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mTOR and lymphocyte cell metabolism

Hu Zeng and **Hongbo Chi***

Hongbo Chi: hongbo.chi@stjude.org

*Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA, Phone: 901-595-6282; Fax: 901-595-5766

Abstract

Upon antigen engagement and proper co-stimulation, naïve lymphocytes exit quiescence and undergo clonal expansion and differentiation into functional effector cells, after which they either die through apoptosis or survive as memory cells. Lymphocytes at different activation stages exhibit distinct metabolic signatures. Emerging evidence highlights a central role for the mechanistic target of rapamycin (mTOR) in bridging immune signals and metabolic cues to direct lymphocyte proliferation, differentiation and survival. Here we review recent advances in understanding the functional significance and signal transduction of mTOR in T cell biology, and the interplay between mTOR signaling and metabolic programs.

INTRODUCTION

Metabolic signatures during lymphocyte activation and differentiation

Mammalian cells are usually exposed to a constant supply of nutrients, but they do not normally take up nutrients and proliferate until they are stimulated by extrinsic factors[1]. Naïve lymphocytes, like most cells in normal tissues, have a quiescent status, in which they primarily rely on catabolic metabolism and derive most of their ATP from oxidative phosphorylation, particularly fatty acid β-oxidation[2,3,4**]. Quiescent lymphocytes also break down intracellular components through autophagy to supply molecules for oxidative phosphorylation[5]. Upon antigen recognition and co-stimulation, lymphocytes downregulate fatty acid β-oxidation and rapidly increase glycolytic, glutaminolytic and pentose phosphate pathways to provide biosynthetic materials and energy for cell growth and proliferation[3,4**,6]. Activated and effector T cells preferentially utilize aerobic glycolysis to meet their energy demands, a phenomenon known as the Warburg effect, which is also a metabolic feature of many cancer cells[1]. After clonal expansion and clearance of invading foreign pathogens, most effector T cells undergo apoptosis while some differentiate into long-lived memory cells. Memory T cells, like naïve T cells, are quiescent and have a catabolic metabolism[7,8]. A separate T cell subset, $FOXP3^+$ regulatory T cells (T_{reg}), also exhibits relatively high fatty acid β-oxidation but low glycolysis[9**,10]. Thus, during immune responses, T cells experience two major metabolic switches, from catabolic naïve T cells to anabolic activated/effector T cells and then again transition into catabolic

Competing interest statement
The authors declare no competing financial interests.

memory T cells (Figure 1). Emerging evidence indicates that metabolism is closely coupled with the differentiation and function of T cells at different stages of their life span[11].

mTOR signaling

The serine/threonine kinase mTOR consists of two distinct complexes: mTOR complex 1 (mTORC1) and 2 (mTORC2). Two scaffold proteins, regulatory associated protein of mTOR (RAPTOR) and rapamycin-insensitive companion of mTOR (RICTOR), are the defining components of mTORC1 and mTORC2, respectively[12]. While mTORC1 is sensitive to rapamycin, mTORC2 can be inhibited by prolonged or high dose of rapamycin treatment in $CD4^+$ T cells[13,14**], but not in effector $CD8^+$ T cells[15*]. Many upstream signals activate mTORC1 pathway through the small GTPase RHEB (RAS homologue enriched in brain). The tuberous sclerosis 1 (TSC1) and TSC2 form a complex that inactivates RHEB through its GAP (GTPase-activating protein) activity, thereby suppressing mTORC1 activity. Further upstream, the PI3K-AKT pathway inactivates TSC1/TSC2 complex while AMP-activated protein kinase (AMPK) enhances its activity. Therefore, TSC1/TSC2 complex functions as a molecular switch that controls mTORC1 activity. S6K1 and 4E-BP1 are two best-characterized downstream targets of mTORC1 that regulates protein translation. Moreover, mTORC1 pathway also promotes glycolysis and lipid biosynthesis while inhibiting autophagy. mTORC2 is activated by PI3K signaling, but detailed mechanism is lacking. mTORC2 controls several AGC family kinases, including AKT, SGK1 and PKC-α and is involved in regulating metabolism, apoptosis and cytoskeletal organization[12]. In particular, phosphorylation of AKT-Ser473 by mTORC2 promotes FOXO1/3a phosphorylation and subsequent cytoplasm translocation and degradation[16,17].

