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Gut microbes: friends or fiends?

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There is now a general consensus that the two major inflammatory bowel diseases (IBDs), Crohn's disease and ulcerative colitis, arise from an abnormal immune response to one or more bacterial components of the very rich community of commensal flora in the large bowel and the more distal parts of the small bowel¹. Theoretically, this abnormal response can have two origins: an increased proinflammatory response to a bacterial component or a decreased regulatory response, which may lead to an excessive effector immune response. In this context, IBD research has recently focused on identifying organisms or components in the gut microflora that facilitate or thwart one of these disease mechanisms.

Previous studies^{2,3} were crucial for showing how a particular gut commensal organism, *Bacteroides fragilis*, which expresses a capsular polysaccharide known as polysaccharide A (PSA), induces an increased immunoregulatory—and protective—response in the colons of normal mice, which is able to lessen colonic inflammation. These studies therefore pointed to a possible way of using this organism, or, more likely, a product of this organism, to treat IBD.

A recent study by Round *et al.*⁴ represents the leading edge of this line of research. The authors showed that monocolonization of germ-free mice with *B. fragilis* induces accumulation of Foxp3⁺ regulatory cells (T_{reg} cells) in the lamina propria in the gut, which produce increased amounts of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β2 (TGF-β2)⁴. This effect was entirely dependent on the expression of PSA, as *B. fragilis* lacking PSA did not have the same inducing effect, and oral administration of PSA in mice resulted in an increased number of T_{reg} cells.

Round *et al.*⁴ also showed that T_{reg} cells from PSA-treated mice compared to those from saline-treated mice show a PSA-specific profile with an enhanced capacity to suppress effector T cells *in vitro* and to express increased levels of IL-10, TGF-β2, granzyme B and CCR6 mRNA. Finally, the authors investigated the possible clinical applicability of these findings, assessing the capacity of PSA to prevent or 'cure' 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in wild-type BALB/c mice—an acute and intense T helper type 1 (T_H1) T cell (interferon-γ (IFN-γ))-mediated colitis—by oral PSA administration either before the onset of colitis or after inflammation had been established⁴. Oral PSA administration indeed ameliorated—but did not completely reverse—colitis under both conditions, probably by increasing the number of T_{reg} cells and their anti-inflammatory cytokines, IL-10 and TGF-β (Fig. 1).

This study of *B. fragilis*⁴ is part of a large group of studies that are attempting to define pro- or anti-inflammatory organisms in IBD. Studies focusing on single organisms have shown that *Faecalibacterium prausnitzii* has a protective function, as a reduced number of these bacteria in the intestine was associated with increased post-operative recurrence of Crohn's disease⁵. In addition, oral administration of *F. prausnitzii* or a supernatant derived from this organism decreased the severity of TNBS-induced colitis and associated production of proinflammatory cytokines⁵. This organism, similarly to *B. fragilis*, can inhibit gut inflammation, although in this case the inhibitory mechanism is far less clear.

Other studies of single organisms, however, have shown that a subset of people with Crohn's disease harbor a potentially proinflammatory 'adherent-invasive' strain of *Escherichia coli* in their small intestine⁶. Although this has been verified by other studies, it remains unclear whether these organisms cause disease or colonize the gut after disease is established⁷.

Studies of organisms in IBD focusing on the bacterial community as a whole comprise the major effort now underway to define the gut microbiome in humans in general and in IBD in particular. Analyses of bacterial 16S rRNA by microarray probes or studies using sequencing of 16S rRNA in clonal libraries derived from bacteria, among other techniques^{8–11}, showed how individuals with IBD present with depletion of some commensal microbes in the phylogenetic divisions Firmicutes and Bacteroidetes, including *F. prausnitzii* and *B. fragilis*, respectively^{5,8,11}. This finding is congruent with the idea that Crohn's disease is due to or aggravated by the loss of bacteria that promote regulatory responses, such as *B. fragilis*; however, the analyses conducted so far have shown that such losses usually involve large groups of organisms rather than specific bacterial strains.

A surprising aspect of the *B. fragilis* studies was that a specific antigen such as PSA has a remarkable ability to induce Foxp3⁺ T_{reg} cells. Induction of T_{reg} cells was absent in Toll-like receptor 2 (TLR2)-deficient mice, implying that induction is due to an innate immune response mediated by TLR2. This finding suggests that PSA has a dual function—it stimulates T cells via conventional presentation to the T cell receptor, which then upregulates T cell expression of TLR2 and allows direct PSA stimulation of naive T cells that results in T_{reg} cell differentiation.

Regardless of the mechanism, it is apparent that this polysaccharide could be the basis of a viable IBD therapy. Yet at least two questions must be answered to prove the feasibility of this approach. First, it was shown that PSA not only induces regulatory T cells that protect from IBD but also induces CD4⁺ T cells to undergo differentiation into IFN- γ -producing cells—T_H1 differentiation—which are potentially proinflammatory T cells¹². As yet, the conditions that elicit a particular arm of this dichotomous response have not been defined, and it is therefore possible that, in some circumstances, PSA administration will induce a proinflammatory T_H1 response, which can exacerbate a preexisting inflammatory disease.

The second question relates to the general idea that induction of T_{reg} cells can treat inflammatory disease. There is now considerable evidence that proinflammatory factors, such as IL-23, which is secreted by APCs in support of T_H17 responses, have specific downregulatory effects on T_{reg} cell development¹³. In addition, T_{reg} cells are considered 'plastic', as they can convert into proinflammatory IL-17-secreting cells when they are exposed to IL-6, a cytokine secreted by inflammatory macrophages¹⁴.

These facts pose the possibility that robust inflammation, such as that present in IBD, can 'trump' an anti-inflammatory T_{reg} cell response induced by PSA, unless the protective T_{reg} cells completely quell an incipient inflammation and prevent countervailing secretion of

inhibitory cytokines such as IL-6, a condition not met in the TNBS-induced colitis study discussed above.

It might therefore be prudent to initially test the efficacy of PSA in people who are close to complete remission from disease as a result of previous treatment by surgery or administration of antibodies against inflammatory cytokines, such as antibody to TNF- α or antibody to IL-12 p40, to determine whether treatment with PSA prevents recurrent disease. This approach would obviate problems derived from the presence of cytokines that facilitate PSA induction of T_H1 cells or the presence of cytokines that inhibit T_{reg} cell expansion or activity.

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Figure 1.

Regulation of colitis by PSA through the induction of T_{reg} cells. PSA produced by the commensal organism *B. fragilis* in the gut lumen is taken up by intestinal dendritic cells. These immune cells then present PSA to naive CD4⁺ T cells, which recognize this antigen and undergo T_{reg} cell differentiation under the influence of TGF-β and retinoic acid secreted by the dendritic cell. This may occur in either the lamina propria or the draining mesenteric lymph nodes. During T_{reg} cell induction, PSA is presented to the T cell via a conventional major histocompatibility complex–antigen–T cell interaction; however, PSA could also influence induction through the activation of TLR2 on the surface of either the presenting dendritic cell or the nascent T_{reg} cell. The induced T_{reg} cells then migrate to the inflamed gut, where they downregulate IFN-γ- or IL-17-secreting proinflammatory T cells (which mediate TNBS-induced colitis) by releasing the antiinflammatory cytokines TGF-β, IL-10 or both.