Inflammatory bowel disease (IBD) remains an idiopathic and incurable condition despite considerable advances in our understanding of its pathogenesis. Known contributors include a genetic predisposition, dysregulation of the mucosal immune system, and reduced epithelial barrier function, confounded by a range of other environmental and epigenetic factors. Indeed, an infective causative agent has yet to be definitively eliminated. Importantly, an imbalance (dysbiosis) between commensal organisms (comprising both bacterial and fungal elements) and pathogens is currently being pursued as a critical factor in IBD pathogenesis and, possibly, its etiology (1). The composition of the enteric microflora and the dynamic state of its microbial ecology are increasingly being associated with an expanding number of seemingly disparate disorders, ranging from the spectrum of infective enteritides to more covert conditions such as chemotherapy-induced mucositis, nonalcoholic steatohepatitis, and even obesity (2). It is perhaps no coincidence that these disorders are characterized variably by degrees of inflammation.

Restoring a healthy bowel microbiota through external dietary intervention is perceived as a logical strategy. Gopalakrishnan et al. (3), in the current issue, explore the potential utility of the milk-derived prebiotic galacto-oligosaccharide (GOS) in a mouse model of the ulcerative colitis variant of IBD. Prebiotics are broadly defined as nondigestible dietary compounds, usually oligosaccharides, capable of restoring bowel homeostasis through selective fermentation by certain commensal organisms. Unlike single probiotics (health-promoting bacteria; usually lactobacilli and bifidobacteria), prebiotics have the potential to induce major shifts in bacterial communities and hence the overall composition of the intestinal microflora. Moreover, certain prebiotics, including GOS, have the potential to directly affect the mucosal immune system, and it is in this context that Gopalakrishnan et al. (3) investigated the associations among colitic disease severity, NK cells, and intestinal cytokine (IL-15) production.

Clinical improvement of ulcerative colitis in a randomized control study was recently reported following ingestion of GOS for 1 y, although the GOS probiotic was in symbiotic combination with a bifidobacterium probiotic (4). However, it would be fair to say that probiotics, in a general sense, have been somewhat overwhelming in their capacity to combat clinical features of inflammatory disorders such as IBD. Unfortunately, this viewpoint may not be a reflection of probiotic ineffectiveness, but rather a mismatch between the nature of the probiotic and the pathogenetic characteristics underscoring the model system in which it has been investigated. Indeed, it is likely that many of the inconsistencies in outcomes from dietary probiotic studies could be attributed to inappropriate model selection and associated endpoint analyses. For example, the probiotic, fructo-oligosaccharide (FOS), has been reported to improve features of colitis in transgenic HLA-B27 rats (5) but to exacerbate colitis in rats with colitis induced by dextran sulfate sodium (6). The mouse model of colitis employed by Gopalakrishnan et al. (3) is induced in Smad3-deficient mice exposed to the pathogen Helicobacter hepaticus. The colitis that manifests in these mice is in part the result of impaired TGF-β signaling. Although this model is not used widely, it is appropriate for studies focused on innate and adaptive immune cells such as NK cells and certain T-cell subsets. However, it would be interesting to determine if the enhanced NK cell activity observed by Gopalakrishnan et al. (3) following GOS administration was unique to this model or more broadly applicable to other immunomodulatory IBD models induced by chemical haptens (e.g., tri-nitro benzene sulfonic acid, di-nitro benzene sulfonic acid), genetic modification (e.g., IL-2 or IL-10 knockout mice), or spontaneous means (e.g., SAMP1/YitFc mice). Indeed, Gopalakrishnan et al. (3) acknowledge that the mechanism by which NK cells downregulate immune responses is likely to be context and model specific. Nevertheless, the opposing effect of enhanced NK cells and decreased colitis severity is an important finding that warrants further investigation in other models of colitis not necessarily restricted to immunomodulatory models. Although it is clearly impractical to employ multiple animal models, the use of somewhat esoteric immunoregulatory colitis models, such as that employed by Gopalakrishnan et al. (3), can sometimes lead to surprise findings. For example, Woodworth et al. (7) in a 2010 study of dietary fish oil utilizing the Smad3/H. hepaticus model actually reported an exacerbation of colitis and the formation of adenocarcinomas that was “contrary to expectations” despite achieving anticipated alterations in T-cell subpopulations.

The importance of perturbations in the enteric microflora and the subsequent impact on the development of inflammation has only recently been recognized, highlighted by the critical role of inflammasomes, a group of protein complexes assembled around several proteins, including NLRP3, NLRC4, AIM2, and NLRP6 (8). Inflammasome-mediated processes are important during microbial infections, further regulating metabolic processes and mucosal immune responses. Recognition of a diverse range of microbial, stress, and damage signals by inflammasomes results in direct activation of caspase-1, which subsequently induces secretion of proinflammatory cytokines and a form of cell death known as pyroptosis (8). Dysregulation of inflammasomes may result in impaired host defense against microbial pathogens and contribute...
to IBD pathogenesis. Studies in NLRP6 inflammasome-deficient mice have revealed that the NLRP6 inflammasome regulates colonic microbial ecology and therefore risk for colitis (9). Moreover, dextran sulfate sodium-induced colitis in mice has been found to be mediated by the NLRP3 inflammasome (10).

Inflammasome-mediated effects are not restricted to gut inflammation, as an inflammasome modulated dysbiosis has recently been associated with nonalcoholic-induced liver inflammation (11) and the subsequent development of obesity. Therein lies the intriguing possibility that microbial homeostasis in the bowel could be restored by specific prebiotics or probiotics targeted at specific elements of the inflammasome. Gopalakrishnan et al. (3) conclude that GOS reduces the severity of colitis by “priming the innate immune system.” This suggests further potential for GOS to modulate colonic inflammation in IBD, potentially via effects on inflammasomes. If successful, such a strategy could benefit a broad range of inflammatory disorders, not necessarily restricted to IBD.

While we still await studies of probiotic and prebiotic effects on inflammasomes, inflammasomics could soon add to the growing repertoire of “-omics-based” approaches aimed at better understanding the immunoregulatory component of IBD etiology and pathogenesis.

Acknowledgments

G.S.H. wrote the paper and had sole responsibility for the final content.

Literature Cited