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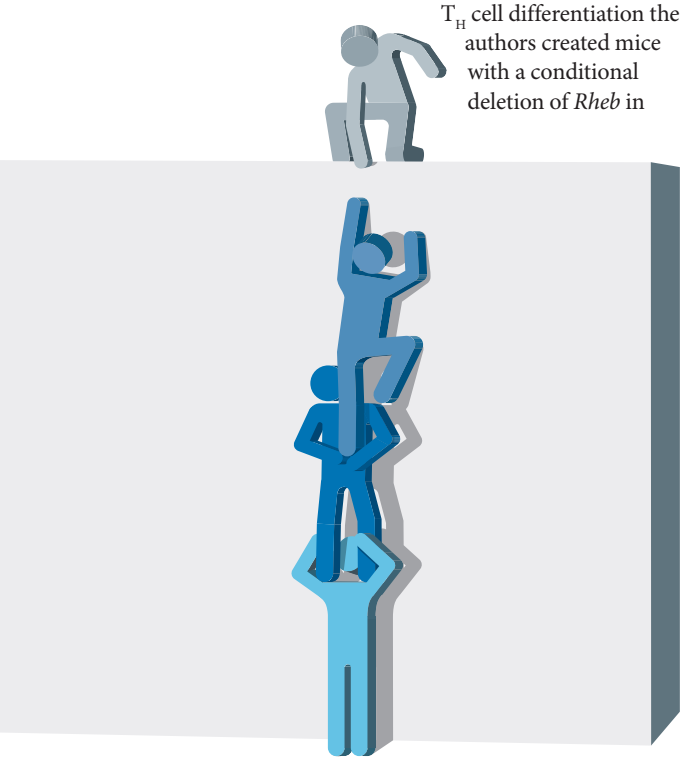
T CELLS

# A little help from mTOR's friends

The effects of mammalian target of rapamycin (mTOR) signalling on the T helper ($T_H$) cell response depend on the partners with which mTOR associates, according to new research published in *Nature Immunology*.

The kinase mTOR regulates cellular metabolism in response to environmental factors, and many recent studies have shown that this pathway controls the differentiation and function of immune cells in response to the immune microenvironment. However, mTOR can form two signalling complexes — mTORC1 and mTORC2 — and this study is the first to show that these complexes have distinct physiological effects on T cells.

RHEB proteins are crucial regulators of mTORC1 signalling, so to investigate the role of mTORC1 in $T_H$ cell differentiation the authors created mice with a conditional deletion of *Rheb* in



$CD4^+$ T cells (T-*Rheb*$^{-/-}$ mice). This deletion resulted in the elimination of all mTORC1 activity, but mTORC2 activity was preserved. *Rheb*$^{-/-}$ T cells from these mice failed to differentiate into $T_H1$ or $T_H17$ cells under appropriate skewing conditions *in vitro*, but could still differentiate into $T_H2$ cells. To investigate the effects *in vivo*, *Rheb*$^{-/-}$ T cells specific for ovalbumin (OVA) were transferred into recipient mice infected with an OVA-expressing vaccinia virus. In this model, the *Rheb*$^{-/-}$ T cells failed to differentiate into interferon-γ (IFNγ)-producing $T_H1$ cells and instead produced interleukin-4 (IL-4). Similarly, *Rheb*$^{-/-}$ T cells could not differentiate into $T_H17$ cells in the gut Peyer's patches. Finally, T-*Rheb*$^{-/-}$ mice had lower clinical disease scores than wild-type mice in a model of experimental autoimmune encephalomyelitis (EAE), which is mediated by $T_H1$ and $T_H17$ cells, and developed a non-classical response mediated by $T_H2$ cells. So, mTORC1 signalling is required for $T_H1$ and $T_H17$ cell differentiation and its absence results in increased $T_H2$ cell differentiation.

By contrast, $CD4^+$ T cells with a conditional deletion of rapamycin-insensitive companion of mTOR (*Rictor*) lacked mTORC2 activity but had normal mTORC1 activity. These cells could differentiate into $T_H1$ and $T_H17$ cells, but not $T_H2$ cells, under appropriate *in vitro* conditions. Moreover, *Rictor*$^{-/-}$ T cells showed normal production of IFNγ in response to vaccinia virus infection and normal susceptibility to EAE, but they failed to produce a $T_H2$ cell response to immunization with OVA plus alum.

The authors next investigated the mechanisms behind these responses. *Rheb*$^{-/-}$ T cells had decreased phosphorylation of $T_H1$ cell-promoting signal transducer and activator of transcription 4 (STAT4) and of $T_H17$ cell-promoting STAT3 in response to IL-12 and IL-6, respectively. However, the phosphorylation of $T_H2$ cell-promoting STAT6 in response to IL-4 was increased in these cells. Conversely, *Rictor*$^{-/-}$ T cells had normal phosphorylation of STAT4 and STAT3 but decreased phosphorylation of STAT6 in response to the relevant cytokines. This differential STAT activation between *Rheb*$^{-/-}$ and *Rictor*$^{-/-}$ T cells was shown to result from increased expression of suppressor of cytokine signalling 3 (SOCS3) or SOCS5, respectively. Knockdown of SOCS3 expression in *Rheb*$^{-/-}$ T cells increased their ability to produce IFNγ, whereas knockdown of SOCS5 expression in *Rictor*$^{-/-}$ T cells increased their ability to produce IL-4. Furthermore, SOCS3 knockdown correlated with increased expression of the $T_H1$ cell-associated transcription factor T-bet, and knockdown of SOCS5 resulted in increased expression of the $T_H2$ cell transcription factor GATA3.

Therefore, the mTORC1 and mTORC2 signalling complexes selectively regulate the ability of $CD4^+$ T cells to respond to cytokines that promote $T_H1$ and $T_H17$ cells or $T_H2$ cells, respectively. This control mechanism involves, in part, SOCS-mediated regulation of the STAT signalling pathways that upregulate lineage-specific transcription factors in response to the cytokine environment.

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**ORIGINAL RESEARCH PAPER** Delgoffe, G. M. *et al.* The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. *Nature Immunol.* 27 Feb 2011 (doi:10.1038/ni.2005)