

## New Concepts in the Pathophysiology of Inflammatory Bowel Disease

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### Clinical Principles

The inflammatory bowel diseases (IBDs), that is, Crohn disease and ulcerative colitis, affect approximately 1 million persons in North America and several million persons worldwide.

Approximately 30% of patients present between 10 and 30 years of age.

Current therapeutic options are limited and include nonspecific anti-inflammatory and immunosuppressive medications.

Surgery is required for 50% to 80% of patients with Crohn disease, while only 20% of patients with ulcerative colitis have surgery.

Novel biological therapeutics have greatly improved the quality of life of patients with IBD.

### Pathophysiologic Principles

Both genetic and environmental factors play important roles in disease pathogenesis.

New hypotheses implicate the innate immune system and the intestinal epithelium in the pathogenesis of the disease.

Lymphocytes, cytokines, and adhesion molecules are dysregulated and have been targeted for therapeutic intervention.

Based on a new understanding of the complicated mechanisms that underlie the disease process, combination therapies are currently being pursued.

A better understanding of the pathophysiologic mechanisms will aid in prevention and more effective maintenance of remission of IBDs.

Ulcerative colitis and Crohn disease are collectively called the inflammatory bowel diseases (IBDs) because of such similarities as a chronic remitting and relapsing course, their inflammatory nature, and their unknown causes. Nevertheless, these 2 disorders are clearly separated by distinct clinicopathologic features, including different locations within the gastrointestinal tract, diverse histologic patterns of inflammation, and the various disease-specific complications. Data that diverge from the traditionally accepted view of the pathogenesis of IBDs have recently been published (1). This new information has substantially challenged our conception on the pathophysiology of IBD and has complicated what was originally believed to be a simple dichotomy between Crohn disease and ulcerative colitis.

According to the currently accepted hypothesis, ulcerative colitis and Crohn disease result from a dysregulated response of the mucosal immune system toward intraluminal antigens of bacterial origin in genetically predisposed persons (2–4). However, this hypothesis has been challenged by unexpected results from animal models of intestinal inflammation, which have led investigators to reject traditional pathogenetic concepts of these diseases (5, 6). Such animal models allow experimental manipulations that

cannot be done in humans and are frequently used to test the efficacy of candidate therapies. In this review, we present emerging pathophysiologic concepts and discuss their effect on the classical paradigms for IBD.

### THE ROLE OF THE INNATE IMMUNE SYSTEM IN IBD

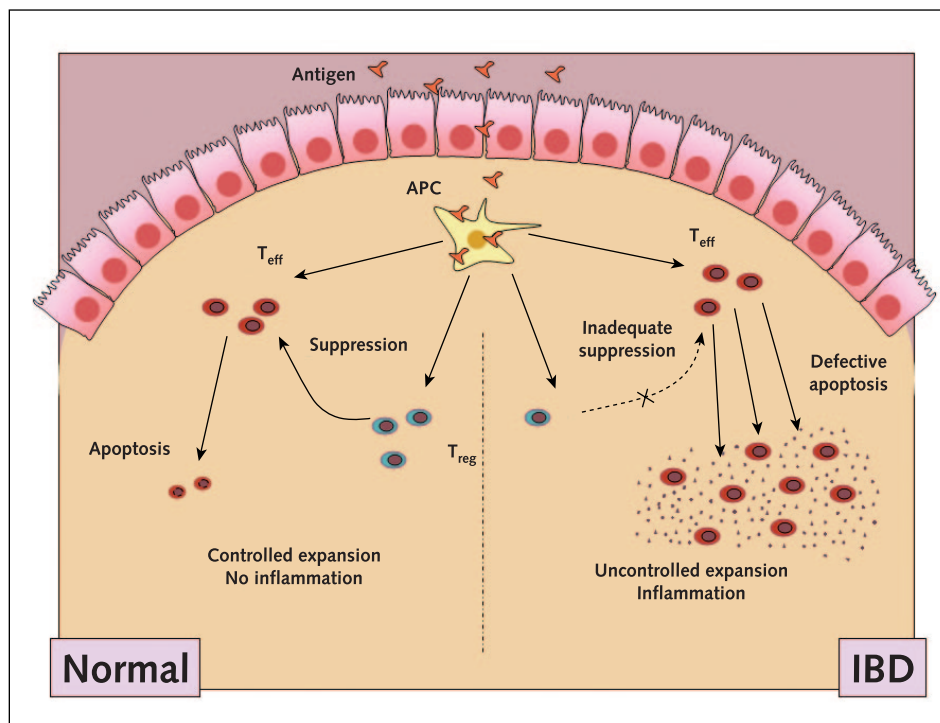
The innate immune system is the body's nonspecific defense against pathogens; it responds immediately or within the first few hours after a challenge. This is commonly considered the first line of defense and includes such physical barriers as the skin and the intestinal mucosa as well as immune cells that identify and remove foreign bodies. The innate immune system reacts to the chemical properties of the antigen rather than to the specific antigen itself. The acquired immune system, however, responds