In lymphocytes, diverse environmental signals, including antigens, growth factors, cytokines and nutrients regulate mTOR to direct immune responses and fate decisions[18,19]. Since the roles of mTOR and metabolic pathways have been extensively studied in mature T cells in the periphery, we will mainly focus on these cells. First, we will briefly describe the roles of mTOR in T cell homeostasis under steady state and antigen-triggered activation and differentiation. Second, we will discuss the functional effects and mechanistic basis of mTOR in sensing and propagating diverse immune signals, especially those mediated by TCR, co-stimulation and cytokine receptors. Third, we will present the emerging evidence on mTOR-dependent metabolic reprogramming of T cell responses, by focusing on the interaction between mTOR and transcription factors associated with cell metabolism such as MYC and HIF1, and the potential interplay between mTOR-controlled metabolites and immune signaling. As our discussion focuses on T cells, we refer the readers to an excellent recent review describing the PI3K-AKT-mTOR pathway in B cells[20].

mTOR, A MASTER CONTROLLER IN T CELL BIOLOGY

mTOR in T cell quiescence

The quiescent status of naïve T cells is not a default state determined by the lack of mitogenic stimuli, but is an actively maintained process[7]. Uncontrolled mTORC1 activation by TSC1 deletion in T cells leads to loss of quiescence and predisposes T cells to apoptotic death[21–23]. Consequently, *Tsc1*$^{-/-}$ mice have markedly reduced peripheral T cell numbers. TSC1-deficient T cells exhibit semi-activated phenotypes, with a larger cell size, increased metabolic gene expression and cell cycle entry. They have enhanced mTORC1 but reduced mTORC2 activity, suggesting a crosstalk between the two complexes[24]. TSC1-deficient mice fail to mount an efficient immune response against bacterial infection[23]. Thus, active control of mTORC1 activity by TSC1 maintains the quiescent status, survival fitness and immune competency of peripheral naïve T cells.

mTOR in CD4$^+$ cell lineage differentiation

Depending on the nature of antigenic stimulation and cytokine milieu, naïve CD4$^+$ T helper cells may differentiate into T_H1, T_H2 and T_H17 effector subsets, or become induced regulatory T cells (iT_{reg})[25]. The importance of mTOR in T cell differentiation is underscored by the inability of mTOR-deficient CD4$^+$ T cells to differentiate into T_H1, T_H2 and T_H17 effector subsets[26**]. mTORC1 and mTORC2 have distinct functions in directing CD4$^+$ T cell lineage differentiation. RHEB-deficient T cells are defective to differentiate into T_H1 or T_H17 cells but have normal T_H2 differentiation[14]. In contrast, loss of RAPTOR leads to impaired T_H17 but normal T_H1 differentiation[27]. The reason behind the discrepant phenotypes between *Rheb*$^{-/-}$ and *Raptor*$^{-/-}$ T cells is unclear, but this may be related to RHEB-independent activation of mTORC1[28]. Deletion of RICTOR has been shown to impair T_H2 differentiation but preserve T_H1 and T_H17 differentiation[14]. However, a separate study shows that RICTOR-deficient T cells have reduced T_H1 and T_H2 differentiation due to impaired AKT and PKC-θ activation, respectively[13]. It is worth noting that metabolic activities have not been measured in these genetic models. Hence, how mTORC1 and mTORC2 signaling regulates specific metabolic programs in CD4$^+$ effector T cells remains to be addressed.

In contrast to effector T cell differentiation, iT_{reg} differentiation is negatively regulated by mTOR. PI3K-AKT-mediated mTOR activation inhibits iT_{reg} generation by downregulating FOXP3 and other T_{reg} transcriptional signature genes, whereas rapamycin enhances FOXP3 induction[29*,30*]. TCR ligation induces FOXP3 expression in *Mtor*$^{-/-}$ T cells even in the absence of exogenous iT_{reg} polarizing cytokines[26]. Both mTORC1 and mTORC2 contribute to this inhibition program[14,26]. Although an increased AKT-mTOR activity has been associated with reduced thymic-derived T_{reg} generation[29*,31*], the underlying mechanisms remain to be fully pinpointed.

