Interleukin-35 mediates mucosal immune responses that protect against T-cell-dependent colitis

Wirtz S, Billmeier U, McHedlidze T, Blumber RS, Neurath MF

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COLIN DE HAAR
Department of Gastroenterology and Hepatology
Erasmus Medical Centre
Rotterdam, The Netherlands

Colin de Haar
is a senior postdoc at the Department of Gastroenterology and Hepatology at the Erasmus Medical Centre in Rotterdam, The Netherlands, with a broad interest in the mucosal immune system, especially with regard to IBD

Introduction

The IL-12 family of cytokines plays an important role in the pathogenesis of IBD. It consists of pro-inflammatory cytokines enhancing inflammation by induction of Th1/ Th17 responses, like IL-12 and IL-23, but also of members with an immunosuppressive function, like IL-27 and IL-35.

Interestingly, the IL-12 family consists of heterodimeric cytokines composed of two subunits, some of which are shared amongst family members. IL-27 is composed of EBI3 (Epstein-Barr virus-induced gene 3) and the IL-27p28 subunit, whereas IL-35 is composed of EBI3 and IL-12p35. In contrast to the well-defined function of IL-12 and IL-23 in IBD, the function of IL-27 and IL-35 is still unclear. In particular, functional studies of IL-35 are hampered by the current limitations in our ability to detect it and the fact that knockout of the EBI3 subunit will also affect IL-27 expression and knock-out of the IL-12p35 unit will also affect IL-12 expression.

Wirtz et al. elegantly circumvented this problem by using mice deficient in both EBI3 (lacking both IL-27 and IL-35) and IL-27p28 (lacking only IL-27) to gain insight into the role of IL-35. The differences between the EBI3 and IL-27p28 deficiency were studied in a variety of established mouse colitis models, using state of the art imaging tools, i.e. murine endoscopy and bioluminescence, to assess colonic inflammation in vivo.

Key findings

Both the EBI3 and the IL-27p28 deficiency trait were crossed into mice lacking STAT3 signalling in their myeloid cells (STAT3 model of spontaneous enterocolitis). Compared to control mice in the STAT3 model, EBI3-deficient mice showed an earlier onset and a more severe phenotype of enterocolitis, whereas IL-27p28-deficient mice did not display any noticeable difference in disease. Similar results were obtained when EBI3 and IL-27p28 deficiency was studied in the T cell-dependent adoptive transfer model of colitis. Although the IL-27p28-deficient mice seemed to have a slightly enhanced transfer colitis, none of the differences reached statistical significance.

The enhanced intestinal inflammation in EBI3-deficient mice using the STAT3 model coincided with an increased mRNA expression of pro-inflammatory mediators. In addition, stimulation of lamina propria mononuclear cells from these mice showed increased production of pro-inflammatory cytokines.

To investigate the therapeutic potential of IL-35, the authors constructed an IL-35 expression vector where the EBI3 gene was fused into the 3' end of the IL-12p35 subunit. Administration of this IL-35 expression vector inhibited dextran sodium sulphate (DSS)-induced colitis in mice in both a preventive and a therapeutic setting.

Overall conclusion

The authors conclude that the EBI3 subunit of the immunosuppressive cytokine IL-35 plays an important role in the regulation of the mucosal immune response. Accordingly, IL-35 may have therapeutic potential in IBD patients.

Critical remarks

In this paper, EBI3- and IL-27p28-deficient mice were used to study the role of IL-35. Although this provided insight into the role of IL-35, it fails to tell us anything about the immunoregulatory role of IL-27.

Since most of the evidence for the regulatory function of IL-35 was based on the STAT3 and transfer colitis models, it was surprising that the authors used DSS-induced colitis to show the therapeutic potential of IL-35. A set of experiments using IL-27 expression vectors to rescue the EBI3-deficient mice in the different colitis model would have been a crucial addition to this paper in order to assess the function of IL-27.