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# mTOR signaling and transcriptional regulation in T lymphocytes

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**The mechanistic target of rapamycin (mTOR) signaling integrates diverse environmental cues, including growth factors, nutrients and immunological signals. Activation of mTOR signaling stimulates protein synthesis and anabolic metabolism and coordinates cell growth, proliferation and fate decisions. In recent years, mTOR signaling has been linked to the entire spectrum of T cell biology, ranging from T cell development and activation to lineage specification and memory formation. Mechanistically, mTOR activation profoundly affects the expression and activity of many immunologically relevant transcription factors to propagate immune signaling and mediate effector functions. These transcription factors orchestrate cell metabolism (MYC, SREBPs and HIF1), lineage differentiation (T-bet, GATA3, RORγt, FOXP3 and Eomesodermin) and immune activation and functions (NF-κB, FOXOs, IRF4, STATs and GFI-1). This review discusses how mTOR signaling, through impinging upon transcriptional factors, regulates T cell development, activation, and effector and memory differentiation.**

**Keywords:** Eukaryotic transcription, transcription factors and co-activators

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## Introduction

The mechanistic target of rapamycin (mTOR) pathway is an evolutionarily conserved mechanism that primarily controls cell growth and metabolism. It consists of two protein complexes, mTOR complex 1 (mTORC1) and complex 2 (mTORC2). They share the kinase catalytic subunit mTOR, but are distinguished by two scaffolding subunits, RAPTOR (regulatory associated protein of mTOR) and RICTOR (RAPTOR-independent companion of mTOR), respectively. mTORC1, which is better studied, is activated by growth factors and nutrients mainly through phosphoinositide 3-kinase (PI3K)-AKT pathway.[1] After activation, mTORC1 phosphorylates the translational initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) and S6 kinase (S6K), which promote protein synthesis primarily from transcripts with 5′ terminal oligopyrimidine (TOP) motifs, 5′ TOP-like motifs or pyrimidine-rich translational elements (PRTE).[2,3] Activation of mTORC1 is sensitive to rapamycin, an immunosuppressive drug. In contrast, how mTORC2 is activated is poorly understood, although mTORC2 is well known to phosphorylate AKT at Ser 473 and contributes to AKT activation. Whereas mTORC2 is insensitive to rapamycin in short-term treatment, long-term or high dose of rapamycin treatment can block mTORC2 activity in a variety of cells[4,5] and $CD4^+$ T cells,[6,7] but not in effector $CD8^+$ T cells.[8]

Recent studies have demonstrated that mTOR signaling is extensively involved in lymphocyte biology. Numerous immune signals, including T cell receptor (TCR), co-stimulatory signals and various cytokines, activate mTOR, which in turn regulates lymphocyte metabolism and dictates lineage differentiation and immune functions.[9-11] Interestingly, many of these physiological effects are mediated by transcription factors whose expression or activity is dependent upon mTOR activation. Here, we review the impacts of mTOR

signaling on transcription factors in different aspects of T cell biology, including lymphocyte development, activation and lineage differentiation.

## mTORC2 Promotes Thymocyte Development Through Concerted Actions of NF-κB and FOXO Pathways

The NOTCH signaling pathway commits BM-derived progenitor cells to T-lineage fate and extinguishes non-T cell potentials. After engaging NOTCH ligands expressed on thymic epithelial cells, NOTCH receptors are cleaved to release the intracellular domain of NOTCH (ICN), which enters nucleus and regulates various target genes.[12] PI3K-AKT pathway has been shown to act downstream of NOTCH and support thymocyte metabolism, proliferation and generation of double-positive (DP) cells. Lee et al. showed that loss of RICTOR in thymocytes impairs NOTCH-mediated NF-κB activation and increases activity of transcription factors FOXO1/3. Expression of constitutive active AKT, or combining constitutive active IKK2 and silencing of FOXO1/3, restores the defective NOTCH-induced differentiation in RICTOR-deficient thymocytes.[13] Therefore, mTORC2, via activating AKT, relays signals from NOTCH receptors to NF-κB and FOXO pathways, and in turn promote DN to DP transition and normal T cell development. The mechanism through which mTORC2 activates NF-κB may involve the interaction between mTOR and IKK,[14] or direct phosphorylation of PKC isoforms,[15,16] which are critical for NF-κB activation in lymphocytes.[17,18] Whether mTORC1 affects transcriptional programs in lymphocyte development remains to be addressed.

