Prospects for Research in Inflammatory Bowel Disease

Richard S. Blumberg, MD
Warren Strober, MD

Inflammatory bowel disease is a chronic inflammatory condition of the gastrointestinal tract that manifests as ulcerative colitis and Crohn disease. Both these clinical entities result from interrelated genetic and environmental factors that may be channeled through an abnormality in mucosal immune function, possibly due to dysregulated or excessive T helper cell (Th)1 (Crohn disease) or Th2 (ulcerative colitis) responses. This article reviews current knowledge of the role of immune factors in inflammatory bowel disease and the potential therapeutic strategies that target the pathways of Th1- or Th2-induced inflammation.

Inflammatory bowel disease is a chronic relapsing and remitting inflammatory condition of the gastrointestinal tract that is manifest as 1 of 2 usually distinct but sometimes overlapping clinical entities, ulcerative colitis (UC) and Crohn disease (CD). Ulcerative colitis affects the colon and is a superficial ulcerative disease, whereas CD is a transmural granulomatous disorder that affects any part of the gastrointestinal tract and has a predilection for the terminal ileum and colon. Both forms of IBD are associated with prominent extra-intestinal manifestations and an increased incidence of gastrointestinal cancer; in addition, both begin relatively early in life and persist for long periods, leading to decreased quality of life indices and a greater than 2-fold increase in mortality rate.

By and large, IBD is a disease of “urbanized” areas such as the United States and Europe, where it occurs at an incidence of 6 to 12 and 5 to 7 per 100,000 population for UC and CD, respectively. This translates to 45,000 new cases per year and 1 million affected individuals in the United States alone and costs the US health care system approximately $1.8 billion per year (1990 estimate).

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Both UC and CD result from interrelated genetic and environmental factors that, in all likelihood, are channeled through an abnormality in mucosal immune function. Genetic factors were initially apparent from the observation that incidence of both UC and CD is increased in families of patients with IBD, particularly in first-degree relatives. Subsequent studies showed that monozygotic twins have a high concurrence rate (approximately 60%) that far exceeds that of dizygotic twins. These genetic studies have been augmented by genome-wide scans of humans with IBD that identified disease loci on chromosomes 1, 3, 6, and 7. These genetic findings are consistent with the notion that IBD is a polygenic disease and explains why familial inheritance patterns are not suggestive of a single causative gene. Environmental factors also play a role, as suggested by association of IBD with urbanization. Although repeated attempts to prove that IBD is due to a mucosal infection have consistently proven negative, the current level of understanding of the pathogenesis of IBD does not completely rule out an infectious etiology or component.

The concept that the proximal cause of IBD is immunologic in nature arose from the observation that IBD is characterized by massive cellular infiltrates and is associated with abnormalities of the immune system that include inappropriate production of antibodies and T-cell dysfunctions. This concept has been clarified by studies of patient lamina propria (LP) cells that show that in CD, cells overproduce cytokines indicative of a typical helper T-cell 1 (Th1) response, namely increased production of interleukin (IL) 12 by LP macrophages and increased production of interferon (IFN)-γ by LP T cells. In addition, LP T cells from patients with UC manifest a cytokine profile compatible with a Th2 response; thus, while the cells do not overproduce the major Th2 cytokine IL-4, they do produce increased amounts of another Th2 cytokine, IL-5. This cytokine production pattern accords with an association of UC (but not CD) with autoantibodies that in general require Th2 responses.

These data provide circumstantial evidence that the 2 major forms of IBD

Author Affiliations: Gastroenterology Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass (Dr Blumberg); Gastroenterology Section, National Institutes of Health, Bethesda, Md (Dr Strober).

Corresponding Author: Richard S. Blumberg, MD, Gastroenterology Division, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115 (e-mail: rblumberg@rics.bwh.harvard.edu).

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are due to dysregulated or excessive T\(_{H_1}\) (CD) or T\(_{H_2}\) (UC) responses (FIGURES 1-3). As to what factors induce these abnormal responses, there is considerable evidence that IBD patients have inappropriate T-cell responses to antigenic components of their own intestinal microflora, either because of dysfunction in the primary or secondary mechanisms that normally drive and regulate such responses or because of some dysfunction in the intestinal epithelial cell barrier that leads to inappropriate penetration of microbial antigens.\(^{10-13}\) In effect, patients with IBD have a disturbance in “oral tolerance,” the normal mucosal immune mechanism that ensures the down-regulation of responses to harmless constituents in the microflora or the food stream, while allowing robust effector cell responses to mucosal pathogens.

