the metabolic drivers of tumor-infiltrating $CD8^+$ T cell dysfunction. Although increased cholesterol level in the plasma membrane potentiates antitumor $CD8^+$ T cell responses [54], cholesterol uptake by tumor-infiltrating $CD8^+$ T cells in the TME activates ER stress response and inositol-requiring enzyme 1 alpha (IRE1α)–X-box binding protein-1 (XBP1) signaling to induce inhibitory receptor expression and $CD8^+$ T cell exhaustion [55], indicating divergent roles of cholesterol metabolism in modulating T cell function. Additionally, methionine metabolism-dependent epigenetic programming is essential to establish $CD8^+$ T cell effector function, but tumor cells often express high levels of the methionine transporter Slc43a2, leading to $CD8^+$ T cell dysfunction by outcompeting $CD8^+$ T cells for methionine in the TME [13]. High expression of Slc43a2 on tumor cells correlates with $CD8^+$ T cell dysfunction in patients, and supplementation of methionine reverses $CD8^+$ T cell dysfunction and restores antitumor responses [13]. It will therefore be important to explore how nutrient fluctuations in the TME drive $CD8^+$ T cell dysfunction.

Although exhausted $CD8^+$ T cells have limited effector function, a subset of tumor-infiltrating exhausted $CD8^+$ T cells preserve a stem cell-like state, with preserved self-renewal capacity and reconstitution of effector subsets. The adoption of a stem-like state is essential for tumor-specific $CD8^+$ T cell persistence and antitumor efficacy [56], and hence there has been great interest in understanding the metabolic programs that promote “stemness” of $CD8^+$ T cells to improve tumor immunotherapy. In particular, pathways that improve mitochondrial fitness have emerged as crucial regulators of stem-like versus dysfunctional T cells in the TME. Indeed, in response to chronic antigen stimulation in the TME, mitochondrial oxidative stress increases in $CD8^+$ T cells, resulting in reduced stemness and antitumor efficacy associated with increased T cell dysfunction [57]. These effects can, in part, be attributed to an accumulation of depolarized mitochondria in tumor-infiltrating $CD8^+$ T cells, owing to reduced mitophagy in these cells [27]. It has recently been shown that altering redox metabolism in favor of a reduced state, either via acute glucose restriction or antioxidant treatment, can improve the antitumor activity of $CD8^+$ T cells; this effect is associated with improved self-renewal capacity of the T cells [37,57,58]. Although high levels of potassium in tumor tissues activate starvation response-associated mitochondrial metabolism that inhibits effector differentiation-associated epigenetic remodeling, potassium-stimulated tumor-infiltrating $CD8^+$ T cells also acquire stemness-associated programs that equip them with potent antitumor activity [59]. Mitochondrial respiratory capacity is also linked to the $CD8^+$ T cell stem-cell-like state, with memory $CD8^+$ T cells displaying high mitochondrial SRC [60–62]. Accordingly, blocking glutamine metabolism in the TME enhances oxidative metabolism and SRC, driving $CD8^+$ T cells to adopt a long-lasting stem cell-like state that is associated with superior antitumor responses [63,64]. Additionally, the adipokine leptin induces metabolic reprogramming in tumor-

infiltrating CD8$^+$ T cells, resulting in increased SRC, stem-cell-like phenotypes, and antitumor function [65]. Finally, it was recently shown that inhibition of MEK signaling could improve mitochondrial OXPHOS driven by fatty acid oxidation and enhance the stemness of CD8$^+$ T cells for antitumor immunity [66]. Thus, pathways that improve mitochondrial function, including SRC and fatty acid oxidation, and reduce oxidative stress represent promising targets to improve T cell longevity, thereby promoting better antitumor responses by T cells.