## mTORC1 Promotes T cell Activation Through MYC and SREBPs

Naïve lymphocytes maintain a quiescent status in which they primarily rely on catabolism, especially fatty acid β-oxidation, to maintain homeostasis. Aberrant activation of mTORC1 upon deletion of its negative regulator Tsc1 disrupts quiescence of T cells, which predisposes them to apoptotic cell death.[19-21] The downstream transcription factors mediating such events are unclear. Upon immune challenges, lymphocyte activation and clonal expansion necessitate rapid metabolic reprogramming, namely from catabolism to anabolism including glycolysis and lipid synthesis.[10] The metabolic reprogramming is preceded by upregulation of several key transcription factors. One of the earliest activated factors is the oncogene MYC, which is responsible for initiating glycolysis and glutaminolysis. Acute deletion of *MYC* impairs TCR-induced expression of multiple glycolytic and glutaminolytic enzymes. Consequently, MYC-deficient T cells fail to activate and proliferate in response to TCR ligation.[22] MYC upregulation is impaired by rapamycin treatment[22] or deletion of Raptor,[23] suggesting that mTOR signaling controls MYC expression. Previous studies using rapamycin have demonstrated that mTOR signaling enhances expression of MYC by promoting its translation, but not transcription or protein stability.[24,25] In glioblastoma cells, activation of mTORC2 reduces class IIa histone deacetylase activity, which leads to increased FOXO acetylation. This in turn increases MYC expression by relieving microRNA-34c-dependent suppression.[26] It is unclear whether this mechanism operates in T cells.

Aside from promoting glycolysis, mTOR signaling also activates lipid biosynthesis.[27] Rapid upregulation of sterol synthesis accompanies lymphocyte activation.[28] Kidani et al. demonstrated that the master transcription factors for lipid biosynthesis, the sterol regulatory element-binding proteins SREBP1 and SREBP2, activate fatty acid and cholesterol synthesis in T cells upon mitogenic stimulation.[29] T cells deficient in the SREBP chaperone molecule SCAP, which controls the processing and subsequent transcriptional activity of SREBPs,[30] fail to undergo metabolic reprograming, including lipid biosynthesis, glycolysis and ATP production. These cells have severe defects in growth and proliferation after mitogenic activation. Since MYC is activated normally in SCAP-deficient T cells, these metabolic defects are likely to be independent of MYC. Notably, the activation defect in SCAP-deficient T cells can be rescued by exogenous cholesterol, highlighting the importance of cholesterol synthesis in T cell activation.[29] Importantly, the induction and processing of SREBPs are inhibited by rapamycin and PI3K inhibitors,[29] or by the loss of Raptor.[23] However, the expression of SREBP1 and SREBP2 mRNA is not affected by Raptor deficiency, suggesting that mTOR controls the expression of SREBPs through posttranscriptional regulation.[23] PI3K-AKT-mTORC1 axis, but not mTORC2, promotes processing of SREBP1 in fibroblasts and epithelial cells.[31,32] A recent study has showed that mTORC1 promotes SREBP activation by inducing nuclear exclusion of Lipin 1; nuclear accumulation of Lipin 1 inactivates SREBPs because it promotes the association of SREBPs to the nuclear matrix.[33] Whether this is the case in T cells remains to be determined. Thus, the PI3K-mTORC1 axis orchestrates lipid synthesis by promoting SREBP expression and processing in T cells.

## mTOR Dictates $CD4^+$ T Cell Lineage Differentiation Through Multiple Transcription Factors

After activation, $CD4^+$ T cells differentiate into different effector lineages, or become induced regulatory T cells (iTreg) dependent on specific cytokine milieu. Different effector lineages are promoted by distinct cytokine-mediated JAK-STAT transcriptional programs and defined by lineage-specific transcription factors.[34] Delgoffe et al. first demonstrated that mTOR-deficient $CD4^+$ T cells fail to differentiate into $T_H1$, $T_H2$ or $T_H17$ effector lineages. This impairment of effector cell differentiation is due to failure of proper activation of specific STAT transcription factors, namely, STAT4 for $T_H1$, STAT6 for $T_H2$ and STAT3 for $T_H17$.[35] mTORC1 and mTORC2 have discrete functions in promoting effector lineage differentiation and transcription factor activation. Deficiency of Ras homolog enriched in brain (RHEB, an important activator of mTORC1) leads to normal $T_H2$ but

