Nature Reviews Immunology | AOP, published online 17 July 2009; doi:10.1038/nri2609

T CELL RESPONSES

Quantity and quality control by mTOR

The immunosuppressive effects of the drug rapamycin, which inhibits Akt–mTOR (mammalian target of rapamycin) signalling, have been attributed to the modulation of many immune cell types. Three new studies clarify T cell-intrinsic roles for mTOR as a regulator of both $CD4^+$ and $CD8^+$ T cell differentiation.

Delgoffe *et al.* generated mice with a conditional deletion of *Frap1* (the gene encoding mTOR) in T cells. $CD4^+$ T cells from these T-*Frap1*$^{-/-}$ mice failed to differentiate into T helper 1 (T_H1), T_H2 or T_H17 effector cells in the presence of appropriate polarizing cytokines *in vitro* or *in vivo*. Despite expressing appropriate receptors for these polarizing cytokines, T-*Frap1*$^{-/-}$ $CD4^+$ T cells had decreased phosphorylation of the downstream signal transducer and activator of transcription (STAT) factors in response to these cytokines and failed to upregulate lineage-specific transcription factors. Instead, the activation of T-*Frap1*$^{-/-}$ T cells resulted in the generation of a larger number of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{Reg}) cells compared with activation of wild-type T cells, and these $FOXP3^+$ T cells had potent suppressive activity *in vitro*. T-*Frap1*$^{-/-}$ T cells had increased baseline levels of phosphorylation of SMAD3, which increased further with the addition of transforming growth factor-β (TGFβ).

These results indicate that mTOR controls the differentiation of effector versus regulatory $CD4^+$ T cells in the periphery by regulating cytokine receptor signalling. In the absence of mTOR, the default pathway is the generation of T_{Reg} cells through hypersensitivity to TGFβ-induced SMAD3 phosphorylation and inhibition of STAT phosphorylation.

Liu *et al.* have shown a similar inhibitory role for Akt–mTOR, activated by sphingosine 1-phosphate (S1P) signalling, in both the differentiation and suppressive activity of natural T_{Reg} cells derived from the thymus. In this study, mice with a conditional deletion of S1PR1 (a receptor for S1P) in T cells had an increased number of thymic T_{Reg} cells, whereas mice with increased expression of S1PR1 in T cells had fewer thymic T_{Reg} cells than wild-type mice. These results were due to an inhibitory effect of S1P on the differentiation of thymic T_{Reg} cells rather than to effects of S1P on their trafficking from the thymus. Moreover, *S1pr1*-transgenic T_{Reg} cells also had impaired suppressive activity both *in vitro* and *in vivo*, leading to a breakdown of T_{Reg} cell-mediated immune tolerance and the development of autoimmunity. S1PR1 overexpression in T cells was associated with increased activation of the Akt–mTOR signalling pathway, and pharmacological inhibition of mTOR with rapamycin restored the generation and suppressive activity of *S1pr1*-transgenic T_{Reg} cells.

Araki *et al.* have extended the role of mTOR to the differentiation of $CD8^+$ T cells. They showed that mice treated with rapamycin during infection with lymphocytic choriomeningitis virus (LCMV) had increased generation of memory $CD8^+$ T cell precursors during the expansion phase of the T cell response and increased survival and memory T cell differentiation of antigen-specific $CD8^+$ T cells during the contraction phase of the response. This resulted in an increased number of memory $CD8^+$ T cells with improved function. Similar results were obtained in mice and non-human primates using both live and inactivated virus vaccines, and the inhibitory role of mTOR in memory $CD8^+$ T cell differentiation was shown to be a T cell-intrinsic effect by comparing T cells with or without expression of mTOR that were adoptively transferred into the same mouse.

The insight provided by these three studies into the role of mTOR in regulating both the quantity and quality of effector, regulatory and memory T cells will be relevant to the design of better immunomodulatory protocols to boost protective immune responses through vaccination or to inhibit autoimmunity and transplant rejection.

Kirsty Minton

ORIGINAL RESEARCH PAPERS Delgoffe, G. M. *et al.* The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. *Immunity* **30**, 832–844 (2009) | Liu, G. *et al.* The receptor $S1P_1$ overrides regulatory T cell-mediated immune suppression through Akt–mTOR. *Nature Immunol.* **10**, 769–777 (2009) | Araki, K. *et al.* mTOR regulates memory CD8 T-cell differentiation. *Nature* 21 Jun 2009 (doi:10.1038/nature08155)
FURTHER READING Thomson, A. W. *et al.* Immunoregulatory functions of mTOR inhibition. *Nature Rev. Immunol.* **9**, 324–337 (2009)