CCL17 promotes intestinal inflammation in mice and counteracts regulatory T cell-mediated protection from colitis.

Abstract:
Priming of T cells by dendritic cells (DCs) in the intestinal mucosa and associated lymphoid tissues helps maintain mucosal tolerance but also contributes to the development of chronic intestinal inflammation. Chemokines regulate the intestinal immune response and can contribute to pathogenesis of inflammatory bowel diseases. We investigated the role of the chemokine CCL17, which is expressed by conventional DCs in the intestine and is up-regulated during colitis. Colitis was induced by administration of dextran sodium sulfate (DSS) to mice or transfer of T cells to lymphopenic mice. Colitis activity was monitored by body weight assessment, histologic scoring, and cytokine profile analysis. The direct effects of CCL17 on DCs and the indirect effects on differentiation of T helper (Th) cells were determined in vitro and ex vivo. Mice that lacked CCL17 (Ccl17(E/E) mice) were protected from induction of severe colitis by DSS or T-cell transfer. Colonic mucosa and mesenteric lymph nodes from Ccl17-deficient mice produced lower levels of proinflammatory cytokines. The population of Foxp3(+) regulatory T cells (Tregs) was expanded in Ccl17(E/E) mice and required for long-term protection from colitis. CCR4 expression by transferred T cells was not required for induction of colitis, but CCR4 expression by the recipients was required. CCL17
promoted Toll-like receptor-induced secretion of interleukin-12 and interleukin-23 by DCs in an autocrine manner, promoted differentiation of Th1 and Th17 cells, and reduced induction of Foxp3(+) Treg cells. The chemokine CCL17 is required for induction of intestinal inflammation in mice. CCL17 has an autocrine effect on DCs that promotes production of inflammatory cytokines and activation of Th1 and Th17 cells and reduces expansion of Treg cells.