Negative control of T cell metabolic activity in antitumor immunity

In addition to these positive regulators of mitochondrial fitness, factors suppressing metabolism and effector T cell expansion and function during antitumor immunity have been revealed. As a result of their high rate of aerobic glycolysis, tumor cells often produce and secrete lactate, which has been shown to diminish T cell responses by limiting the activation of CD8$^+$ T cells and aerobic glycolysis in CD4$^+$ T cells [67,68]. Ovarian tumors have been found to suppress mitochondrial metabolism in CD4$^+$ and CD8$^+$ T cells by inducing ER stress and downstream XBP1 signaling in T cells; notably, targeting XBP1 restores tumor-infiltrating effector T cell mitochondrial respiration, function, and antitumor effects against ovarian tumors [69]. Additionally, although *S*-2-hydroxyglutarate produced by activated CD8$^+$ T cells promotes the proliferation and antitumor activity of CD8$^+$ T cells [70], its enantiomer *R*-2-hydroxyglutarate is produced by isocitrate dehydrogenase (*IDH*)-mutated tumors and accumulates in tumor tissues to dampen mitochondrial respiration and paralyze both CD4$^+$ and CD8$^+$ effector T cells in the TME [71]. Inhibiting *R*-2-hydroxyglutarate production in the TME restores antitumor effector CD8$^+$ T cell response and impairs tumor growth [71]. Thus, external factors present in the TME can suppress the antitumor activity of T cells.

Cell-intrinsic negative regulators of metabolic reprogramming of T cells have also been reported. For example, signaling via the checkpoint blockade molecules PD-1 and CTLA4 can alter the metabolic status, including reducing glycolysis, of activated CD4$^+$ and CD8$^+$ T cells [72,73], suggesting that immunotherapies targeting these molecules may act, in part, by rewiring metabolic programs of tumor-infiltrating T cells. Moreover, the endoribonuclease Regnase-1 is a major negative regulator of effective antitumor CD8$^+$ T cell responses via its suppression of BATF-dependent mitochondrial fitness, and Regnase-1 inhibition unleashes robust tumor-specific CD8$^+$ T cell expansion in tumor sites [47]. Sirtuin-2 (Sirt2), a NAD$^+$-dependent deacetylase, inhibits glucose, lipogenic, and mitochondrial metabolism by repressing expression of key metabolic enzymes, and inhibition of Sirt2 potentiates both CD4$^+$ and CD8$^+$ T cell proliferation and antitumor function. The repression of T cell metabolism and antitumor responses by SIRT2 is also observed in patients with cancer [74]. Collectively, these findings demonstrate that metabolism is an essential determinant of antitumor T cell expansion and effector function. Further studies are required to reveal how the various positive and negative regulatory factors of metabolic fitness are coordinated in the TME.

T_{reg} cell metabolism and tumor immunosuppression

T_{reg} cells often accumulate in tumors, where they establish an immunosuppressive TME and inhibit antitumor effector responses, making them both a major hurdle and a promising target for cancer immunotherapy [4]. Given the indispensable role of T_{reg} cells in maintaining self-tolerance and immune homeostasis [3], the selective disruption of T_{reg} cell function in tumors is a considerable challenge. As an example, T_{reg} cell-specific deletion of RagA, a guanine nucleotide-binding protein that mediates amino acid-induced mTORC1 activation, reinvigorates antitumor T cell responses and inhibits tumor growth; however, loss of RagA also promotes development of delayed onset autoimmunity, and combined deficiency of RagA and RagB leads to *Scurfy*-like autoimmunity in mice, as is seen in mice lacking T_{reg} cells [28,29]. Similarly, deletion of the mitochondrial transcription factor A (Tfam), which is important for mitochondrial respiratory chain activity, in T_{reg} cells impairs tumor-infiltrating T_{reg} cell accumulation and lineage stability and dampens tumor growth. However, T_{reg} cells with mitochondrial respiratory chain deficiency also cannot maintain self-tolerance [20–23]. Therefore, the consequences of the rewiring of T_{reg} cells metabolic programs are complex, and how to enforce functional adaptation selectively in tumors remains to be explored.