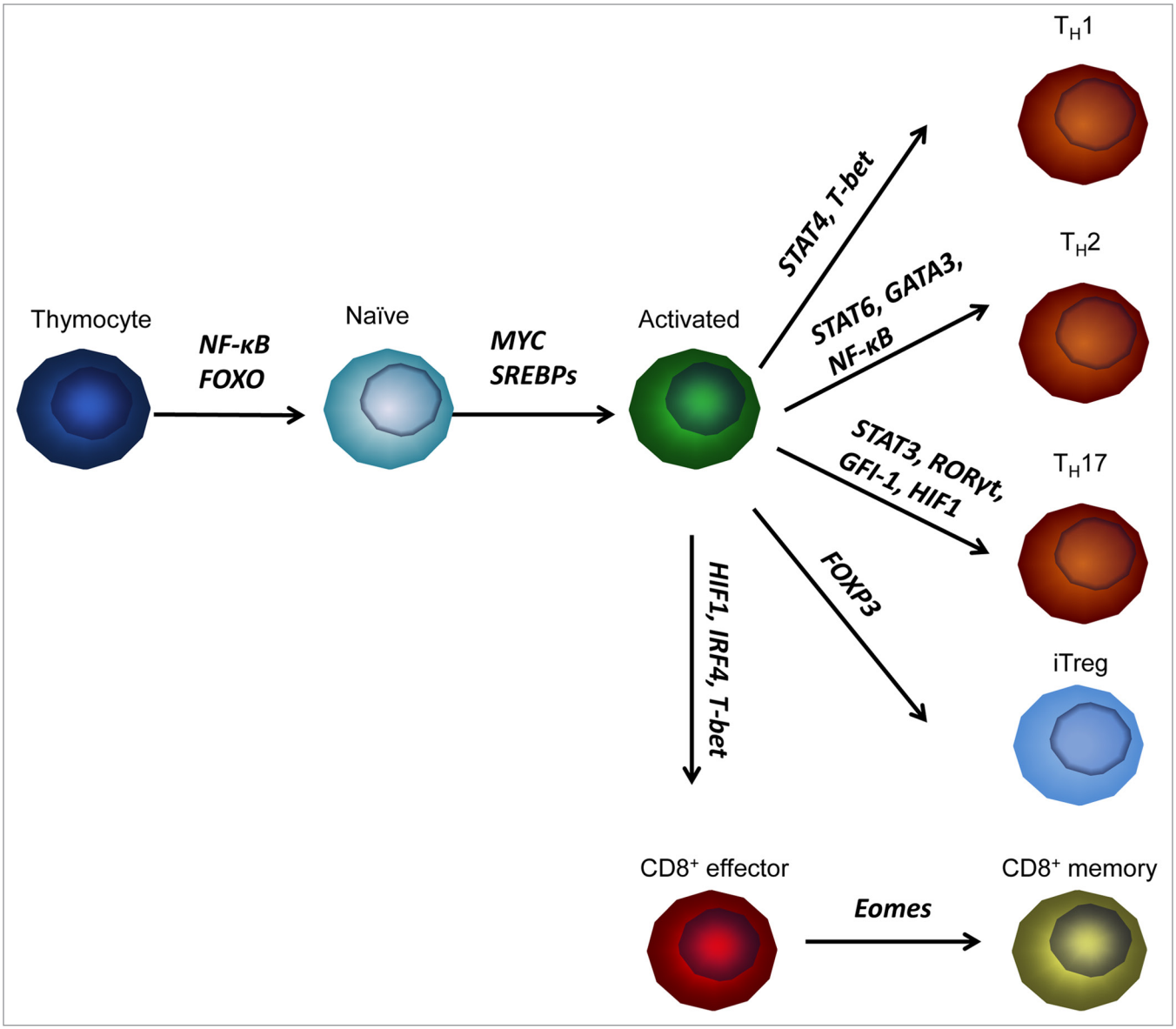


**Figure 1.** Schematics of T cell development, activation, lineage differentiation and memory formation. mTOR-controlled transcription factors that regulate different stages are highlighted in bold.

impaired $T_H1$ and $T_H17$ differentiation, because of reduced STAT4 and STAT3 activation, respectively. This is also correlated with diminished expression of T-bet, a $T_H1$ master transcription factor, and RORγt, a $T_H17$ master transcription factor.[7] However, RAPTOR-deficient T cells showed relatively normal $T_H1$, but defective $T_H17$ differentiation.[36] Recently, Yang et al. found that RAPTOR deficiency impairs TCR-induced metabolic reprogramming and IL-4 receptor expression, leading to a severe defect in $T_H2$ differentiation. Such defect is associated with impaired STAT activation and GATA3 induction.[23] The discrepancy between RHEB and RAPTOR deficiencies likely results from RHEB-independent activation of mTORC1.[37] Indeed, RHEB is not required for sustained mTORC1 activation in $CD4^+$ T cells.[23]

