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Combined blockade of IL-17A and IL-17F may prevent the development of experimental colitis

Leon P McLean[1,2], **Raymond K Cross**[1], and **Terez Shea-Donohue**[*,1,2,3]

[1]University of Maryland School of Medicine, Department of Medicine, Division of Gastroenterology & Hepatology, MD, USA

[2]University of Maryland School of Medicine, Mucosal Biology Research Center, 20 Penn Street, HSF II, Room s349, Baltimore, MD 21201, USA

[3]University of Maryland School of Medicine, Department of Radiation Oncology, MD, USA

Abstract

The contribution of Th17 cells to the development of colitis is well described. The effector cytokines IL-17A and IL-17F have been proposed as potential therapeutic targets for the treatment of patients with inflammatory bowel disease. In a proof-of-concept study for the treatment of patients with Crohn's disease, secukinumab, a monoclonal antibody directed against IL-17A, was ineffective and associated with more adverse events than placebo. Wedebye Schmidt *et al.* propose that blockade of both IL-17A and IL-17F, rather than either cytokine alone, attenuates the development of colitis in a T-cell transfer model of experimental colitis. These findings suggest that combined blockade of IL-17A and IL-17F may be an effective strategy for the treatment of patients with inflammatory bowel disease.

Keywords

Crohn's disease; IL-17A; IL-17F; secukinumab; Th17; ulcerative colitis

T cells play an important role in the development of chronic pathogenic inflammatory states. Th1, Th2 and Th17 cells have been implicated in the development of autoimmunity. Initially, Crohn's disease (CD) was considered a manifestation of Th1 immunity, whereas ulcerative colitis (UC) was felt to be Th2-driven. More recently, Th17 cells, a distinct Th lineage that provides protection against extracellular microorganisms, have been found to contribute to the development of inflammatory bowel disease (IBD) [1-4].

Activated T cells differentiate into Th17 cells in the presence of IL-23, TGF-β and IL-6. Th17 cells release cytokines implicated in autoimmunity, including IL-17A, IL-17F, IL-22, and TNF-α. IL-17A binds to the IL-17 receptor complex, which consists of IL-17RA and IL-17RC, and down-stream signaling occurs via the NF-κB pathway. Th17 cells have been targeted successfully in the treatment of psoriasis, rheumatoid arthritis and ankylosing spondylitis [5]. Secukinumab, an anti-IL-17A monoclonal antibody, was not effective for the treatment of patients with moderate-to-severe CD and was associated with more adverse events than placebo [6].

[*]Author for correspondence: tdonohue@mbrc.umaryland.edu.

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Although it is clear that Th17 cells are associated with the development of CD, whether various effector cytokines are protective or deleterious has not been definitively established. The role of IL-17A, in particular, has been debated. Both proinflammatory [1,7,8,9] and anti-inflammatory properties [10,11] of IL-17A have been reported. IL-17F has been shown to play a pathogenic role in a murine model of intestinal inflammation. Genetic deletion of IL-17F was associated with reduced susceptibility to dextran sulfate sodium colitis [11], supporting a proinflammatory role for this cytokine. The proinflammatory effects of IL-17F, and possible proinflammatory effects of IL-17A, suggest that the transcription factor RORγt, which is required for the development of Th17 cells, or the cytokines IL-17A or IL-17F, could be targeted for the treatment of IBD [7].

Rather than focusing on the blockade of IL-17A or IL-17F alone, Wedebye Schmidt *et al*. examined the effects of blockade of both IL-17A and IL-17F. They report that combined blockade of IL-17A and IL-17F prevents colitis development in a T-cell transfer model of colitis. Their data suggests that this strategy could potentially be used to treat patients with IBD.

Summary of methods & results

In the current paper, Wedebye Schmidt *et al.* examine the Th17 cytokines IL-17A and IL-17F and their effects on the induction and maintenance of experimental colitis [12]. The authors transferred $CD4^+CD25^-$ T cells to severe combined immune deficiency mice to induce colitis and used flow cytometry to examine Th-cell populations from lamina propria (LP), spleen and mesenteric lymph nodes (MLNs) in mice with varying degrees of colitis. They measured IFN-γ^+ (Th1) and IL-$17A^+$ (Th17) single-positive (SP) cells, as well as IFN-γ^+IL-$17A^+$ (Th1/17) double-positive (DP) cells as a proportion of total $CD4^+$ cells. Mice with more severe colitis scores had nearly twice as many IL-$17A^+$ SP cells in MLNs compared with mice with no evidence of disease. The proportion of IL-$17A^+$ SP cells present in the spleen also increased with worsening colitis, but less dramatically. IFN-γ^+ SP cells present in MLNs and the spleen remained relatively unchanged in mice with and without colitis; however, IFN-γ^+IL-$17A^+$ DP cells present in MLNs and the spleen decreased with worsening colitis.

The proportion of IL-$17A^+$ SP cells present in the LP, spleen or MLNs increased at day 40 when compared with day 10, although these cells accounted for only approximately 10% of the $CD4^+$ cells present. During this period, the proportion of IFN-γ^+ SP cells, which accounted for between 20 and 40% of the $CD4^+$ cells present, did not differ significantly in the LP, spleen or MLNs. The proportion of IFN-γ^+IL-$17A^+$ DP cells present in the spleen and MLNs decreased significantly, dropping from approximately 10 to less than 5%. There was no significant change in the proportion of IFN-γ^+IL-$17A^+$ DP cells present in cells obtained from the LP. As expected, when compared with wild-type controls, there was an increased proportion of IL-$17A^+$ and IFN-γ^+ SP $CD4^+$ cells in the LP from colitic mice.

