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> FOXO1 also has a crucial role in maintaining the function of T_{Reg} cells in a manner independent of FOXP3

Forkhead box O (FOXO) family transcription factors have a well-identified role in T cell commitment to a regulatory phenotype, in part by inducing the expression of the master regulator of regulatory T (T_{Reg}) cells — FOXP3. New data published in *Nature* show that FOXO1 also has a crucial role in maintaining the function of T_{Reg} cells in a manner independent of FOXP3.

These studies were carried out using a series of mutant mice labelled for expression of FOXO1 and/or FOXP3, some of which had a conditional deletion of *Foxo1* in FOXP3$^+$ T_{Reg} cells or expressed a mutant form of FOXO1 that cannot be exported from the nucleus. In live-imaging experiments, the authors showed that low-dose CD3-specific antibody treatment triggered the translocation of FOXO1 from the nucleus to the cytosol in conventional T cells, but this did not occur in T_{Reg} cells owing to markedly decreased AKT-mediated phosphorylation of FOXO1 in T_{Reg} cells. Therefore, T_{Reg} cells seem to be relatively resistant to the T cell receptor-induced clearance of FOXO1 from the nucleus compared with conventional T cells.

Conditional deletion of *Foxo1* in T_{Reg} cells did not affect the number of T_{Reg} cells but led to severe pathology — including splenomegaly and lymphadenopathy — comparable to that of T_{Reg} cell-deficient FOXP3-mutant mice. So the lymphoproliferative disease resulting from the loss of FOXO1 is a consequence of the loss of T_{Reg} cell function. Expression of a permanently nuclear FOXO1 mutant in FOXO1-deficient T_{Reg} cells completely rescued the pathology, showing that nuclear FOXO1 activity is required for T_{Reg} cell function.

By cross-referencing putative FOXO1-binding sites in the nuclei of T_{Reg} cells against gene expression in wild-type, FOXO1-deficient and nuclear-FOXO1-mutant T_{Reg} cells, the authors identified 310 direct FOXO1 target genes. A comparison of the direct target genes of FOXO1 and FOXP3 showed that 90–99% of the targets were specifically regulated by only one of the transcription factors. One such FOXO1-specific target gene in T_{Reg} cells is the gene encoding interferon-γ (IFNγ).

A prominent feature of wild-type T_{Reg} cells is the inability to produce pro-inflammatory cytokines. By contrast, FOXO1-deficient T_{Reg} cells had high levels of IFNγ mRNA and protein. In a T cell-transfer model of colitis, disease could be attenuated by wild-type or *Foxo1*$^{-/-}$*Ifng*$^{-/-}$ T_{Reg} cells, but not by *Foxo1*$^{-/-}$ T_{Reg} cells. Together, the data indicate that *Ifng* is a crucial target gene repressed by FOXO1 for the control of T_{Reg} cell function.

Kirsty Minton

ORIGINAL RESEARCH PAPER Ouyang, W. *et al.* Novel Foxo1-dependent transcriptional programs control T_{reg} cell function. *Nature* 7 Nov 2012 (doi:10.1038/nature11581)