MUCOSAL IMMUNOLOGY

Microbiota-induced T cells block allergic inflammation

> “RORγt$^+$ T cell populations ... negatively regulate type 2 immunity”

Disturbing the microbiota early in life is associated with a greater risk of developing allergic disorders. The reasons for this have not been clear, but a study in *Science* now suggests that the intestinal microbiota restrains type 2 immune responses by inducing the development of RORγt-expressing T cells.

The microbiota has previously been shown to support the development of RORγt$^+$ T cell populations, such as T helper 17 (T_H17) cells and a subset of forkhead box P3 protein (FOXP3)-expressing regulatory T (T_{Reg}) cells. Using dual reporter mice, the authors found that the majority of RORγt$^+$ T cells in the colon co-express FOXP3 and showed that they are RORγt$^+$ T_{Reg} cells. RORγt$^+$ T_{Reg} cell populations were expanded with age in mice but were markedly reduced in germ-free or antibiotic-treated mice. By contrast, thymus-derived T_{Reg} cells and GATA3$^+$ T_{Reg} cells were not reduced in germ-free or antibiotic-treated mice. Germ-free mice that were recolonized with microbiota had normal numbers of RORγt$^+$ T_{Reg} cells, confirming that the microbiota supports the generation of these cells. The development of RORγt$^+$ T_{Reg} cells was also found to depend on MHC class II molecules and dendritic cells (DCs), as well as on the STAT3-activating cytokines interleukin-6 (IL-6) and IL-23.

To examine whether these microbiota-induced RORγt$^+$ T_{Reg} cells regulate type 2 immune responses, the authors generated mice with a conditional knockout of the gene encoding RORγt in FOXP3$^+$ cells. These mice specifically lacked RORγt$^+$ T_{Reg} cells and showed increased frequencies of GATA3$^+$ T_H2 cells and GATA3$^+$ T_{Reg} cells in the intestine. Compared with littermate controls, the RORγt$^+$ T_{Reg} cell-deficient mice developed more severe disease in an oxazolone-induced colitis model, which depends on the type 2 cytokines IL-4 and IL-13. In addition, mice lacking RORγt$^+$ T_{Reg} cells showed greater resistance to a helminth infection. The suppression of T_H2 cells was not dependent on the production of IL-10 by RORγt$^+$ T_{Reg} cells but instead involved their expression of cytotoxic T lymphocyte antigen 4 (CTLA4); CTLA4 seemed to suppress T_H2 cell induction by regulating DC expression of the co-stimulatory molecules CD80 and CD86. Notably, T_H17 cells were also found to contribute to the suppression of type 2 immune responses, as T_H2 cell populations were further expanded in mice with a complete RORγt deficiency compared with mice with a T_{Reg} cell-specific RORγt deficiency.

The authors suggest that reduced microbial exposure prevents the development of RORγt$^+$ T cell populations that have the capacity to negatively regulate type 2 immunity; this might explain why allergies are on the rise in industrialized nations.

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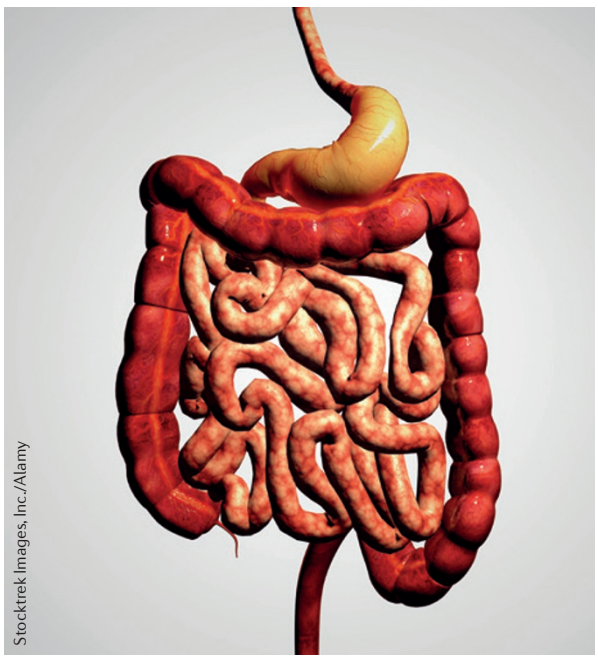

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