In contrast, loss of RICTOR preserves $T_H1$ and $T_H17$, but impairs $T_H2$ differentiation, which is associated with reduced STAT6 activation and defective expression of GATA3.[7] A separate report found that mTORC2 promotes $T_H2$ and $T_H1$ differentiation through PKCθ-NF-κB and AKT signaling, respectively, without affecting STAT activation.[6] These discrepancies remain to be resolved. The mechanistic basis underlying mTOR-mediated activation of various transcription factors also warrants further investigation.

We have limited understanding as to how mTOR signaling regulates T cell lineage transcription factors. It is unclear whether mTOR signaling directly regulates their activation or through other intermediates. Nonetheless, the PI3K-mTOR axis has been shown to promote GATA3 translation, which could partially explain the defective $T_H2$ differentiation in RAPTOR and RICTOR-deficient T cells.[38] Furthermore, several mechanisms

could underlie mTORC1-mediated transcriptional control of $T_H17$ differentiation. First, mTOR has been shown to directly phosphorylate STAT3 and promotes its activation in various systems,[39,40] which could potentially explain the defective STAT3 phosphorylation in mTOR-deficient T cells.[35] Second, PI3K-mTORC1-S6K1 axis suppresses GFI-1, a transcription repressor that inhibits $T_H17$ differentiation.[41,42] mTORC1-S6K1 activates EGR2 (Early growth response 2), a transcription factor that inhibits GFI-1 expression by directly binding to its promoter. Accordingly, transduction of constitutive active form of S6K1 partially rescues $T_H17$ differentiation of rapamycin-treated T cells.[36] Third, PI3K-mTORC1-S6K2 axis promotes RORγt nuclear translocation.[36] S6K2 is the nuclear-localized counterpart of S6K1, and its expression is enhanced by mTORC1 activation likely through posttranscriptional mechanisms. S6K2 interacts with RORγt and facilitates its nucleus translocation.[36] Lastly, mTOR signaling induces HIF1 expression and HIF1-dependent glycolytic program in differentiating $T_H17$ cells, which promotes $T_H17$ cell generation and at the same time, suppresses iTreg differentiation.[43] mTOR signaling enhances HIF1 mRNA transcription and protein translation, as well as HIF1 transcriptional activity that is likely mediated by interaction between RAPTOR and HIF1.[31,44-46] Thus, the mTORC1-HIF1 axis reciprocally controls $T_H17$ and iTreg differentiation.

Although mTOR deficiency disables effector lineage differentiation, it diverts $CD4^+$ T cells into iTreg cells even without exogenous iTreg-polarizing cytokines.[35] Activation of mTOR by PI3K-AKT pathway suppresses the expression of FOXP3, the master transcription factor for regulatory T cells.[47-51] Conversely, inhibition of mTOR with rapamycin or by limiting essential amino acids promotes FOXP3 expression and differentiation of iTreg cells.[47,48,52] Both mTORC1 and mTORC2 contribute to the suppression of FOXP3 expression, as deletion of either RHEB or RICTOR fails to spontaneously generate iTreg cells.[7,35] However, despite mounting evidence linking mTOR to FOXP3, little is known regarding the detailed molecular mechanism underlying mTOR-mediated FOXP3 suppression. It is also important to note that deletion of RAPTOR or RICTOR impairs the function or generation of thymus-derived $FOXP3^+$ Treg cells, respectively.[53]

## mTORC1 Promotes $CD8^+$ T Cell Effector Differentiation Through HIF1 and IRF4

After TCR activation and initial clonal expansion, $CD8^+$ T cells differentiate into effector cytotoxic effector cells by expressing an array of effector molecules, including perforin, interferon-γ (IFN-γ) and granzymes. The transcription factor hypoxia-inducible factor 1 (HIF1) is induced early during T cell activation in an mTOR-dependent manner.[8,22,46] Although its deficiency does not affect initial T cell activation, proliferation or metabolic reprogramming,[8,22] HIF1 is required for sustained glycolysis and pyruvate metabolism in effector $CD8^+$ T cells. Furthermore, HIF1-deficient effector $CD8^+$ T cells have defective expression of perforin and certain granzymes, but not other effector molecules, such as interferon-γ, suggesting that the mTORC1-HIF1 axis regulates a specific transcriptional program in effector $CD8^+$ T cells.[8] TCR-induced mTOR signaling promotes HIF1 protein synthesis, likely through 4E-BP1-eIF4 mediated cap-dependent translation.[31,46]