T_{reg} cells exhibit a metabolic profile distinct from that of effector T cells [18,19,75], suggesting that the identification of pathways associated with their unique metabolic state, especially in the TME, could provide powerful insights for cancer immunotherapy. A recent study has made progress in this regard, demonstrating that glucose metabolism is important for supporting the suppressive function of human peripheral blood T_{reg} cells, and inhibition of glucose metabolism through TLR8 activation dampens T_{reg} cell activity in both lymphoid tissue and tumors [75]. The scavenger receptor CD36, which mediates the uptake of long-chain fatty acids, is upregulated on tumor-infiltrating T_{reg} cells [76]. CD36 is specifically required for T_{reg} cell accumulation in tumors by maintaining peroxisome proliferator-activated receptor-β (PPAR-β) signaling-dependent mitochondrial fitness [76]. In contrast, inhibition of fatty acid binding protein 5 (FABP5), a lipid chaperone that is required for lipid uptake, enhances the suppressive function of T_{reg} cells, which is associated with altered mitochondrial fitness [77], suggesting that fatty acid uptake through FABP5 represses T_{reg} cell suppressive activity. Accordingly, tumor-infiltrating T_{reg} cells are found to take up fewer fatty acids than peripheral T_{reg} cells, and display both the mitochondrial alterations observed in FABP5-deficient T_{reg} cells and enhanced suppressive activity [77]. Further studies are required to uncover the requirements and underlying mechanisms by which lipid metabolism dictates T_{reg} cell fitness in tumors, which may help reconcile these seemingly disparate findings. It is also urgent to investigate whether and how T_{reg} cell functional fitness can be selectively shaped in the TME by modulating intracellular metabolic networks.

Conclusions and prospects

Although multiple cellular metabolic pathways control effector T cell and T_{reg} cell functional fitness in the TME and inflamed tissues, it is unclear how inputs from various metabolic factors are coordinated in complex disease contexts. Several important questions remain to be addressed. First, context-specific functions of cellular metabolism in

modulating T cell functional states need to be clarified. For example, Gpi1-dependent metabolism is indispensable for $CD4^+$ Th17 cells in hypoxic inflammatory but not homeostatic conditions [78], illustrating the need to further explore immunometabolism in specific diseases. Identifying functionally relevant regulators and pathways in each physiological context will be necessary to define how immunometabolic pathways can be therapeutically modified in the TME, especially to avoid the development of autoimmunity or irAEs. The successful application of pooled CRISPR-Cas9 mutagenesis screening of metabolism-related factors, such as that employed in the antitumor $CD8^+$ T cell response [47], will enable the systematic and unbiased discovery of key metabolism-related molecules and pathways controlling a given T cell function in defined conditions. In addition, the metabolic states of T cells need to be profiled in disease contexts, such as by using robust metabolic tracing methods in $CD8^+$ T cells that can uncover fundamental differences between T cell metabolic phenotypes profiled *in vivo* and *in vitro* [15].

Second, given the heterogeneity of T cell functional populations in the TME and organs under steady state, the roles of metabolic factors in modulating T cell functions and fate decisions in these diseases should be investigated at the single-cell resolution. For example, recent single-cell RNA-sequencing results revealed the respective roles of Regnase-1 and mTORC1 in defining a memory cell-like subset among bulk tumor-specific $CD8^+$ T cells and $CD4^+$ Th17 cells [47,79]. The development of cutting-edge technologies, such as combining pooled CRISPR screening and single-cell transcriptome profiling [80–82], further enables the systematic identification of functionally-relevant factors in T cell functions and fate decisions at the single-cell resolution. Emerging single-cell metabolic profiling techniques that can reveal metabolic heterogeneity among T cell subsets or those in diverse tissue environments may also be useful in characterizing the cell populations with the highest antitumor efficacies, including certain stem-like populations [83–85].