mTOR in CD8$^+$ cell effector and memory differentiation and trafficking

In CD8$^+$ T cells, mTORC1 controls glucose uptake and glycolysis during initial activation as well as in effector cells[15*,32]. Furthermore, rapamycin impairs CD8$^+$ effector cell differentiation[33]. Therefore, mTORC1 is critical for both CD4$^+$ and CD8$^+$ effector cell differentiation. As CD8$^+$ T cells transition from effector to memory cells, their metabolism switches from anabolism to catabolism. Several studies have demonstrated a negative role of mTORC1 for CD8$^+$ memory formation. Inhibition of mTORC1 by rapamycin[33,34**,35**] or silencing RAPTOR expression[34**] promotes memory cell generation and function. Importantly, Pearce *et al.* found that failure to upregulate fatty acid β-oxidation impedes memory T cell formation, which could be ameliorated by mTOR inhibition[35]. These data indicate that mTOR signaling prohibits memory T cell generation, at least partially, by modulating cell metabolism.

Proper immune cell trafficking is critical for a successful immune response and is orchestrated by the expression of chemokine receptors and adhesion molecules[36]. Treatment of CD8$^+$ T cells with rapamycin or deficiency of PI3K or PDK1 prevents TCR or cytokine-induced downregulation of CD62L, CCR7 and S1PR1, molecules important for naïve T cell trafficking[32,37]. Conversely, activation of mTOR through PTEN or TSC1 deficiency is sufficient to downregulate these molecules[23,37]. Mechanistically, mTOR may regulate trafficking molecule expression through KLF2 (Krüppel-like factor 2)[37], FOXO1[38], or HIF1[15*]. Thus, mTOR activation endows T cells with an increased ability to migrate to sites of inflammation instead of retention in secondary lymphoid organs.

mTOR AND REGULATION OF IMMUNE SIGNALS

mTOR activity can be positively or negatively regulated by multiple inputs (Figure 2). The classic model posits that three major signals are required for proper T cell activation and differentiation: TCR engagement by antigen-MHC complex, costimulatory signals, and inflammatory cytokines. These signals, together with additional immune-modulatory receptors including Toll-like receptors (TLRs) and G protein-coupled receptors (GPCRs), are sensed and integrated by mTOR; once activated, mTOR can in turn interact with and impinge upon T cell signaling pathways. Thus, the interplay between mTOR and immune signals constitutes an important component to determine the outcome of adaptive immune responses[39].

Signaling by TCR and co-stimulation

mTORC1 is activated by TCR engagement and the magnitude of its activation is correlated with antigen dose and the duration of the interaction between T cells and antigen-presenting cells[40,41]. CD28-mediated signal is required for the optimal activation of mTOR[42] and, importantly, for increased glycolytic flux[43]. Importantly, mTORC1 activation by optimal TCR and co-stimulation can occur independently of IL-2[44]. In contrast, ligation of the inhibitory receptors CTLA-4 and PD-1 attenuates mTOR activity and promotes iT_{reg} generation[45,46]. Inhibition of mTOR during T cell activation leads to anergy even in the presence of CD28 signaling and blocking of CTLA-4[47–49].

As for the signaling components involved in the interplay between mTOR and TCR signaling, a notable example is the interaction between PI3K-AKT and mTOR. PI3K-AKT delivers a classical signal for mTORC1 activation, which in turn institutes feedback inhibition of PI3K-AKT[23,24]. In addition, mTORC2 plays a crucial role for the full activation of AKT by phosphorylating the Ser473 residue[13,14]. Thus, mTOR can be both downstream and upstream of PI3K-AKT signaling. Moreover, a PI3K-AKT-independent, but PDK1-dependent pathway has been identified for the activation of mTORC1 in $CD8^+$ T cells[15*,32]. Additional TCR signaling components have also been shown to interact with mTOR. TCR stimulation activates Src family protein kinases LCK and FYN, which phosphorylate and activate ZAP-70. This in turn leads to activation of PLC-γ and ultimately several major signaling and transcriptional pathways: NFAT, NF-κB and MAP kinase (MAPK) cascade[50]. Both LCK and FYN are required for TCR-induced mTOR activation[51], whereas rapamycin impairs LCK and ZAP-70 activation[52], suggesting a crosstalk between TCR proximal signaling and mTOR. TCR-induced mTOR activation also depends on intact MAPK signaling[51,53]. Conversely, inhibition of mTOR can result in MAPK activation in cancer cells[54], although whether this is operative in lymphocytes is unknown. Further, mTOR activation, particularly mTORC2, is required for NF-κB activation through PKC-θ[13,52], but whether NF-κB can directly affect mTOR pathway remains unclear.