A major advance in the study of IBD that provides important evidence that immune factors are in fact the cause of IBD rather than just an accompaniment of IBD was the discovery of mouse models of mucosal inflammation that resemble IBD.\(^{14}\) A variety of genetic abnormalities can lead to mucosal inflammation. Nevertheless, in all of the models, the inflammation is either associated with a T\(_{H_1}\) response and resembles CD\(^{15-17}\) or a T\(_{H_2}\) response and resembles UC.\(^{18,19}\) Thus, multiple defects appear to be funneled into 1 of the 2 “final common pathways” of inflammation associated with the human disease. By analogy, the underlying defects in CD and UC are probably due to multiple underlying defects that are ultimately expressed as T\(_{H_1}\)- or T\(_{H_2}\)-induced inflammations.

This conclusion has 2 important implications. First, it indicates that it is not absolutely necessary to address the underlying genetic abnormalities present in IBD to treat the disease; only the final common pathways must be addressed. Second, since a great deal has already been learned about T\(_{H_1}\) and T\(_{H_2}\) responses, multiple ways to correct an abnormality of these responses can be envisioned. For example, because IL-12 drives T\(_{H_1}\) responses, several animal models of IBD have been treated with anti-IL-12, and, in each case, the disease has been abrogated. Similarly, because counterregulatory cytokines (such as transforming growth factor [TGF] \(\beta\) and IL-10) can down-regulate mucosal responses in relation to oral tolerance, disease in the animal models has been treated successfully with intranasally administered DNA-encoding TGF-\(\beta\).\(^{20,21}\)

Studies of models of intestinal inflammation that resemble human IBD also show that normal bacterial flora plays an essential role in experimental inflammation. This is seen first in that no inflammation occurs in any of the models when the rodents are in a germ-free environment and that treatment of rodents with some models of inflammation with antibiotics reduces intestinal inflammation.\(^{22}\) In addition, manipulation of bacterial flora can exacerbate or

![Figure 1. Pathogenesis of Inflammatory Bowel Disease: Antigen Recognition and Immunoregulation](Image 56x188 to 378x548)
ameliorate disease. These observations provide strong support for the theory that abnormal responses to antigens in the normal bacterial flora, ie, breaks in oral tolerance, are the driving force for the abnormal immunologic response and buttress the idea that the normal flora contains antigens that induce or initiate the immune responses that cause human IBD.

Approaches other than targeting the Th1/Th2 final common pathway or the bacterial flora involve inhibition of the traffic of lymphoid cells to mucosal sites and provision of cytokines to improve intestinal epithelial barrier function (and thus decrease exposure to inducing bacterial antigens). These additional approaches suggest that human IBD can be treated by combined therapy directed at different aspects of the disease process to create treatment synergy.

Insights gleaned from studies of models of inflammation lead to or provide a rationale for bold new therapies for human IBD. The translation of this new knowledge into practical therapies and the definition of the algorithms for their use is the immediate challenge to clinical investigators of IBD. One immunologically related approach already used in the treatment of CD is the administration of anti–tumor necrosis factor (TNF) antibody or soluble TNF receptor, both agents that block the action of TNF-α. The use of these agents conforms to the paradigm set up above that holds that blockade of the Th1 pathway can be a successful means of treating IBD caused by an abnormality of this pathway. Similarly, clinical studies are now under way to test the use of anti–IL-12 in the treatment of CD. This new antibody-based treatment is a direct outgrowth of studies of the murine models and promises to be effective because it targets the master cytokine of the Th1 response. In addition, agents that block the traffic of cells into mucosal inflammatory sites are also currently under investigation. Further down the road, but already in development, is the development of treatment approaches that rely on novel means of delivery of cytokines or anticytokines. Thus, it may be possible to administer cytokines that suppress abnormal T-cell responses such as TGF-β by using gene therapy techniques.