IL-17F was expressed by both IL-$17A^+$ SP cells and IL-$17A^+$IFN-γ^+ DP cells, but not by IFN-γ^+ SP cells. Sustained expression of IL-17F in IL-$17A^+$ cells was noted in MLNs from mice with colitis, suggesting that IL-$17A^+$ cells and IL-17F contribute to the development of experimental colitis.

Immunohistochemistry was performed in order to confirm IL-17A and IL-17F expression in colonic tissue of mice with colitis. Few IL-$17A^+$ SP cells were present in mice without colitis. IL-17A staining was increased in mice with colitis and was concentrated in the LP, as well as areas with inflammatory infiltrates. IL-17F was distributed in a similar pattern to IL-17A.

In order to determine the role of IL-17A and IL-17F in colitis development, T-cell transplanted severe combined immune deficiency mice were treated with antibodies directed against IL-17A, IL-17F or both IL-17A and IL-17F. Treatment with an IL-17A antibody alone or antibodies against both IL-17A and IL-17F at the time of T-cell transfer was associated with a significant decrease in rectum weight when compared with mice treated with a control antibody. Treatment with an antibody directed against either IL-17A or IL-17F alone did not improve colitis scores when compared with mice treated with a control antibody. Treatment with antibodies against both IL-17A and IL-17F significantly improved colitis scores when compared with mice treated with a control antibody.

In order to more closely mimic patients with pre-existing IBD, antibodies were administered 18 days after colitis induction. Simultaneous administration of antibodies against IL-17A and IL-17F was associated with a significant decrease in rectum weight when compared with treatment with a control antibody. A decrease in the colitis score in mice treated simultaneously with antibodies against IL-17A and IL-17F was also reported when compared with mice treated with a control antibody; however, this difference was not statistically significant ($p = 0.0979$). A significant decrease in colitis score was observed in mice treated with antibodies against both IL-17A and IL-17F when compared with colitic mice that did not receive a control antibody. Treatment with antibodies against either IL-17A or IL-17F alone was not associated with a significant decrease in colitis score when compared with mice treated with a control antibody.

Discussion & significance

The findings of Wedebye-Schmidt *et al.* suggest that dual blockade of IL-17A and IL-17F is more effective at preventing the development of experimental colitis than blockade of either cytokine alone [12]. The degree of colitis observed in animals treated with dual blockade at the time of T-cell transfer was significantly less than those treated with a control antibody. In mice with pre-existing colitis, blockade of both IL-17A and IL-17F resulted in a significant decrease in colitis when compared with untreated colitic mice; however, when compared with animals treated with a control antibody, the difference in colitis did not reach statistical significance. It should be noted that use of the Student's t-test to examine differences between means within the six treatment groups may not be the most appropriate statistical test for analyzing this type of data. Performing analysis of variance followed by *post-hoc* analysis examining groups of interest would be more appropriate.

Previous attempts to modulate Th17 activity have had mixed results. As noted above, secukinumab was not successful for the treatment of CD and was associated with more adverse events than placebo. Ustekinumab, an antibody directed against the common p40 subunit of IL-12 and IL-23, is more effective than placebo at inducing and maintaining remission in patients with moderate-to-severe CD previously exposed to anti-TNF therapy [13]. IL-12 and IL-23 promote the induction of Th1 and Th17 immunity, respectively; therefore, the therapeutic benefit of ustekinumab may be due to modulation of Th1 immunity in addition to Th17 immunity, rather than Th17 modulation alone. At present, there is no agent available that targets Th17 immunity alone for the treatment of patients with IBD.

Future perspective

Additional therapies for patients with moderate-to-severe CD or UC are needed. Although TNF-α inhibitors work well in a number of patients with CD or UC, the proportion of patients who do not respond to induction therapy or who lose response over time is substantial. The data presented by Wedebye Smith *et al.* is an important step towards a

better understanding of the role of Th17 effector cytokines and their impact on the development and maintenance of colitis. The authors propose that dual blockade of IL-17A and IL-17F is more effective at attenuating colitis development than blockade of either cytokine alone. Whether dual blockade of IL-17A and IL-17F also reduces the severity of pre-existing colitis requires further investigation. It is clear that further study of dual IL-17A/IL-17F blockade is warranted and may represent a novel approach for the treatment of patients with IBD.

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Executive summary

- Increased numbers of Th17 cells are found in inflamed tissue from patients with Crohn's disease and ulcerative colitis.
- IL-17A and IL-17F affect the pathogenesis of Crohn's disease and ulcerative colitis, although their precise role in the development of these disorders requires further characterization.
- Secukinumab, a monoclonal antibody directed against IL-17A, was not effective for the treatment of patients with moderate-to-severe Crohn's disease.
- The paper under evaluation reports prevention of experimental colitis with blockade of both IL-17A and IL-17F and possible attenuation of colitis in mice with pre-existing disease.
- These observations suggest a potential therapeutic role for combined blockade of IL-17A and IL-17F in the treatment of inflammatory bowel disease, rather than blockade of either cytokine alone.