Third, recent studies highlight that tumor cells can functionally paralyze T cells by modulating the availability of metabolites in the TME [13,71]. More studies are needed to further identify how nutrient-sensing processes influence T cell function in tumors. Indeed, there is emerging evidence that systemic nutritional status can impact antitumor immunity or cancer therapy [86,87]. Moreover, evidence from clinical trials support the notion that dietary alterations may improve clinical prognosis to cancer therapies [87], although the impacts on the immune system require additional investigation. Thus, understanding the mechanisms underlying how cell- or microenvironment-specific nutrient transport, sensing, and signaling occurs in conventional T cells or T_{reg} cells may lead to novel therapies for targeting of immunometabolism in cancers without leading to adverse events, including autoimmunity or irAEs. Collectively, a detailed profile and comprehensive understanding of T cell metabolism in disease contexts will translate into innovative therapies for cancer and autoimmune diseases.

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Papers of particular interest, published within the period of review, have been highlighted as:

● of special interest

●● of outstanding interest

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Highlights

1. Cell-intrinsic and -extrinsic factors influence the metabolic state of T cells
2. Glucose and mitochondrial metabolism regulate antitumor activity of T cells
3. Targeting T_{reg} cell metabolism has therapeutic potential for tumor immunity
4. Future perspectives in immunometabolism and antitumor immunity are discussed

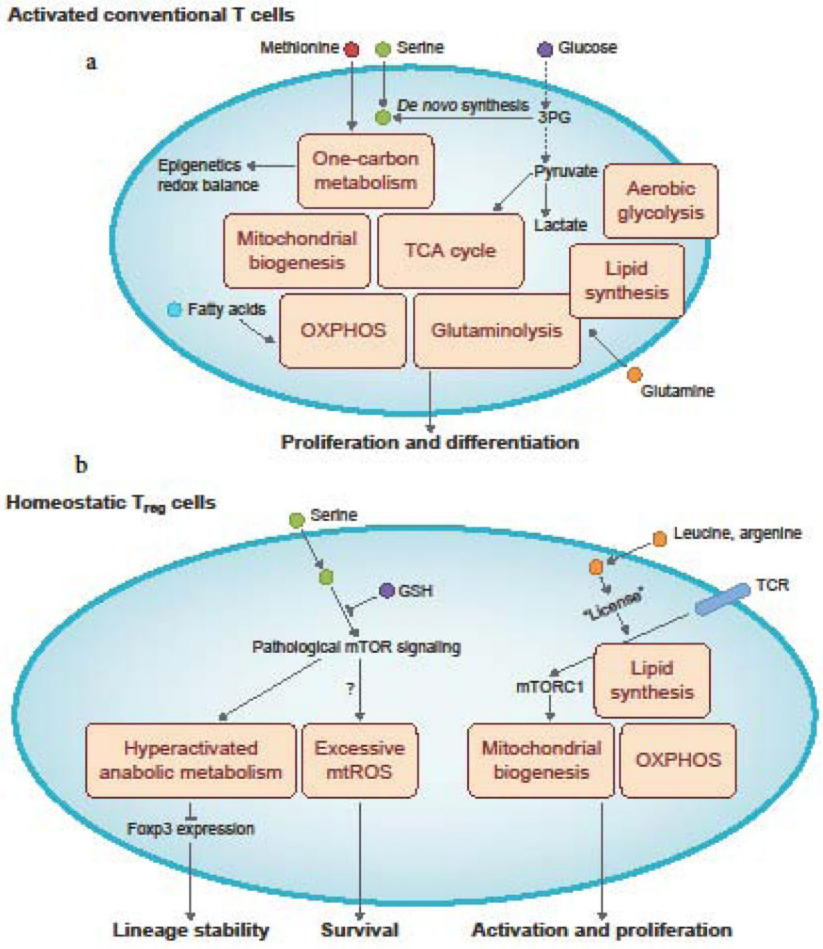

Figure 1: Cellular metabolism of activated conventional T cells and homeostatic T_{reg} cells.

