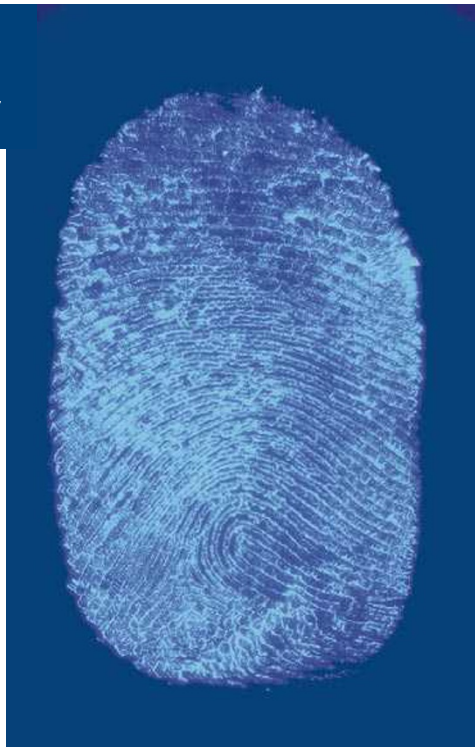
REGULATORY T CELLS

MicroRNAs maintain identity



Three recent papers published in *The Journal of Experimental Medicine* show that microRNAs are needed to safeguard the function of regulatory T (T_{Reg}) cells.

T_{Reg} cells are known to be essential for immune homeostasis and act by suppressing the activation of autoreactive T cells. Accordingly, the ablation of T_{Reg} cells or mutation of the gene that encodes the T_{Reg}-cell-defining transcription factor forkhead box P3 (FOXP3) results in a devastating autoimmune lymphoproliferative disease in mice. The new data further support this important function of T_{Reg} cells and reveal that microRNAs are required to maintain T_{Reg}-cell activity, which befits their suggested role in 'buffering' gene expression in conditions of environmental stress.

MicroRNAs, which regulate gene expression at the post-transcriptional level, are generated from longer RNA transcripts through sequential processing by the enzymes Drosha and Dicer; deletion of these enzymes can therefore be used to study the effects of microRNA deficiency. In all three studies, mice with a T_{Reg}-cell-specific deletion of *Dicer* developed a spontaneous, aggressive autoimmune disease that was indistinguishable from that observed in mice that lack *Foxp3* or T_{Reg} cells. Chong *et al.* also found that conditional deletion of *Drosha* in T_{Reg} cells had the same devastating effect, which confirms that Drosha and Dicer function in the same pathway. The finding that mice in which *Dicer* (or *Drosha*) was deleted in all T cells suffered a less severe, delayed lymphoproliferative disease suggested that unknown defects in the activation or function of conventional T cells caused by the absence of microRNAs could mask the devastating consequences of Dicer deficiency in T_{Reg} cells.

T_{Reg}-cell-targeted microRNA deficiency did not grossly affect the thymic development, proliferation or survival of T_{Reg} cells, although a decrease in the frequency of $FOXP3^+$ thymocytes and mature peripheral T_{Reg} cells (possibly a consequence of impaired peripheral homeostasis, as suggested by Liston *et al.*) were noted by all groups. More importantly, however, Dicer-deficient T_{Reg} cells showed evidence of altered differentiation and defective function in the periphery. Zhou *et al.* reported that Dicer-deficient T_{Reg} cells seemed to be more activated and expressed genes that are normally associated with effector T cells, including granzymes, interferon-γ and CD127. Similarly, Liston *et al.* showed that in an inflammatory setting, Dicer-deficient T_{Reg} cells lost their normal anergic phenotype and had impaired homeostasis. Zhou *et al.* observed downregulation of FOXP3 expression in a subset of Dicer-deficient T_{Reg} cells and altered expression of other T_{Reg}-cell-associated markers, such as neuropilin-1 and cytotoxic T-lymphocyte antigen 4, in most other T_{Reg} cells, which suggests that microRNAs are important for maintaining a stable T_{Reg}-cell phenotype.

Further characterization of the function of Dicer-deficient T_{Reg} cells by all three groups revealed a marked defect in their suppressive capacity *in vitro* and *in vivo*. Importantly, Liston *et al.* noted that the suppressive defect was most profound in T_{Reg} cells under inflammatory conditions and suggested that this could account for the rapid onset of severe disease in mice with a targeted deletion of *Dicer* in T_{Reg} cells.

So, although it is not clear which individual microRNAs are involved, these studies highlight an essential role for microRNA-dependent regulation of gene expression in the maintenance of T_{Reg}-cell homeostasis and suppressive function.

Lucy Bird

ORIGINAL RESEARCH PAPERS Zhou, X. *et al.* Selective miRNA disruption in T reg cells leads to uncontrolled autoimmunity. *J. Exp. Med.* **205**, 1983–1991 (2008) | Liston, A., Lu, L.-F., O'Carroll, D., Tarakhovsky, A. & Rudensky, A. Y. Dicer-dependent microRNA pathway safeguards regulatory T cell function. *J. Exp. Med.* **205**, 1993–2004 (2008) | Chong, M. M. W., Rasmussen, J. P., Rudensky, A. Y. & Littman, D. R. The RNAselIII enzyme Drosha is critical in T cells for preventing lethal inflammatory disease. *J. Exp. Med.* **205**, 2005–2017 (2008)