Interferon regulatory factor 4 (IRF4) is a transcription factor critical for many immune cell differentiation and function.[54] IRF4 expression is induced by TCR engagement and correlates with TCR strength.[55,56] Rapamycin treatment impairs TCR-mediated IRF4 induction, indicating that mTOR signaling regulates IRF4 expression.[55] Similar to HIF1, IRF4 is dispensable for early T cell activation and proliferation. However, IRF4 maintains $CD8^+$ T cell survival and is required for ongoing clonal expansion and effector function in a dose-dependent manner.[55,56] Further, IRF4 sustains the high aerobic glycolysis in activated $CD8^+$ by promoting the expression of multiple glycolytic enzymes.[56] Consequently, IRF4-deficient $CD8^+$ T cells fail to generate a productive effector response upon viral challenge.[55,56] The molecular mechanism whereby mTOR signaling promotes TCR-induced IRF4 expression remains unclear.

## mTOR Controls Memory $CD8^+$ T Cell Generation Through T-bet and Eomesodermin

After effector cell generation, a small subset of T cells differentiates into long-lived memory T cells. A metabolic transition from anabolism to catabolism accompanies memory T cell differentiation. Several studies have demonstrated that whereas mTORC1 promotes effector $CD8^+$ T cell generation, it negatively regulates memory T cell development. Rapamycin treatment or silencing of RAPTOR enhances memory cell generation and function.[57-59] Importantly, inhibition of mTORC1 reduces IL-12-induced expression of T-bet, a transcription factor essential for effector differentiation, and activates Eomesodermin (Eomes), a transcription factor that enhances memory cell formation.[59,60] Thus, mTOR dictates effector and memory differentiation in part through differentially regulating the corresponding transcription factors. Interestingly, a recent study indicated that mTOR promotes IgG1 memory B cells differentiation into plasma cells by suppressing the transcription repressor BACH2,[61] indicating different roles of mTOR signaling in memory T and B cell differentiation and function.

## Concluding Remarks

The physiological importance of mTOR signaling is underscored by the fact that dysregualtion of mTOR is associated with many human diseases. Although mTOR signaling was traditionally linked to protein translation, recent studies have demonstrated that mTOR also controls gene transcription in T cells as well as other experimental systems.[62] mTOR signaling modulates T cell development, activation, differentiation, memory generation, and function through a diverse set of transcription factors (**Fig. 1**),[10] highlighting the complexity of the involvement of mTOR in lymphocyte biology.

These transcription factors orchestrate cell metabolism (MYC, SREBPs and HIF1), lineage differentiation (T-bet, GATA3, RORγt, FOXP3 and Eomesodermin), and immune activation and functions (NF-κB, FOXOs, IRF4, STATs and GFI-1). Despite these exciting findings, we have insufficient understanding in regard to the molecular mechanisms that link mTOR to these transcription factors, especially in the context of T cell biology. How mTOR signaling regulates specific transcription factors in different T cell lineages is an important question awaiting future investigation. Another fascinating, yet poorly studied area is how transcription factors may influence mTOR signaling. Recent studies have revealed an intricate crosstalk between MYC and mTOR signaling. MYC cooperates with AKT-mTOR signaling to promote ribosome biogenesis.[63] Pourdehnad et al. found that mTOR-dependent phosphorylation of 4EBP1 is required for cancer cell survival in MYC-driven tumor initiation and maintenance.[64] 4EBP1, but not S6K, is highly phosphorylated in cancer cells induced by MYC overexpression. New class of mTOR active site inhibitors, which potently inhibit 4EBP1-eIF4E axis, induce apoptosis in MYC-driven cancer cells, delay tumorigenesis, and prolong animal survival.[64] Furthermore, MYC-deficient T cells exhibit impaired mTOR activity.[22] These findings further highlight the complexity of the interplay between mTOR signaling and transcription factors. We anticipate that more mechanistic studies will unravel the detailed connections between mTOR and gene transcription, which may contribute to the development of novel diagnostics and treatments of immune-related diseases.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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