a. Upon their activation, conventional T cells upregulate the metabolic pathways of aerobic glycolysis, glutaminolysis, and lipid synthesis. They also increase mitochondria biogenesis to upregulate mitochondria-associated metabolic processes, including oxidative phosphorylation (OXPHOS), the tricarboxylic acid (TCA) cycle, and the methionine- and serine-dependent one-carbon metabolism pathway that is necessary for epigenetic programming and redox balance. Extracellular nutrients, including glucose, glutamine, methionine, and serine, are crucial for the induction of these different metabolic programs. Glucose metabolism can also support serine synthesis via its metabolic 3-phosphoglycerate (3PG). Fatty acids can also be used as a fuel source for OXPHOS in subsets of activated T cells. **b.** Mitochondrial biogenesis and OXPHOS, as well as lipid synthesis, are crucial for maintaining T_{reg} cell functional activation and proliferation. These metabolic processes are activated downstream of mechanistic target of rapamycin complex 1 (mTORC1) signaling, which is induced by TCR engagement in the presence of the amino acids, leucine and arginine. Notably, excessive mitochondrial ROS (mtROS) production reduces T_{reg} cell survival. Furthermore, excessive levels of anabolic metabolism (e.g. mitochondrial oxidative respiration or aerobic glycolysis), as a consequence of increased mTOR signaling, dampens T_{reg} cell lineage stability. T_{reg} cell stability can be counteracted by certain metabolites,

including glutathione (GSH) that limits serine uptake and serine-induced mTORC1 activation in T_{reg} cells.