See also:

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Figure 1. The traditional paradigm for the pathogenesis of inflammatory bowel disease (IBD).



Presentation of intraluminal antigens to mucosal lymphocytes by antigen-presenting cells (APCs) leads to the generation of effector responses. In the normal gut (*left*), overt inflammation is prevented by controlling the activation of mucosal effector T cells ( $T_{eff}$ ) through at least 2 distinct mechanisms. First, regulatory T-cell subpopulations ( $T_{reg}$ ) in the mucosal immune system suppress effector T-cell activity in part through the production of interleukin-10 and transforming growth factor- $\beta$ . Second, control is also provided by eliminating  $T_{eff}$  by apoptosis, thereby preventing undesired overexpansion. In individuals with IBD, both of these regulatory mechanisms seem to be defective (*right*). Aberrant signaling of regulatory cytokines such as transforming growth factor- $\beta$  has been well described in Crohn disease.

specifically to antigens. The antigen is processed and recognized, and immune cells that are specific to that antigen are then selectively proliferated. Memory is also a part of adaptive immunity, which improves the efficiency of future immunologic responses.

The traditional view of the pathogenesis of inflammatory bowel disease is that intestinal inflammation is mediated by cells of the acquired immune system (Figure 1). The chronic inflammation could result from overly aggressive activity of effector lymphocytes and proinflammatory cytokines, which overcome the control mechanisms. Alternatively, IBD may result from a primary failure of regulatory lymphocytes and cytokines, such as interleukin-10 and transforming growth factor- $\beta$ , to control inflammation and effector pathways (7, 8). In addition, a central pathogenic mechanism in Crohn disease is the resistance of T cells to undergoing apoptosis after activation. The exact cause of this phenomenon has not yet been fully elucidated; nonetheless, the ability of anti-tumor necrosis factor and anti-interleukin-12 antibodies to efficiently prevent or reverse clinical and experimental IBD is largely mediated by their ability to restore mucosal homeostasis and redirect mucosal effector T cells into apoptotic pathways. In both scenarios, lymphocytes are considered to be the major culprits. However, there is emerging evidence that defects in

the innate immune system may play an equal or even more important role in IBD (9, 10).

Evidence of the role of the innate immune system comes from the recently discovered association between Crohn disease and loss-of-function mutations in the caspase-activating and recruitment domain 15 gene (card15—so named because the protein it encodes contains a CARD protein-protein interaction domain), which is also known as nod2. The NOD2 protein is an intracellular receptor for a component of the bacterial cell wall and plays an important role in triggering cells of the innate immune system.

## THE NOD2 GENE

Genetic factors play an important role in the pathogenesis of IBD, with 5% to 10% of patients reporting a positive family history (11). Although family and twin concordance studies support a stronger genetic influence in Crohn disease than in ulcerative colitis, both diseases represent complex polygenic traits (12). Genome-wide searches have identified at least 7 loci that confer susceptibility to Crohn disease or ulcerative colitis or both (Table 1) (13).

The first locus to be identified and best characterized is

IBD1, which is located at chromosome position 16q12 (14, 15). Because several genes are included within this locus, converging techniques have been used to identify predisposing genes. These techniques have singled out *nod2* as playing an important role in the predisposition to IBDs associated with this locus (16–18).