Signaling by cytokines and other immunomodulatory factors

Multiple cytokines activate mTOR as an important mechanism to shape T cell homeostasis and activation. For instance, a properly controlled mTOR activity is required for naïve T cell survival and homeostasis in response to IL-7[23,55]. IL-2 activates mTOR to prevent anergy in TCR-stimulated cells[47,56] and to sustain glycolysis, glucose and amino acid uptake in $CD8^+$ effector T cells[15*,57**]. More importantly, the interplay between mTOR and cytokine signaling orchestrates T cell differentiation. IL-12 activates mTOR to facilitate $CD8^+$ effector T cell differentiation[33]. During $CD4^+$ T cell differentiation, mTOR is activated by different polarizing cytokines, such as IL-1 and IL-23 during T_H17 differentiation[58,59]. Reciprocally, mTORC1 contributes to STAT4 and STAT3 activation

mediated by IL-12 and IL-6, respectively, while IL-4 mediated STAT6 activation requires mTORC2 activation[14**]. This is largely mediated by mTOR-dependent effect on the expression of SOCS family members[14**]. Consistent with a key role for mTOR in cytokine signaling and T cell differentiation, expression of lineage-specific transcription factors T-bet and RORγt is impaired in RHEB-deficient T cells, whereas RICTOR deficiency diminishes GATA3 expression[13,14**]. Moreover, mTOR signaling influences epigenetic modifications that accompany T cell differentiation. Rapamycin treatment during T cell activation leads to increased CpG methylation at promoter regions of *Il4* and *Ifng*[60], but reduces CpG methylation and increases permissive histone methylation at *Foxp3* promoter region[30,60]. Interestingly, epigenetic regulation is likely an evolutionarily conserved function of mTOR, as TOR signaling in yeast is linked to histone acetylation[61]. Altogether, various interactions between mTOR and cytokine signaling appear to converge into transcriptional and epigenetic events to dictate T cell fate decisions.

mTOR bridges the interaction between immunomodulatory factors and the pleiotropic cytokine TGF-β, which signals primarily through transcription factors SMAD2 and SMAD3[62]. S1PR1 is a GPCR that mediates lymphocyte trafficking by sensing lipid sphingoshine-1-phosphate (S1P)[63]. S1PR1 activates mTOR signaling to promote T_H1 differentiation while suppressing T_{reg} generation through inhibition of SMAD3 activation[31,64]. Conversely, deletion of mTOR or inhibition of mTOR pathway in T cells increases SMAD2/3 phosphorylation and enhances iT_{reg} generation[26**,65]. Neutralization of TGF-β largely blocks the excessive iT_{reg} generation in mTOR-deficient T cells, implicating the obligate role of TGF-β signaling in this process[26]. However, FOXP3 induction by PI3K/mTOR inhibition has also been shown to occur independently of TGF-β[30]. Thus, the extent to which mTOR-mediated regulation of iT_{reg} generation is contingent upon TGF-β signaling remains to be established[66]. A recent study also reveals that the anaphylatoxins C3a and C5a, through complement receptor C3aR and C5aR, activate mTOR and interfere with TGF-β-mediated iT_{reg} generation[67].

