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Lessons from type I interferons in ulcerative colitis

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Ulcerative colitis (UC) is a complex polygenic disease that arises in the context of as yet unknown environmental factors.¹ One biological pathway that has arisen as being important to UC, but not Crohn's disease (CD), is that associated with dysregulated CD1d-restricted, natural killer T (NKT) cell responses.^{2–4} CD1d-restricted NKT cells are a specialised subset of T cells that recognise lipid antigens presented by CD1d, a non-polymorphic major histocompatibility complex (MHC) class I-related molecule, on antigen-presenting cells. Upon ligation of their T cell receptor (TCR), NKT cells immediately release a large spectrum of cytokines such as interferon γ (IFN γ), interleukin 4 (IL-4), IL-13 and many others. The lipid ligands responsible for NKT cell activation in UC are however unknown, but probably include both endogenous and exogenous lipids from microbes.⁴

The mechanistic relationship between NKT cells and UC derives mostly from animal models and correlative human studies.² The earliest observations on the ontogeny of these concepts was the recognition that CD1d is expressed on mouse and human intestinal epithelial cells^{5,6} and that CD1d on epithelial cells is functionally able to activate NKT cells.⁷ These studies were later followed by the discovery that NKT cells secreting IL-13 were critical for the induction of experimental colitis resembling human UC.² Subsequent careful studies of colonic lamina propria T cells obtained from patients with UC confirmed a similar CD1d-dependent upregulation of IL-13 secretion. These studies not only draw attention to CD1d-restricted pathways but also raise a number of questions such as the role of lipid antigen recognition and its relationship to environmental factors in the pathogenesis of these disorders and the mechanism(s) by which the genetic risk loci for UC connect to dysregulated CD1d-restricted NKT cell activation, if at all.

The studies described above have also focused attention on IL-13 as a therapeutic target for the treatment of UC. It is therefore of interest that type I IFNs were previously shown to

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profoundly down-regulate IL-13 expression while not affecting IL-4 secretion in peripheral blood mononuclear cells and T cells.⁸⁹ As such, these properties rendered type I IFNs as an interesting potential treatment option for UC. Indeed, subsequent to an initial uncontrolled open-label pilot trial that yielded promising results,¹⁰ several randomised controlled trials of different recombinant type I IFNs were conducted.^{11–14} In the latest and largest of these trials, 194 patients with active UC were randomised to receive either IFN β 1a at 44 μ g or 66 μ g three times weekly, or placebo.¹⁴ After 8 weeks of treatment, 29% in the 44 μ g arm and 23% in the 66 μ g arm were in remission (including an endoscopy score of 0 and 1), which compared with 23% in the placebo group. Although these differences were not particularly dramatic and supportive of a general efficacy of type I IFNs in the vast majority of patients with UC, it appeared that type I IFNs may have a benefit in a subset of such patients.

In their paper published in *Gut* (*see page 449*), Mannon and colleagues have sought to understand the biological reason for this differential responsiveness and, in so doing, have further highlighted the importance of IL-13 in UC pathogenesis.¹⁵ They studied cytokine secretion from lamina propria and peripheral blood mononuclear cells before and after IFN β 1a treatment with the intention to compare responders with non-responders. Response to treatment was stringently evaluated by endoscopy. Mannon and colleagues report that responders exhibited substantially less IL-13 secretion at the end of treatment compared with non-responders, while IL-13 levels in non-responders remained high. Moreover, elevated IL-17 and IL-6 secretion from mononuclear cells prior to IFN β 1a treatment was also indicative of later non-responsiveness.

There are several lessons that can be learnt from these results. First, these data bolster the mechanisms established through earlier preclinical models that support a central role for IL-13 in the pathophysiology of UC which should hopefully prompt future trials of direct IL-13 blockade. Secondly, there would appear to be a subpopulation of patients with active UC who might benefit from IFN β 1a treatment. In this regard, the authors highlight the case of one patient within the trial who achieved remission after 12 weeks of IFN β 1a treatment in association with a dramatic decrease in IL-13 secretion from lamina propria T cells. After 16 weeks of remission, this patient relapsed in association with a surge in IL-13 production by lamina propria T cells. A second 12 week course of IFN β 1a treatment restored remission, and IL-13 secretion fell to undetectable levels. A similar re-induction of remission was observed previously upon retreatment of select patients with UC who had responded to type I IFNs within a clinical trial (H Tilg, personal communication). Thirdly, and finally, this selective responsiveness to novel therapeutics might in fact be a substantially more general phenomenon that goes well beyond recombinant type I IFNs and UC. It can be speculated that there is a good chance that individual compounds which failed in clinical trials (but proved safe in general) might indeed be highly effective in selected patients. The challenge is to define potential responders and, more importantly, the biological mechanisms for these failures. The last few years have revealed an enormous genetic complexity of polygenic diseases in general, including CD and UC of course. Almost 100 genetic loci have been associated with inflammatory bowel disease to date with estimates that this still represents less than one-third of the genetic heritability of these diseases. This highlights the genetic complexity of these disorders which is made even more complex by the lack of

understanding about the environmental factors that drive disease. Given this complexity and the syndromic nature of UC (and CD) is it still reasonable to expect that any given novel therapeutic needs to be effective in the majority of patients entering into a clinical trial?

The study by Mannon *et al* thus serves as an excellent example of how a clinical trial can be organised to yield important pathophysiological insights beyond the immediate goal of simply defining the efficacy of a therapeutic under study. Unfortunately, most clinical trials, from phase 2a to 3, are simply aimed at defining efficacy without the goal of revealing pathophysiological insights which would be useful in ‘personalising’ the therapeutic intervention. However, in the absence of such efforts, such clinical trials are a missed opportunity for yielding mechanistic insights into the pathophysiology of the human disease. In the absence of proper basic science embedded in clinical trials as highlighted by the study by Mannon and colleagues,¹⁵ we are forced to rely nearly entirely on animal models to reveal such insights with all of their associated limitations.

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