DOI:
10.1038/nri2143

REGULATORY T CELLS

Reciprocal regulation by retinoic acid

How can transforming growth factor- β (TGF β) induce the differentiation of both regulatory T cells and T helper 17 (T_H17) cells — two T-cell subsets that have opposing functions? Recent studies have indicated that the presence of additional pro-inflammatory cytokines, such as interleukin-6 (IL-6), is necessary for T_H17-cell differentiation. Now Mucida *et al.* show that the vitamin A metabolite retinoic acid is a key regulator of TGF β -induced T-cell differentiation.

The authors compared the ability of mucosal and splenic dendritic cells (DCs) to promote the differentiation of T_H17 cells and found that, in the presence of TGF β and IL-6, mesenteric lymph node (MLN) DCs were less effective than splenic DCs at inducing T_H17-cell differentiation. Because previous studies have functionally linked retinoic acid and mucosal DCs, the authors determined whether there was a role for retinoic acid in the reduced capacity of MLN DCs to promote T_H17-cell differentiation. The culture of T cells with MLN DCs, TGF β , IL-6 and a retinoic-acid receptor (RAR) antagonist reversed the reduced ability of MLN DCs to promote T_H17-cell differentiation, resulting in the differ-

entiation of similar numbers of T_H17 cells as with splenic DCs. By contrast, addition of all-*trans* retinoic acid to cultures with splenic DCs inhibited their induction of T_H17 cells. Retinoic acid also inhibited the expression of the T_H17-cell-associated transcription factor retinoic-acid-receptor-related orphan receptor- γ t (ROR γ t) in T_H17-cell-inducing conditions. So, retinoic acid inhibits TGF β - and IL-6-driven T_H17-cell differentiation. The suppressive effect of retinoic acid on T_H17 cells was also confirmed *in vivo*.

Next, the authors asked if MLN DCs preferentially promoted the differentiation of TGF β -dependent regulatory T cells, as determined by their expression of forkhead box P3 (FOXP3). MLN DCs induced more FOXP3⁺ T cells in the presence of TGF β compared with splenic DCs. The addition of a RAR antagonist reduced this TGF β -dependent FOXP3 induction, whereas addition of retinoic acid enhanced it. Regulatory T cells generated in the presence of both TGF β and retinoic acid were functional *in vivo* and protected mice from colitis, whereas TGF β -induced regulatory T cells were only partially protective.

Under conditions that promote T_H17-cell differentiation (TGF β and

IL-6), retinoic acid induced the differentiation of regulatory T cells, indicating that retinoic acid might override the promotion of TGF β -induced T_H17-cell differentiation by IL-6.

So, the data show that retinoic acid regulates the reciprocal differentiation of TGF β -induced regulatory T cells and T_H17 cells. This study has important implications for the understanding of vitamin A deficiency and highlights the therapeutic potential of retinoic acid in diseases in which there is an imbalance in the numbers of TGF β -dependent T_H17 cells and regulatory T cells.

More recently, three papers published in *The Journal of Experimental Medicine* (see Further Reading) show that the induction of regulatory T cells by DCs in the gut depends on TGF β and retinoic acid, highlighting a specific role for retinoic acid in the mucosal immune system.

Olive Leavy

“...retinoic acid is a key regulator of TGF β -induced T-cell differentiation.”

ORIGINAL RESEARCH PAPER Mucida, D. *et al.* Reciprocal Th-17 and regulatory T cell differentiation mediated by retinoic acid. *Science* 14 June 2007 (doi:10.1126/science.1145697)

FURTHER READING Sun, C.-M. *et al.* Small intestine lamina propria dendritic cells promote *de novo* generation of Foxp3⁺ T reg cells via retinoic acid. *J. Exp. Med.* 9 July 2007 (doi:10.1084/jem.20070602) | Benson, M. J., Pino-Lagos, K., Roseblatt, M. & Noelle, R. J. All-*trans* retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J. Exp. Med.* 9 July 2007 (doi:10.1084/jem.20070719) | Coombes, J. L. *et al.* A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF- β - and retinoic acid-dependent mechanism. *J. Exp. Med.* 9 July 2007 (doi:10.1084/jem.20070590)