TLRs recognize pathogen associated molecular patterns and can be expressed on T cells. TLR-2 expressed by $CD8^+$ T cells transduces a costimulatory signal to activate mTOR, increase T-bet expression and enhance $CD8^+$ T cell effector function[68]. MYD88, the essential adaptor molecule for many TLR signaling, is required for IL-1β and IL-23-mediated mTOR activation and T_H17 differentiation[59].

mTOR AND REGULATION OF METABOLIC PROGRAMS

mTOR is activated by hormones and nutrients

mTOR signaling is intimately linked with cellular metabolism. Hormones and nutrients are important factors that modulate systemic and cellular metabolism and they feed into the mTOR pathway. Leptin is an adipocyte-derived hormone that controls food intake and metabolism. Recent studies have demonstrated that leptin-induced mTOR activation is critical for effector T cell proliferation[52], whereas it maintains the *in vitro* anergic status of T_{reg} and negatively controls T_{reg} proliferation[69,70]. Leptin promotes T_H1 differentiation and inflammatory cytokine production, but suppresses T_H2 differentiation[71]. Moreover, leptin-induced mTOR activation also mediates survival and activation of autoreactive $CD4^+$ T cells[72]. As leptin is a well-characterized “fat-sensor”, these studies establish leptin-mTOR signaling as a direct link between nutritional status and lymphocyte function.

While it is well documented that mTOR senses amino acids, energy level and reactive oxygen species in other cell types[12,73], we are just beginning to appreciate this regulation in T cells. Deprivation of amino acids, glucose or energy through limiting essential amino acids or pharmacological inhibition leads to mTOR inactivation, accompanied by T cell

anergy[42] and FOXP3 induction[74]. A recent study demonstrates that amino acid uptake by T cells activates mTORC1. Specifically, TCR engagement induces expression of System L transporter, SLC7A5, which mediates uptake of large neutral amino acids, such as leucine. Furthermore, expression of SLC7A5 is required for MYC expression and MYC-mediated metabolic reprograming. Consequently, SLC7A5-deficient T cells cannot be activated by immunization[57**]. How mTOR senses energy level and other nutrients in T cells awaits further investigation.

mTOR coordinates metabolic programs through key transcription factors

Preceding the metabolic reprogramming of T cell activation is the rapid upregulation of selective transcription factors responsible for the induction of metabolic genes. Among them, the oncogene MYC is critical for T cell activation-induced glycolysis and glutaminolysis[4**]. Acute deletion of MYC impairs upregulation of multiple glycolytic and glutaminolytic enzymes and induction of glutamine antiporter CD98, which modulates amino acid availability and mTOR activation[75]. Consequently, MYC-deficient T cells have severe defects in growth and proliferation. Rapamycin treatment diminishes MYC expression, whereas MYC-deficient T cells display reduced mTOR activation[4**], indicative of an intimate link between MYC and mTOR signaling. Interestingly, the TSC1/2-mTOR and MYC pathways can promote each other's activity in a feed-forward loop to amplify their oncogenic effects in cancer cells[76]. Hence, just as T cell activation shares many metabolic features with cancer cells, they may adopt similar signaling connections as well.

HIF1α is another transcription factor associated with T cell metabolic reprogramming[4**, 77]. Although its deficiency does not impair initial T cell activation or metabolism[4**], it is specifically required for the glycolytic program in T_H17 cells[9] and the balance between T_H17 and iT_{reg} differentiation[9,78]. HIF1α is preferentially expressed in T_H17 cells and its induction is dependent upon mTOR[9,77]. Under T_H17-polarizing conditions, HIF1α-deficient T cells have diminished T_H17 but increased iT_{reg} differentiation, accompanied by reduced glycolytic activity. This phenotype is recapitulated by pharmacological inhibition of glycolysis, highlighting the importance of metabolic regulation of T cell fates[9]. Furthermore, HIF1α controls these two lineages by directly interacting with lineage-specific transcription factors RORγt and FOXP3 to modulate their function and stability[78]. Therefore, mTOR directs $CD4^+$ T cell metabolic, transcriptional and posttranslational changes partly through HIF1α induction. Recently, Finlay *et al.* reported an important role of mTOR-induced HIF1 expression in effector $CD8^+$ T cell metabolism, function and trafficking[15*]. HIF1 does not initiate glycolysis in naïve $CD8^+$ T cells, but is crucial for glucose uptake and glycolytic metabolism in effector $CD8^+$ T cells. HIF1β-deficient effector $CD8^+$ T cells have diminished induction of perforin and granzymes, but increased expression of trafficking molecules. Thus, mTOR-induced HIF1 expression controls effector $CD8^+$ T cell differentiation[15*].