Forecast of Research Advances

These therapeutic strategies all are within the category of treatments directed toward the final common pathways of disease, the end-stage abnormalities of the Th1 or Th2 responses. The follow-up challenge of the coming decades will be to identify the more basic abnormalities that are akin to the individual genetic defects present in the murine models and under control of the mutant genes in humans with IBD. First and foremost in this endeavor is the definition of the genetic basis of the IBD so as to identify not just genetic loci but actual genes associated with the disease. At least, this will

![Figure 2. Pathogenesis of Inflammatory Bowel Disease: Induction of Inflammatory Cascade](image-url)

Bacterial antigens inappropriately leak across the intestinal epithelial cell barrier. Tissue macrophages and dendritic cells (DCs) present these antigens to resident CD4+ T cells and activate proinflammatory T cells relative to regulatory T cells (Tr1, Th3, and NK-T cells) leading to excess proinflammatory cytokine release (IL-1, TNF-α) from the macrophages. Activation of the immune and vascular systems is regulated by nerve cells and their mediators (substance P). NK-T cell indicates natural killer T cell; TNF, tumor necrosis factor. See legend to Figure 1 for other abbreviations and explanation of symbols.
allow identification of genetic markers that can be used in diagnosis and provide insight into the probable course of disease in individual patients. At the most, it will produce new targets of gene therapy that will lead to permanent reconstitution and cure.

A second category of factors to be identified relates to environmental effects. The high research priority in this area is the definition of the microbial universe in the mucosa to identify the individual elements that, on the one hand, initiate or perpetuate disease and, on the other, prevent disease in the general population. The response to mucosal antigens is inherently complex in that it consists of both positive (effector) and negative (suppressor) pathways. Furthermore, the negative pathways can be expressed by bystander cells that secrete cytokines that nonspecifically suppress responses. The upshot is that persons susceptible to IBD in urbanized environments may develop disease because in these environments people do not encounter the microbial antigens necessary to elicit T cells that produce suppressor factors. In this light, IBD might not be a disease but rather a maladaptation to what is, in effect, a changed microbial environment. With more comprehensive knowledge of the intestinal microbiota and how the latter interacts with the host’s immune system, it may be possible to define specific microbial substances in specific patients that are either present or absent from the normal flora to cause disease.

Future research also must focus on the mucosal immune system itself, particularly with respect to how that system deals with mucosal antigens to mount appropriately strong responses to potential pathogens on the one hand and appropriately weak or tolerogenic responses to harmless antigens in the resident microbiota, food stream, or both, on the other. This will require a comprehensive understanding of how antigens are processed in the mucosal immune system and, once processed, how they are presented to T cells that determine the outcome of the response. Along these lines, the mucosal response is unique in that it is juxtaposed on the layer of epithelial cells. There is little knowledge of how these cells influence immune responses by the production of cytokines and chemokines and how they provide barrier function or act as antigen-presenting cells. In addition, epithelial cells, through the production of chemokines, are a major

**Figure 3. Pathogenesis of Inflammatory Bowel Disease: Amplification of Inflammatory Cascade and Repair**

The proinflammatory cytokines activate the endothelium of the postcapillary venules leading to up-regulation of vascular addressins and the recruitment of leukocytes (lymphocytes and polymorphonuclear [PMN] cells) and monocytes into the lamina propria via a series of molecular interactions between the endothelium and recruited cells. The influx of activated leukocytes and monocytes leads to the production of inflammatory mediators that amplify the inflammation and cause tissue injury. An attempt is made to activate processes related to reestablishing the integrity of the intestinal epithelium. MADCAM indicates mucosal addressin cell adhesion molecule; L-selectin, leukocyte selectin; E-selectin, endothelium selectin; P-selectin, platelet selectin; LFA-1, leukocyte function-associated antigen; and ICAM, intracellular adhesion molecule. See legend to Figure 1 for other abbreviations and explanation of symbols.
factor in the chemotaxis of acute inflammatory cells into IBD lesions and thus initiate the tissue destruction caused by such infiltration.

Conclusion

Research into pathogenesis and treatment of IBD has provided major insights and understanding of this complex disorder. Today the cause of IBD is no longer considered unknown; rather clinicians and researchers now understand the broad outlines of the problem and are ready to go forward to attack the disease on several levels. Fortunately, the technology to accomplish this goal is at hand.

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