

## **mTOR: Master regulator of T cell differentiation and function**

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Based on the integration of multiple environmental signals T cells may differentiate into effector subsets characterized by  $T_H1$ ,  $T_H2$  and  $T_H17$  cells, or regulatory cells characterized by Foxp3 expression. In yeast and mammalian cells, the Target of Rapamycin (TOR) integrates environmental cues and directs cell growth and proliferation. By analogy, in T cells we hypothesize that mTOR integrates environmental cues and dictates the outcome of antigen recognition. To test this hypothesis we generated mice in which mTOR is specifically deleted in T cells. Phenotypically, these mice display Wt levels of CD4+, CD8+ and Foxp3+ T cells and the mTOR<sup>-/-</sup> T cells produce Wt levels of IL-2 upon initial activation. However, both *in vitro* and *in vivo* mTOR<sup>-/-</sup> T cells fail to skew into Th1, Th2 or Th17 effectors. Instead, when activated under Th1, Th2 or Th17 activating conditions, mTOR<sup>-/-</sup> T cells differentiate into Foxp3+ regulatory T cells. mTOR signals through two known signaling complexes, TORC1 and TORC2. TORC1 contains Rheb, mTOR, GBL, and raptor, while TORC2 contains mSin1, mTOR, GBL, and rictor. In order to determine the specific role of TORC1 in T cell lineage commitment we conditionally deleted Rheb in T cells. Upon activation such cells fail to phosphorylate the TORC1 substrate S6K-1 while demonstrating normal TORC2 activity. As was the case for the mTOR<sup>-/-</sup> T cells, Rheb<sup>-/-</sup> T cells fail to differentiate into Th1 and Th17 cells. However, unlike mTOR<sup>-/-</sup> T cells, the Rheb deficient T cells are capable of becoming Th2 cells. Furthermore, in spite of lacking TORC1 activity, T cells lacking Rheb do not develop into Foxp3+ cells. In order, to assess the role of TORC2 we conditionally deleted rictor in T cells. Functionally, these cells behaved as the mirror image of the Rheb knockouts in that they failed to be skewed into Th2 effectors but readily differentiated into Th1 and Th17 cells under appropriate conditions. Overall, our data identify mTOR as a regulator of T cell lineage commitment through which TORC1 and TORC2 signaling differentially regulate T cell fate. TORC1 is responsible for Th1 and Th17 differentiation while TORC2 regulates Th2 differentiation. Furthermore, our data support a new paradigm whereby the default pathway for TCR engagement is toward regulatory cells, and that accessory signals leading to the activation of mTOR are required to redirect antigen recognition toward active immunity.

1. Zheng Y, Collins S, Lutz MA, Allen AN, Kole TP, Zarek PE, Powell JD. A role for the mammalian target of rapamycin in regulating T cell activation versus anergy. *J Immunol.* 2007 Feb 15;178(4):2163-70.
2. Powell JD, Zheng Y. Dissecting the mechanism of T-cell anergy with immunophilin ligands. *Curr Opin Investig Drugs.* 2006 Nov;7(11):1002-7. Review.