T cell activation is accompanied by rapid upregulation of lipid biosynthesis and its gene expression program[79]. The sterol regulatory element-binding proteins SREBP1 and SREBP2 are transcription factors that activate cholesterol and fatty acid biosynthesis. Inhibition of mTOR by either rapamycin or PI3K inhibitor treatment prevents the processing of full-length SREBP and subsequent accumulation of mature SREBPs in the nucleus[80*]. Thus, mTOR promotes T cell lipogenesis through activation of SREBPs.

The estrogen-related receptor-alpha (ERRα) is another T cell activation-induced transcription factor that mediates effector T cell metabolism and differentiation. ERRα-deficient T cells have impaired metabolism and proliferation, associated with altered mTOR activity. Further, increasing mTOR activity through TSC2 deficiency renders T cell

independent of ERRα, suggesting a potential interaction between ERRα and mTOR signaling[81].

Crosstalk between mTOR-controlled metabolism and immune signaling

Many posttranslational modifications, such as methylation, acetylation, glycosylation and prenylation, are mediated by metabolites. Emerging evidence suggests that metabolite-sensitive protein modifications can modulate signal transduction[82,83], with several examples identified in lymphocytes. For instance, UDP-N-acetylglucosamine (UDP-GlcNAc), a metabolite in the hexosamine biosynthetic branch of glucose metabolism, is required for IL-3 receptor (IL-3R) glycosylation and its membrane presentation. Absence of glucose downregulates membrane IL-3R expression and cell growth but these defects are reversible by supplement of GlcNAc, suggesting that glucose metabolism through the hexosamine biosynthetic pathway directly influences lymphocyte signaling[84]. Protein prenylation and palmitoylation were also found to influence TCR signaling and T cell differentiation[85–87]. Currently, no evidence is available that directly links mTOR-mediated metabolic programs to lymphocyte signaling. However, given the central role of mTOR in cell metabolism, it is conceivable that mTOR could influence immune signaling through metabolite production or availability. We propose that mTOR is uniquely situated in T cells to bridge immune signals and metabolic cues, and this could be partly mediated by mTOR-associated nutrients and metabolites (Figure 2).

CONCLUSION

T cells are at the center of adaptive immunity that protects the body from pathogen infections, or mediates self-destructive autoimmune diseases. mTOR integrates immune signals and metabolic cues to direct T cell homeostatic and functional fates, and this is shaped by the extensive interplay between mTOR signaling and cell metabolism. Despite the recent remarkable advances, a number of questions remain to be answered. We have yet to fully understand mTOR-associated upstream signal inputs and downstream effector pathways in T cells. Also, how mTOR-mediated metabolism interacts with immune signaling is another fascinating question. Further, modulation of mTOR activity with newly developed inhibitors, or direct targeting of specific metabolic pathways, holds promises as novel strategies for therapeutic intervention of immune-mediated diseases.

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Highlights

- Different T cell activation states have distinct metabolic profiles and mTOR activity
- mTOR orchestrates T cell quiescence, functional activation, and fate decisions
- mTOR is activated by and impinge upon antigen receptor and other immune signaling
- mTOR senses metabolic cues and coordinates T cell metabolic reprograming

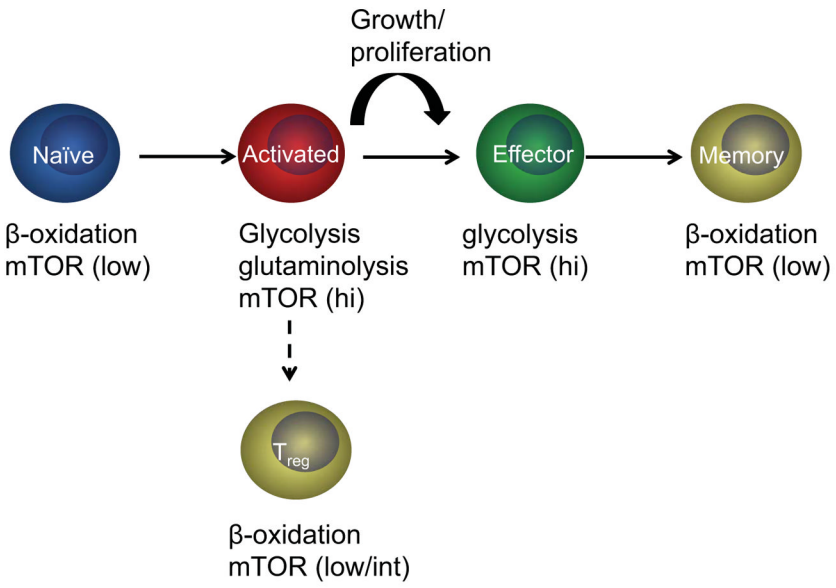

Figure 1.

