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Flt3 ligand expands CD103+ dendritic cells and FoxP3+ T regulatory cells, and attenuates Crohn's-like murine ileitis

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Introduction

Conventional therapeutics cannot prevent complications in Crohn's disease (CD) and although novel treatment strategies, including TNF-neutralizing antibodies, have greatly increased the therapeutic armamentarium, many patients still have to undergo surgery (1). For this reason, development of new treatments that induce long-term remission is required.

Regulatory T cells (Treg) are key players in maintaining peripheral tolerance, preventing autoimmune diseases and limiting chronic inflammation (2). Therefore, strategies that aim for therapeutic tolerance induction may take advantage of the functions of Treg (3). Treg can be induced by a distinct subset of dendritic cells (DCs), the tolerogenic CD103+ DCs (4). Thus, exploring the role of tolerogenic CD103+ DCs in the pathophysiology of colitis and determining the effect of altering their frequency could lead to novel therapeutic agents for the treatment of CD.

What is this paper about?

This paper sets out to analyze the effect of inflammation on tolerogenic CD103+ DCs and the therapeutic potential of altering their frequency by administration of Flt3-L in chronic ileitis. For this purpose the authors use TNFΔARE mice, a well established mouse model of CD (5;6). Flt3-L is a haemopoietic growth factor that was chosen for its preferential proliferative effect on the tolerogenic CD103+ DCs (7).

First the authors show that there is a deficiency of tolerogenic CD103+ DCs during chronic ileitis. Thereafter it was demonstrated that Flt3-L administration preferentially expands CD103+ tolerogenic DCs subsets in TNFΔARE mice and significantly decreases active, chronic and total inflammatory indices. The absolute number of Treg significantly increased in Flt3-L treated mice in the spleen, the mesenteric lymph nodes and the lamina propria compared with controls; there was also an increase in Treg in the thymus of Flt3-L treated mice. The increase in the thymus is especially interesting, since this could indicate an effect of Flt3-L treatment during inflammation not only in the peripheral tissues, but also on the primary mechanisms involved in T cell maturation and education. The question thereafter remained if there is a direct relation between the Flt3-L treatment and induction of Treg. Treg are characterized by a high expression of the surface marker CD25 (8) and therefore the authors depleted Treg using an anti-CD25 antibody. This antibody treatment abrogated the protective effect of the Flt3-L treatment. Therefore it can be concluded that Flt3-L administration exerts a potent anti-inflammatory effect on chronic ileitis mediated by Treg.

Conclusion

This study demonstrates the therapeutic effect of Flt3-L supplementation in a chronic model of IBD and since the safety of Flt3-L administration has been demonstrated in healthy human subjects (9), Flt3-L could be further explored as a novel biological therapy for CD. Additionally this study demonstrates that the therapeutic effect of Flt3-L administration is mediated by the preferential expansion of tolerogenic CD103+ DCs and Treg cells.

In this study Flt3-L administration started when mice were 20 weeks old. Interesting would be to know if an earlier start of the treatment could prevent the onset of ileitis. Future studies should also be aimed at better understanding the origin and biology of the tolerogenic CD103+ DCs (10) and for the induced Treg it is crucial to determine their induction mechanisms and whether they are functionally stable under various conditions (11). Additionally since there is an effect of Flt3-L treatment on Treg in the thymus, it is of interest to investigate if Flt3-L treatment is able to both induce Treg in the periphery as well as activate naturally occurring Treg centrally in the thymus.

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