Induction of Colonic Regulatory T Cells by Indigenous Clostridium Species

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For some time it has been recognised that alterations in the gut bacteria are associated with Inflammatory Bowel Disease. However, it is unclear which is the chicken and which is the egg – does this "dysbiosis" arise due to genetic differences in affected individuals or because of the inflammatory conditions present in the intestine, or is it causative and a prerequisite for disease to develop, and if so how?

Recent studies in mice have beautifully highlighted how certain bacterial species can have very specific effects upon the intestinal immune system, with the observation that segmented filamentous bacteria (SFB) specifically drive the development of T-helper-17 (Th17) cells within the gut (Ivanov et al Cell 2009). This report created great excitement as Th17 cells have been implicated in the pathogenesis of IBD both through genetic studies and animal models. However, it soon transpired that the human gut is not colonised by this species and thus this observation is of limited relevance in human IBD.

In a paper in Science, Atarashi and colleagues describe a second specific interaction between bacterial species in the gut and changes that they induce in the mucosal immune system. They report that the spore-forming, gram-positive component of the intestinal microbiota, specifically clusters IV and XIVa of the genus Clostridium, are required to promote regulatory T-cell (Treg) accumulation in the murine colon. Tregs are a subgroup of CD4+ T-cells which can suppress immune responses and limit inflammation. They have previously been linked to IBD in both human and animal models, and – in several diseases – have been shown to be increased by therapies such as anti-TNFα monoclonal antibodies.

The findings reported in this paper therefore represent a major advance in our understanding of how bacteria may interact with the gut to modulate subsequent immune responses. Indeed, these authors went on to demonstrate that by supplementing the gut bacteria of mice with more of these species, they could make them resistant to induced colitis. Unlike the SFB story, these findings do have direct implications for human IBD as these species of bacteria do colonise the human gut. Indeed, it is notable that several of the bacterial species that comprise these Clostridium clusters have been shown to be underrepresented in patients with CD (Frank et al. PNAS 2007; Joossens et al. Gut 2011) and that one in particular, Faecalibacterium prausnitzii, which is underrepresented in both UC and CD (particularly in CD patients with higher rates of postoperative recurrence) has been previously reported to have anti-inflammatory properties (Sokol et al. PNAS 2007; Sokol et al. Inflamm Bowel Dis 2009).

One notable absence from the paper by Atarashi and colleagues was an explanation of the molecular mechanism by which the metabolites of these Clostridium clusters were able to generate the environment necessary for Treg induction. The future understanding of this mechanism would provide considerable insight into how gut bacteria can regulate immune responses and could reveal novel therapeutic targets, which might ultimately lead to better targeted therapies for our patients. However, despite this mechanism being absent, this remains a landmark paper in terms of elucidating the specific effects that bacterial species can have on the intestinal immune system and has direct relevance for our understanding of the pathogenesis of IBD.