T cells at different activation stages exhibit distinct metabolic phenotypes and mTOR activities. Naïve T cells rely on catabolism, particularly fatty acid β-oxidation, to maintain homeostasis. They also show low mTOR activity. Antigenic stimulation activates mTOR and markedly upregulates anabolic programs especially glycolysis and glutaminolysis, while downregulating fatty acid β-oxidation. The interplay between mTOR and metabolic programs collectively contributes to antigen-induced T cell growth and proliferation. Effector T cells maintain high glycolytic flux and mTOR activity, but their differentiation to memory T cells is accompanied by a metabolic switch from anabolism to catabolism, particularly upregulation of fatty acid β-oxidation, as well as downregulation of mTOR activity. A separate T cell lineage comprised of $FOXP3^{+}$ T_{reg} cells also has high fatty acid β-oxidation but low/intermediate mTOR activities.

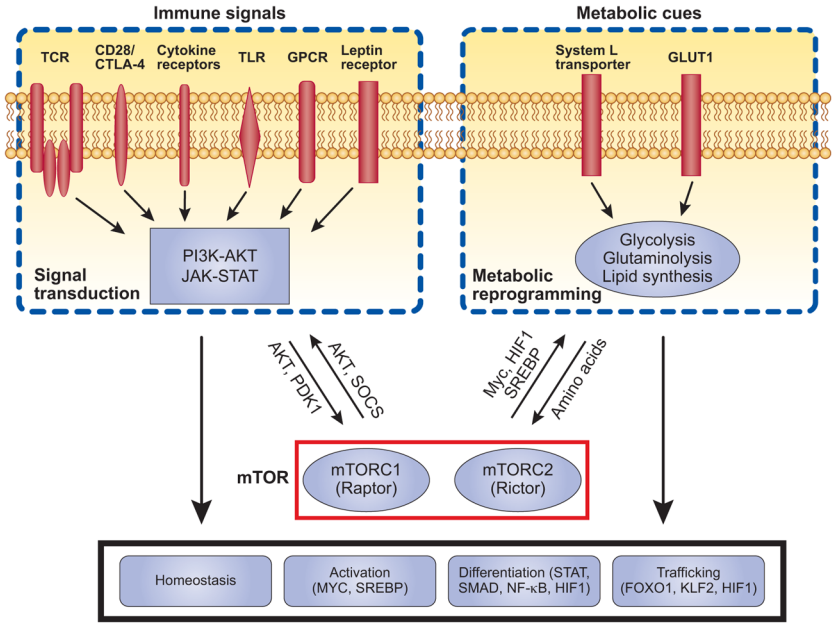

Figure 2.

mTOR bridges immune signals and metabolic cues to regulate T cell responses. Multiple immune signals regulate mTOR activity, including TCR, costimulatory signals and cytokine receptors, as well as TLR, selective G protein-coupled receptors (GPCRs) and leptin receptors. Nutrients, such as amino acids and glucose, also mediate mTOR activation. These upstream inputs, through PI3K-AKT, JAK-STAT, and additional unidentified pathways, engage mTOR signaling. Once activated, mTOR shapes TCR and cytokine signaling through AKT and SOCS, and probably more importantly, reprograms metabolic activities including glycolysis through transcription factors MYC and HIF1. mTOR-dependent signaling pathways and metabolic programs are important regulators in T cell biology, including homeostasis, activation, lineage differentiation and memory formation. We propose that mTOR serves as a signal integration hub to bridge immune signals and metabolic cues, and the coordinated activation of these two major inputs by mTOR ensures proper execution of adaptive immunity in response to environmental signals