

## **Role of the orphan nuclear receptor ROR $\gamma$ t in immune system homeostasis**

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T helper cells differentiate into lineages with distinct effector functions in response to the diverse cytokines induced following infection or tissue damage. In addition to Th1 and Th2 cells, T helper cells that secrete IL-17, IL22, and other pro-inflammatory cytokines (Th17 cells) were recently described. Cells of this lineage have key roles in mouse models of autoimmunity, and they are induced by a combination of TGF- $\beta$  and IL-6, while their maintenance and expansion requires IL-23. Induction of Th17 cells is dependent on the orphan nuclear receptor ROR $\gamma$ t, which is expressed in response to either TGF- $\beta$  or IL-6. Since overexpression of ROR $\gamma$ t in naïve T cells results in induction of IL-17, it is puzzling that only the combination of the cytokines is effective in Th17 differentiation. We have found that Foxp3, which is also induced upon treatment with TGF- $\beta$  alone and, to a lesser extent, by a combination of TGF- $\beta$  and IL-6, represses ROR $\gamma$ t-induced expression of IL-17. The decision of a naïve T helper cell to differentiate into a Foxp3<sup>+</sup> regulatory T cell versus a Th17 cell thus appears to rely, at least in part, on the balance of Foxp3 and ROR $\gamma$ t expression. IL-6 treatment also results in the induction of IL-23R. As a consequence, IL-23 can also inhibit Foxp3 gene expression while it synergizes with TGF- $\beta$  to elevate the level of IL-17. The IL-23R-dependent induction of IL-17 is also dependent on the presence of ROR $\gamma$ t. This nuclear receptor thus regulates a large part of the differentiation program of Th17 cells in response to different signals.

In mice kept in an SPF facility, we have found that T cells expressing ROR $\gamma$ t and IL-17 are found only in the intestinal lamina propria, and these cells are absent in IL-6-deficient mice. T cells lacking expression of ROR $\gamma$ t were defective in induction of inflammatory bowel disease and also of EAE. ROR $\gamma$ t is also required for selection of a suitable T cell repertoire and for the development of lymphoid tissue inducer cells, which direct the differentiation of lymphoid organs and inflammatory intestinal follicles. In the intestine, regulation of ROR $\gamma$ t function, potentially by a ligand, may thus contribute to the homeostasis of the microbial flora and to protection of the epithelial barrier by controlling differentiation of follicles as well as Th17 cells. Together, our results suggest that ROR $\gamma$ t may be an attractive therapeutic target in a variety of autoimmune diseases.

### **References:**

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