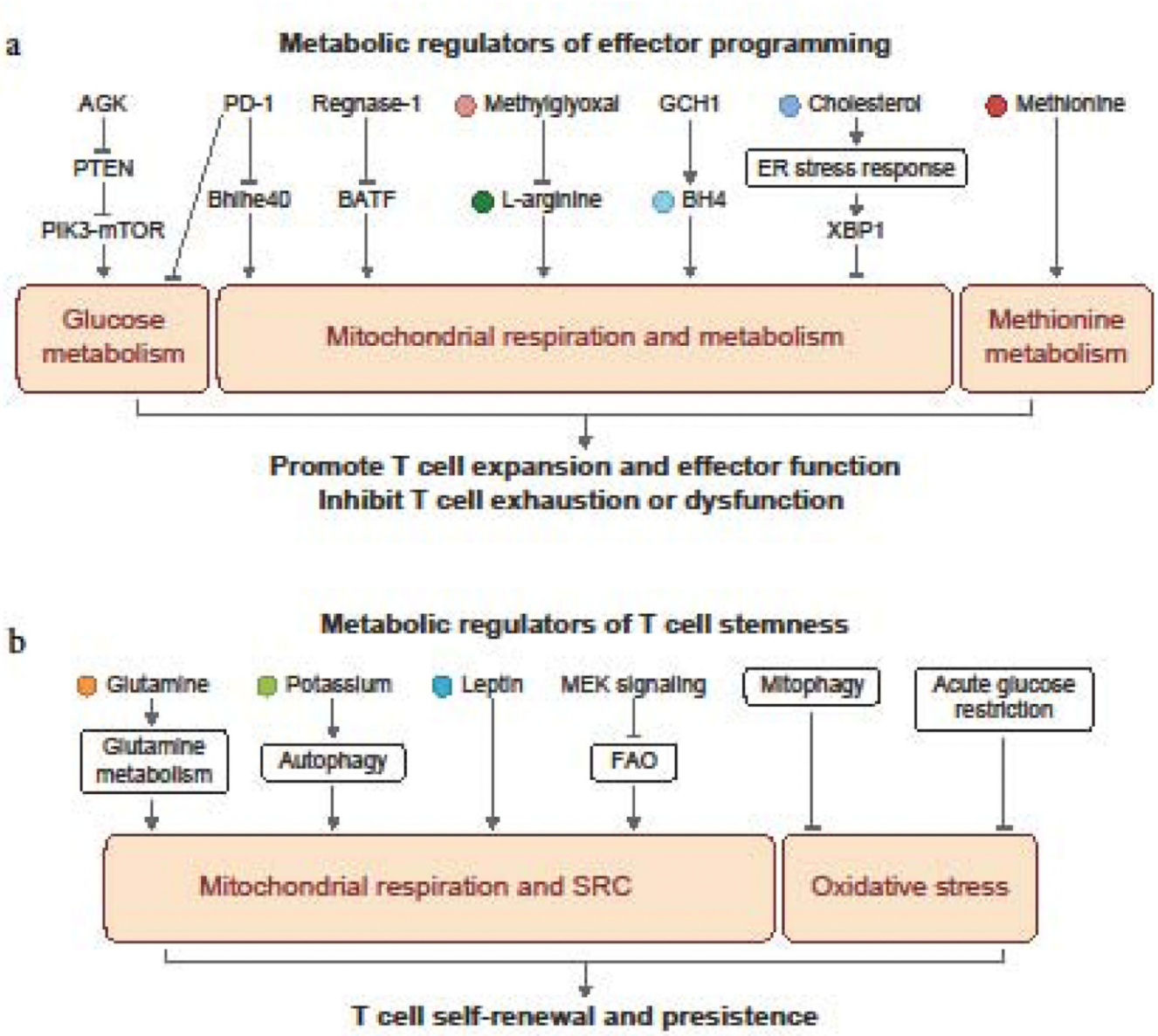

Figure 2: Cellular metabolism shapes tumor-infiltrating effector T cell responses and differentiation.

a. Effector T cell expansion and function are controlled by glucose metabolism downstream of the AGK–PTEN–PI3K-mTOR signaling axis, which can be antagonized by PD-1 signaling. Further, mitochondrial respiration and metabolism support the function of tumor-infiltrating effector T cells, with metabolites BH4 (synthesized via the enzyme GCH1) and extracellular L-arginine (whose levels are antagonized by methylglyoxal produced by tumor cells) acting as important metabolite regulators of mitochondrial function. Bhlhe40 and BATF are crucial transcriptional regulators of mitochondrial function in tumor-infiltrating T cells, which are inhibited by PD-1 and Regnase-1 signaling, respectively. Cholesterol can also induce the ER stress response–XPB1 signaling axis that suppresses mitochondrial function. Methionine metabolism induced by methionine uptake is crucial to support the effector programming of tumor-infiltrating T cells. **b.** Stem-like programs that promote T

cell longevity and persistence in the TME are programmed downstream of selective metabolic programs. Specifically, the acquisition of stem-like programs is associated with an increase of mitochondrial respiration and spare respiratory capacity (SRC), which can be mediated by glutamine-dependent glutamine metabolism, potassium-induced autophagy, leptin signaling, or fatty acid oxidation (FAO) that is antagonized by MEK signaling. In addition, a stem-like state is adopted upon mitigation of oxidative stress, such as via engaging mitophagy to clear damaged mitochondria or transient glucose restriction.