Mutations in the *nod2* gene are present in as many as one third of individuals with Crohn disease. Three common single nucleotide polymorphisms that independently associate with Crohn disease have been identified in the *nod2* gene. Carriage of 1 pathologic allele increases the risk for Crohn disease by 2- to 4-fold, compared with a 15- to 40-fold increase when 2 risk alleles are present (11). Despite this gene–dose effect, fewer than 2% of individuals with 2 risk alleles eventually develop Crohn disease. Indeed, 20% of healthy white controls carry 1 risk allele and 1% carry 2 risk alleles. Examination of genotype–phenotype relationships in Crohn disease showed an association of mutations in *nod2* with ileal disease rather than colonic disease, an earlier age of disease onset, and possibly fibrostenosis (19). In contradistinction to Crohn disease, mutations in *nod2* do not seem to be a significant risk factor in ulcerative colitis.

NOD2 is an intracellular protein that senses bacterial products and activates components of the innate immune system. The functional significance of Crohn disease–associated mutations in NOD2 is currently being investigated, with several controversies remaining to be resolved (20). However, the current observations indicate that an impaired inflammatory response rather than an overly aggressive inflammatory response by a defective intestinal innate immune system may underlie the initial phase of IBD. In this context, the lack of appropriate secretion of defensins (peptides that are produced by enterocytes to control the levels of commensal microbes) may be relevant to the pathogenesis of IBD (21). **Figure 2** summarizes the current theories regarding the role of NOD2 in IBD.

**Table 1. Genetic Associations in Inflammatory Bowel Diseases\***

Loci Designation	Chromosome Location	Disease Association	Candidate Genes	Phenotype Correlation
IBD1	16q12	CD	CARD15/NOD2	Earlier disease onset, small intestinal localization and strictures
IBD2	12q13	Indeterminate colitis and terminal ileal CD	VDR, NRAMP2, STAT6, and MMP-18	Not reported
IBD3	6p13	CD and UC	Major histocompatibility complex and TNF	Not reported
IBD4	14q11	CD	TCR $\alpha/\delta$ , leukotriene B4 receptor, and major histocompatibility complex type I, antigen presentation–associated proteasome cluster	Not reported
IBD5	5q	Indeterminate colitis and colonic and ileal–colonic CD	Cytokine cluster (IL-3, IL-4, IL-5, and IL-13; IRF-1; and CSF-2)	Perianal disease and early onset
IBD6	19p	CD	ICAM-1 and DDXL	Not reported
IBD7	1p	CD and UC	Mucin 3, EGFR, and HGF	Not reported

\* CARD = caspase-activating and recruitment domain; CD = Crohn disease; CSF-2 = colony-stimulating factor isoform-2; DDXL = DEAD/DEAH box helicase; EGFR = epidermal growth factor receptor; HGF = hepatocyte growth factor; IBD = inflammatory bowel disease; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; IRF-1 = interferon regulatory factor isoform-1; MMP = matrix metalloproteinase; NRAMP2 = natural resistance-associated macrophage protein 2; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; TNF = tumor necrosis factor; UC = ulcerative colitis; VDR = vitamin D receptor.

## THE ROLE OF THE EPITHELIUM

The intestinal epithelium, which is considered to be part of the innate immune system, plays an active role in the maintenance of mucosal homeostasis (22). Consequently, dysfunction of epithelial cells can contribute to and may even be the primary defect in IBD. Epithelial cells form a tight, highly selective barrier between the body and the intraluminal microenvironment. Failure of this barrier may result in intestinal inflammation, most likely through exposure to fecal antigens leading to inappropriate activation of the mucosal immune system. Indeed, mice with genetically introduced defects in intestinal permeability develop intestinal inflammation (23, 24).

