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REGULATORY T CELLS

The PTEN stabilizer

> PTEN signalling in T_{Reg} cells suppresses the spontaneous development of a lymphoproliferative disease

Forkhead box P3-positive ($FOXP3^+$) regulatory T (T_{Reg}) cells maintain immune tolerance and thus, defining the mechanisms that control T_{Reg} cell function and stability is crucial for understanding how the immune system is regulated. Previous studies have implicated the phosphatase PTEN, which is the main negative regulator of phosphoinositide 3-kinase (PI3K), in T_{Reg} cell activation. Now, two studies published in *Nature Immunology* show that PTEN, through the regulation of PI3K and mammalian target of rapamycin (mTOR) complex 2 (mTORC2), is crucial for maintaining T_{Reg} cell homeostasis, function and stability.

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Using similar techniques, both groups generated mice in which T_{Reg} cells specifically lacked *Pten* (*Pten*$^{fl/fl}$*Foxp3*-Cre mice). Over time, these mice developed an autoimmune and lymphoproliferative disease with renal pathology. Further analysis of these mice showed an accumulation of germinal centre B cells, high levels of serum autoantibodies and high number of T cells with an activated or memory phenotype. T cells from these mice expressed high levels of interferon-γ (IFNγ) and CXC-chemokine receptor 3, which are both signatures of T helper 1 (T_H1) cells. In addition, high numbers of follicular helper T cells (T_{FH} cells) were observed in *Pten*$^{fl/fl}$*Foxp3*-Cre mice compared with control mice. Shrestha *et al.* showed that the increased T_{FH} cell, germinal centre and autoimmune responses were dependent on the increased production of IFNγ in *Pten*$^{fl/fl}$*Foxp3*-Cre mice. These data suggest that PTEN signalling in T_{Reg} cells suppresses the spontaneous development of a lymphoproliferative disease involving B cells, T_H1 cells and T_{FH} cells.

Surprisingly, given the loss of immune tolerance in these mice, high numbers of $FOXP3^+$ T_{Reg} cells, in particular $FOXP3^+CD25^-$ T_{Reg} cells, were observed in *Pten*$^{fl/fl}$*Foxp3*-Cre mice. Huynh *et al.* provided data to suggest that PTEN-deficient T_{Reg} cells might be pathogenic *in vivo*. Using a lineage-tracing system, both groups found that in addition to a loss of CD25 expression, PTEN-deficient T_{Reg} cells lost expression of FOXP3 over time and, as shown by Shrestha *et al.*, these 'ex-T_{Reg} cells' upregulated the expression of molecules characteristic of T_H1 cells and T_{FH} cells. These data indicate that PTEN maintains T_{Reg} cell stability.

T_{Reg} cells from *Pten*$^{fl/fl}$*Foxp3*-Cre mice were shown by both groups to have increased glycolytic metabolism compared with control T_{Reg} cells, which might disrupt T_{Reg} cell stability and homeostasis. Loss of PTEN in T_{Reg} cells also resulted in increased activation of mTORC2 (but not mTORC1) compared with control cells. Abrogation of mTORC2 activity in PTEN-deficient T_{Reg} cells either through deletion of the mTORC2 component *Rictor* (Shrestha *et al.*) or through inhibition of AKT (Huynh *et al.*), which is downstream of mTORC2, restored CD25 expression. As shown by Shrestha *et al.*, abrogation of mTORC2 activity also blocked the spontaneous development of T_H1 cells, T_{FH} cells and germinal centre B cells, as well as renal pathology, in *Pten*$^{fl/fl}$*Foxp3*-Cre mice. Inhibition of PI3K, which is upstream of mTORC2, also prevented the loss of CD25 and FOXP3 in PTEN-deficient T_{Reg} cells *in vitro* (Huynh *et al.*).

Thus, the control of PI3K and mTORC2 activity by PTEN maintains T_{Reg} cell lineage stability, T_{Reg} cell-mediated control of effector responses and thus immune homeostasis.

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ORIGINAL RESEARCH PAPERS Shrestha, S. *et al.* T_{Reg} cells require the phosphatase PTEN to restrain T_H1 and T_{FH} cell responses. *Nature Immunol.* http://dx.doi.org/10.1038/ni.3076 (2015) | Huynh, A. *et al.* Control of PI(3) kinase in T_{Reg} cells maintains homeostasis and lineage stability. *Nature Immunol.* http://dx.doi.org/10.1038/ni.3077 (2015)