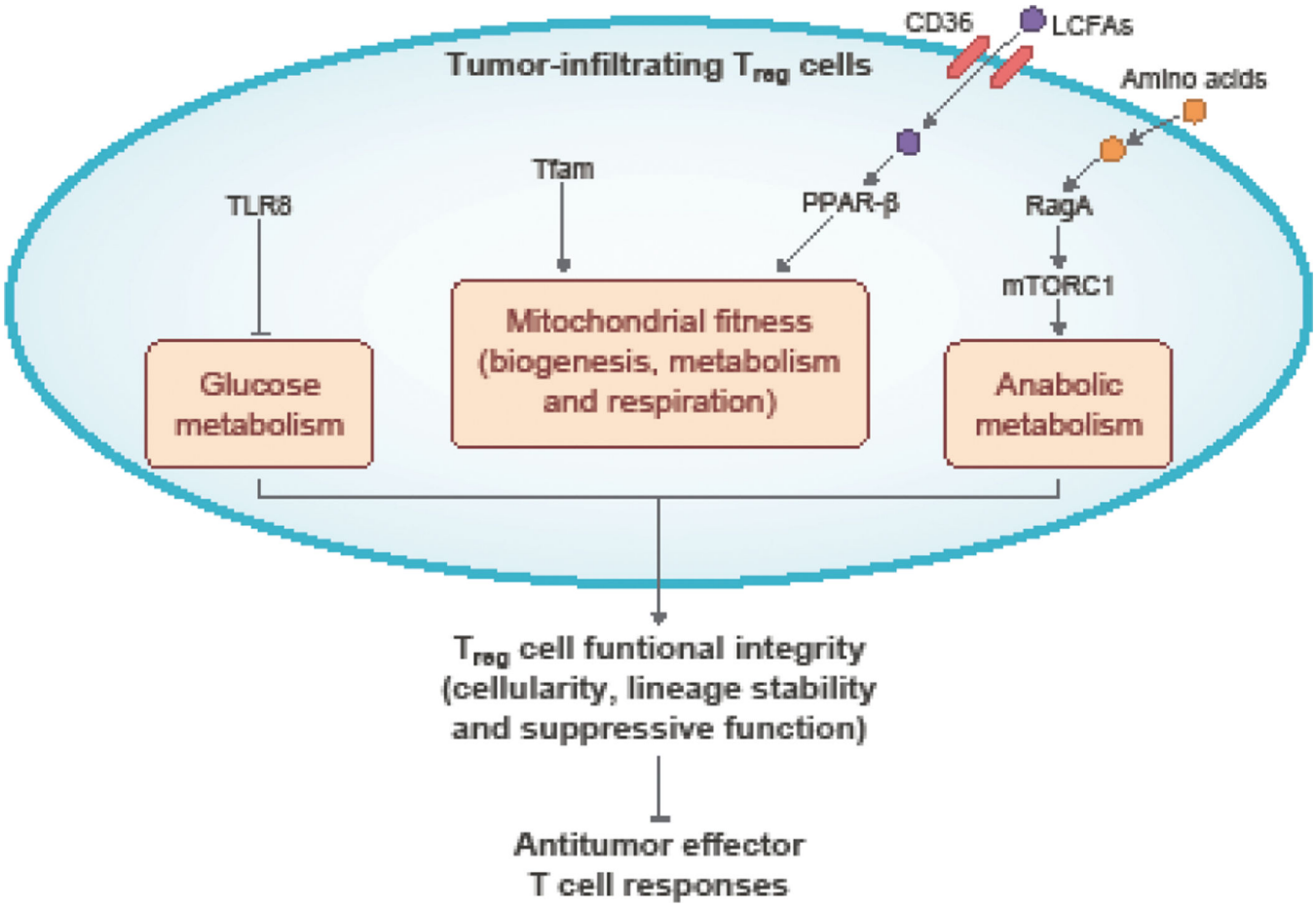

Figure 3: Cellular metabolism modulates T_{reg} cell functional fitness in tumors.

T_{reg} cells accumulate in tumors and inhibit antitumor effector T cell responses to establish an immune suppressive TME. The functional integrity (cellularity, lineage stability, and suppressive function) of T_{reg} cells is mediated by metabolic adaptations. Tfam-dependent mitochondrial respiration supports tumor-infiltrating T_{reg} cell accumulation and lineage stability. T_{reg} cells also upregulate CD36 expression and uptake long-chain fatty acids to activate PPAR-β signaling and support mitochondrial fitness, supporting T_{reg} cell survival and suppressive function. Amino acids, by signaling through RagA–mTORC1 that induces anabolic programming, are also required for tumor-infiltrating T_{reg} cell suppressive function. In contrast, TLR8 activation dampens T_{reg} cell functionality in tumors by inhibiting glucose metabolism.