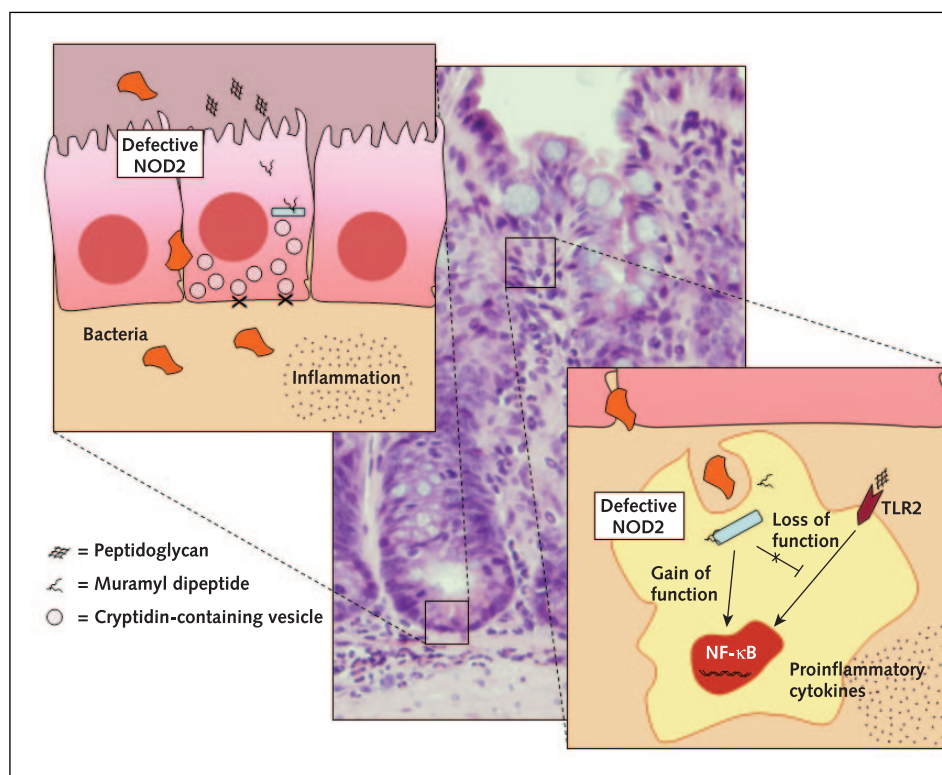
Within the intestinal mucosa, there is constant cross-talk between the epithelium and cells of the immune system (25). Epithelial cells can act as antigen-presenting cells because they are able to take up and process antigens and present them to cells of the immune system, along with appropriate activating stimuli. Aberrant communication, therefore, has the potential to create inappropriate signals that activate effector cells and lead to inflammation.

Epithelial cells are avid producers of chemokines, which regulate recruitment of acute and chronic inflammatory cells within the intestinal mucosa. In addition, many cytokines that are considered central to the pathogenesis of IBD, such as tumor necrosis factor, interleukin-1, and interleukin-6, are expressed in the intestinal epithelium. Aberrant secretion of these proinflammatory chemokines and cytokines by epithelial cells is an integral part of the dysregulated immune response that initiates or perpetuates intestinal inflammation (26, 27).

## THE EFFECTOR IMMUNE RESPONSE IN IBD

In addition to being thought to result from dysfunction of the acquired immune system, Crohn disease and ulcerative colitis are also believed to display distinct immu-

Figure 2. Proposed functional significance of NOD2 mutations in Crohn disease.



Intracellular NOD receptors and transmembrane Toll-like receptors (*TLRs*) are important molecules for the recognition of pathogen-associated molecular patterns, activation of the innate immune system, and maintenance of mucosal homeostasis. Muramyl dipeptide, a component of the bacterial cell wall, binds to CARD15/NOD2, which then activates nuclear factor- $\kappa$ B (*NF- $\kappa$ B*). NOD2 is expressed in macrophages (*right*) and in Paneth cells at the base of intestinal crypts (*left*). An epithelial-oriented “loss of function” pathway may be associated with inability to effectively clear intraluminal microorganisms, as a result of decreased antibacterial peptide (defensins) secretion by Paneth cells (*left*). Alternatively, the “loss of function” may also affect the ability of NOD2 to attenuate signaling through TLR-2 in macrophages, the net result being enhanced *NF- $\kappa$ B* activation and proinflammatory cytokine production (*right*). An alternative hypothesis describes a “gain-of-function” phenotype, that is, direct MPD/NOD2-mediated increase in *NF- $\kappa$ B* signaling, with a similar end result of increased secretion of proinflammatory cytokines and chronic intestinal inflammation. More important, none of the NOD2 mutations results in spontaneous colitis in mice.

nologic phenotypes. Crohn disease is usually described as a prototypical T-helper (Th) 1 disease because the primary mediators of inflammation are the Th1 cytokines interleukin-12, interferon- $\gamma$ , and tumor necrosis factor (28). However, ulcerative colitis is often viewed as a Th2-type condition because of reports of increased mucosal expression of the Th2 cytokine interleukin-5, although a clear association with interleukin-4, the definitive Th2 cytokine, has never been established (28). This is in line with a traditional paradigm that has been used to classify many diseases. However, this classic paradigm has recently been challenged by several reports that support the hypothesis that these pathways may not be mutually exclusive (29–32). Individual cytokines can have diverse and even opposing functions in various clinical and immunologic settings, although disease models that involve mixed phenotypes have been described (33, 34).

