Inflammatory bowel disease results from a dysregulated immunologic response to commensal microbial flora residing in the intestinal lumen. Although this response is probably due at least in part to a genetic predisposition, patients with inflammatory bowel disease have also been reported to house an abnormal intestinal microbiota. Whether this altered flora is the cause or result of the associated chronic inflammation remains unclear. Also unclear is the extent to which inflammatory bowel disease may be transmissible.

A recent study by Garrett et al. sheds new light on this issue and on whether specific microbes contribute to the development of this disease. The authors have identified a new role for the transcription factor T-bet, known to regulate adaptive and innate proinflammatory immune responses, in controlling the host–commensal interface. They engineered mice that were deficient in both T-bet and the adaptive immune response since they lacked $\text{Rag2}$, which encodes a protein that processes antibodies. Severe colitis, which resembled human ulcerative colitis, developed in these mice (called TRUC mice).

Garrett et al. observed an increase in colonic levels of tumor necrosis factor $\alpha$ (TNF-$\alpha$) when the mice were 2 weeks old. The TNF-$\alpha$ level was associated with enhanced intestinal permeability and the extent of colonocyte apoptosis, which preceded the onset of colitis. It turned out that colonic dendritic cells, which sample the intestinal microbial flora, were the source of TNF-$\alpha$ owing to their loss of negative TNF-$\alpha$ transcriptional regulation by T-bet. Treatment of the mice with TNF-$\alpha$ antibodies cured the colitis, and colitis did not develop in mice that were triply deficient in T-bet, Rag-2, and TNF receptor 1, which showed that TNF-$\alpha$ is the key driver of disease in TRUC mice. Reconstitution of T regulatory cells in the TRUC mice controlled the colitis; microscopic imaging suggests that these cells interact with and thus down-regulate the proinflammatory program of the T-bet–deficient dendritic cells.

A role for microbes in inflammatory bowel disease is supported by the fact that mouse models develop colitis only in the presence of intestinal bacteria, and several human studies have shown a response of patients with inflammatory bowel disease to antibiotic therapy. However, the study by Garrett et al. is particularly exciting, since it includes a description of the development of a colitogenic gut flora. Colitis in TRUC mice abated after treatment with metronidazole, suggesting a role for anaerobes. Colitis was transmitted to progeny of untreated mothers but not to progeny of treated mothers; the disease was transmitted even to T-bet–sufficient $\text{Rag2}^{+/-}$ or wild-type progeny cross-fostered from birth by TRUC mothers, as well as to adult T-bet–sufficient mice that were housed with adult TRUC mice. However, TNF-$\alpha$ levels were not elevated in T-bet–sufficient animals with colitis, which suggests that the microbiota from TRUC mice induce colitis in T-bet–sufficient hosts through a mechanism independent of signaling induced by TNF-$\alpha$.

The data described by Garrett et al. support a model for the development of inflammatory bowel disease in which the intestinal microbiota activate immune cells, leading to dysregulated cytokine production and ensuing intestinal inflammation. However, the immunologic milieu in the TRUC model is novel in engendering a colitogenic flora. Although the mechanism and the identity of the culprit organisms remain obscure, the observation indicates that increased concentrations of cytokines may affect other luminal processes — that is, increased cytokine production may modulate the composition of the commensal flora or alter gene expression in specific bacterial subgroups that are then responsible for the continuation and even transmission of colitis. For example, $\text{Pseudomonas aeruginosa}$ binds
interferon γ through an outer membrane protein, porin OprF, leading to activation of the quorum-sensing machinery that regulates the expression of virulence genes by detecting bacterial density and phase of growth. This, in turn, leads to downstream expression of virulence genes, including an adhesin.

The study by Garrett et al. raises the interesting possibility that the appropriate environment leads to a colitogenic gut flora whose behavior is then modulated by T regulatory cells. In the early phase of the TRUC mouse model of inflammatory bowel disease, colonic dendritic cells that are deficient in T-bet, a negative regulator of the transcription of tumor necrosis factor α (TNF-α), have an exaggerated response to luminal flora that is exacerbated by the absence of T regulatory cells. Resulting high levels of TNF-α increase both intestinal permeability and colonocyte apoptosis. Late stages of the TRUC model are characterized by epithelial discontinuities, which probably allow TNF-α into the intestinal lumen.

The diagram illustrates the clinical implications of basic research, showing the effects of T-bet deficiency and TNF-α on intestinal permeability and colonocyte apoptosis, and the potential transmission of bacteria.

Figure 1. A TRUCload of Trouble for the Colon.
In the normal intestine, an intact epithelium provides a barrier between the contents of the lumen, which contains a complex microbiota, and the underlying immune system, which comprises various inflammatory cells. Dendritic cells continually sample the luminal contents, and response to this sampling is modulated by T regulatory cells. In the early phase of the TRUC mouse model of inflammatory bowel disease, colonic dendritic cells that are deficient in T-bet, a negative regulator of the transcription of tumor necrosis factor α (TNF-α), have an exaggerated response to luminal flora that is exacerbated by the absence of T regulatory cells. Resulting high levels of TNF-α increase both intestinal permeability and colonocyte apoptosis. Late stages of the TRUC model are characterized by epithelial discontinuities, which probably allow TNF-α into the intestinal lumen.
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