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T CELL RESPONSES

Anger management for T_H17 cells

> redirection of pro-inflammatory T_H17 cells to the small intestine may be a physiological mechanism to prevent excessive immuno-pathology

A key feature of the intestinal immune system is its ability to promote tolerogenic responses to food antigens and commensal organisms. Now, Richard Flavell and colleagues have shown that the small intestine can also 'calm' pro-inflammatory T helper 17 (T_H17) cells that are generated in extraintestinal sites.

Antibodies specific for CD3 promote immune tolerance via activation-induced cell death of T cells; however, these antibodies also induce a 'cytokine storm' and transient intestinal inflammation. Interleukin-6 (IL-6) and transforming growth factor-β (TGFβ), which are important for T_H17 cell differentiation, are among the cytokines upregulated during CD3-specific antibody treatment, so the authors proposed that this treatment might promote T_H17 cell development. Accordingly, mice treated with CD3-specific antibodies showed increased serum levels of IL-17A, despite the disappearance of peripheral T cells. Strikingly, the source of this IL-17A appeared to be T_H17 cells that accumulated in the small intestine, particularly in the duodenum. IL-17-producing T cells also accumulated in the small intestine of T cell receptor (TCR)-transgenic mice that were injected systemically with their specific peptide. These data suggest that accumulation of T_H17 cells in the small intestine might occur in response to strong TCR stimulation.

T_H17 cells are known to express CC-chemokine receptor 6 (CCR6), so the authors next explored the expression of the CCR6 ligand, CC-chemokine ligand 20 (CCL20), in the intestine. They found that CCL20 was expressed constitutively in the small intestine and strongly upregulated following CD3-specific antibody treatment. CCL20 expression was highest in the duodenum and gradually decreased along the length of the intestinal tract, mirroring the pattern of T_H17 cell accumulation that was observed following treatment with CD3-specific antibodies. Notably, T_H17 cells were not detected in the small intestine of CCR6-deficient mice treated with CD3-specific antibodies. However, compared with wild-type control mice, increased numbers of T_H17 cells were found in the spleen and lymph nodes of the CCR6-deficient mice. This suggests that the CCR6–CCL20 axis is important for the accumulation of T_H17 cells in the small intestine, rather than for their development.

So what is the function of the T_H17 cells that accumulate in the small intestine? Although intestinal pathology coincided with the recruitment of T_H17 cells to the intestine, the disease was transient. Some T_H17 cells were found in the intestinal lumen and may have been passively washed out during the inflammatory response. Interestingly, the T_H17 cells that remained in the duodenum were actively proliferating, rather than apoptotic, and when intestinal IL-17A$^+$FOXP3$^-$ T cells were isolated from mice treated with CD3-specific antibodies, remarkably these cells showed immunosuppressive functions both *in vitro* and *in vivo*. The intestinal IL-17-producing cells expressed T_H17 cell-associated genes (such as *Rorc*, *Rora* and *Il17a*) but, compared with splenic T_H17 cells from mice with experimental autoimmune encephalomyelitis (EAE), they showed reduced expression of other pro-inflammatory cytokines and increased expression of *Il10*. Further experiments showed that their suppressive activity was partly dependent on IL-10, cytotoxic T lymphocyte antigen 4 (CTLA4) and TGFβ. Notably, T_H17 cells isolated from the spleen of CCR6-deficient mice did not show suppressive activity and produced high levels of tumour necrosis factor, indicating that migration to the small intestine was necessary for the acquisition of regulatory function.

The authors found that pro-inflammatory T_H17 cells generated during EAE could also acquire regulatory functions in the small intestine following treatment with CD3-specific antibodies. In addition, T_H17 cells with suppressive activity could be isolated from the small intestine of mice with bacterial sepsis. Finally, experiments with humanized mice showed that human T_H17 cells also accumulate in the intestine during CD3-specific antibody treatment. The authors propose that the redirection of pro-inflammatory T_H17 cells to the small intestine may be a physiological mechanism to prevent excessive immunopathology.

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ORIGINAL RESEARCH PAPER Esplugues, E. *et al.* Control of T_H17 cells occurs in the small intestine. *Nature* 17 Jul 2011 (doi:10.1038/nature10228)