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REGULATORY T CELLS

Another roll of the Dice(r)

New findings in *The Journal of Experimental Medicine* show that naturally occurring $CD4^+CD25^+$ regulatory T (T_{Reg}) cells and conventional $CD4^+$ ($CD25^-$) T cells have distinct microRNA (miRNA) profiles, and that the ribonuclease III enzyme Dicer, which is required for embryonic development, is involved in the development of T_{Reg} cells.

Mature miRNAs are short (21–22 nucleotides), single-stranded RNAs that are generated from longer precursors by Dicer. miRNAs regulate gene expression at the post-transcriptional level by targeting matching pieces of messenger RNA for degradation, thereby decreasing the production of the corresponding protein, and they have been proposed to have a role in haematopoiesis. In their study of T_{Reg}-cell biology, Cobb *et al*. analysed miRNA expression in both T_{Reg} cells and conventional $CD4^+$ T cells in mice. These two cell populations had distinctly different expression profiles, with 68 miRNAs being differentially expressed between T_{Reg} cells and $CD4^+$ T cells. Interestingly, on activation, $CD4^+$ T cells transiently adopted a profile of miRNA expression that was similar to that of T_{Reg} cells. Forced expression of the transcription factor forkhead box P3 (FOXP3), a major marker and regulator of the development and function of mouse T_{Reg} cells, in $CD4^+$ T cells showed that 9 of the 10 miRNAs that were upregulated in FOXP3-expressing cells were among the top 20 miRNAs preferentially expressed in T_{Reg} cells. Therefore, either directly or indirectly, FOXP3 was contributing to the T_{Reg}-cell miRNA expression profile.

Deletion of Dicer from the T-cell lineage resulted in the absence of miRNA expression, reduced numbers of T_{Reg} cells and the development of immune pathology in the colon, lung and liver of a proportion of the mice examined. But is Dicer involved in T_{Reg}-cell differentiation, or in T_{Reg}-cell maintenance or homeostasis? Further investigation focused on the first wave of T_{Reg}-cell development in the thymus and revealed that thymic differentiation of Dicer-deficient (and therefore also mature miRNA-deficient) T_{Reg} cells was impaired. The induction of FOXP3 in peripheral naive $CD4^+$ T cells by transforming growth factor-β (TGFβ) was also compromised in the absence of Dicer.

In a cell-autonomous manner, therefore, Dicer is required to maintain normal numbers of T_{Reg} cells in peripheral lymphoid organs, for T_{Reg}-cell development in the thymus and for the efficient induction of FOXP3 expression by TGFβ in $CD4^+$ T cells. These findings indicate a novel role for Dicer in immune regulation.

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ORIGINAL RESEARCH PAPER Cobb, B. S. *et al.* A role for Dicer in immune regulation. *J. Exp. Med.* 23 Oct 2006 (doi:10.1084/jem.20061692)

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