### IMMUNOLOGIC DIVERSITY IN IBD

The studies that have been conducted thus far into the Th1/Th2 paradigm in mucosal inflammation have been

limited, and a better understanding of the variability that occurs within the spectrum of IBD is needed. Indeed, data are accumulating that support the notion that the clinicopathologic diversity in ulcerative colitis and Crohn disease may be a reflection of distinct immunogenetic pathways.

First, patients with mutations in the *nod2* gene seem to belong to a distinct subgroup with earlier disease onset, ileal localization, and a stricturing phenotype. Second, responses to treatment with biological agents emphasize the phenotypic variation. Although a central role for failure of regulatory mechanisms has been proposed in the pathogenesis of IBD, administration of the anti-inflammatory cytokine interleukin-10 did not induce remission in patients with Crohn disease and even enhanced secretion of proinflammatory cytokines, implying that more complicated pathways exist (35, 36). Infliximab, an antibody that blocks tumor necrosis factor, cannot induce remission in a substantial percentage of patients with Crohn disease, which may be explained by the presence of different effector pathways in responders compared with nonresponders (37). In addition, the notion that ulcerative colitis is a

strictly Th2-polarized condition has been disputed by reports of a favorable response to treatment with anti-tumor necrosis factor (38–40). Of interest, a recent study found that patients with ulcerative colitis could be classified into 3 groups according to mucosal cytokine profiles, which were subsequently associated with different responses to treatment (41).

Finally, the ongoing discovery and functional characterization of novel cytokines further underline the plasticity of the immune response. In particular, it has become clear that effector Th1 responses are not confined to the interleukin-12–interferon- $\gamma$ –tumor necrosis factor axis. Rather, it seems that novel cytokines (for example, interleukins-23, -27, -21, and TL1A) may play equal and potentially more important roles in chronic mucosal inflammation (42–47). Similar observations regarding the involvement of novel cytokines are emerging for effector Th2 responses (48, 49).

### MIXED IMMUNOLOGIC PHENOTYPES IN IBD

Both Crohn disease and ulcerative colitis are characterized by periods of remission that are interrupted by acute flares. Studies in humans and animals have indicated that induction of active disease and perpetuation of chronic inflammation are immunologically distinct phenomena. This was clearly shown in studies of the SAMP1/YitFc mouse, a model of small intestinal inflammation that has many similarities to Crohn disease (Figure 3) (50, 51). The spontaneous chronic ileitis that develops in SAMP1/YitFc mice is similar to that in Crohn disease because it is discontinuous and transmural, with frequent formation of granulomas and occasional associated perianal manifestations. Ileitis in SAMP1/YitFc mice commences with an induction phase that precedes the development of histologic disease. At this stage, disease is strictly Th1-polarized, with early increases in mucosal expression of interferon- $\gamma$  and tumor necrosis factor. However, after ileitis enters the chronic phase, the mucosal phenotype shifts toward a mixed Th1/Th2 pattern (52). In addition to interferon- $\gamma$  and tumor necrosis factor, elevations of mucosal interleu-

kin-13 and interleukin-5 are observed. Similar phase-specific changes occur in the expression of adhesion molecules and their ligands. During the induction phase, lymphocytes that are similar to those in the healthy mucosa are recruited through homeostatic mechanisms. On commencement of the chronic phase, these homeostatic pathways are substantially upregulated (53). In addition, alternative pathways that involve proinflammatory chemokines, adhesion molecules, and integrins are triggered at this time. This results in heavy infiltration of the lamina propria with inflammatory cells.

The SAMP1/YitFc mouse is of particular interest because it is the only animal model that develops spontaneous ileitis but does not develop colitis. There has been some speculation that ileal Crohn disease may have a different immunologic profile than ulcerative colitis, but this hypothesis has not been thoroughly addressed in humans. Nonetheless, 1 study in humans has shown that various cytokines predominate in early as opposed to late Crohn disease (54). Similarly, immunomodulation of early IBD in pediatric patients results in longer periods of remission than those reported for adults (55, 56). This difference may be explained by the fact that the dysregulated immune response is at an earlier stage in children, rendering it more susceptible to definitive reversion by aggressive therapies.

### THE ROLE OF THE ENVIRONMENT IN THE PATHOGENESIS OF IBD

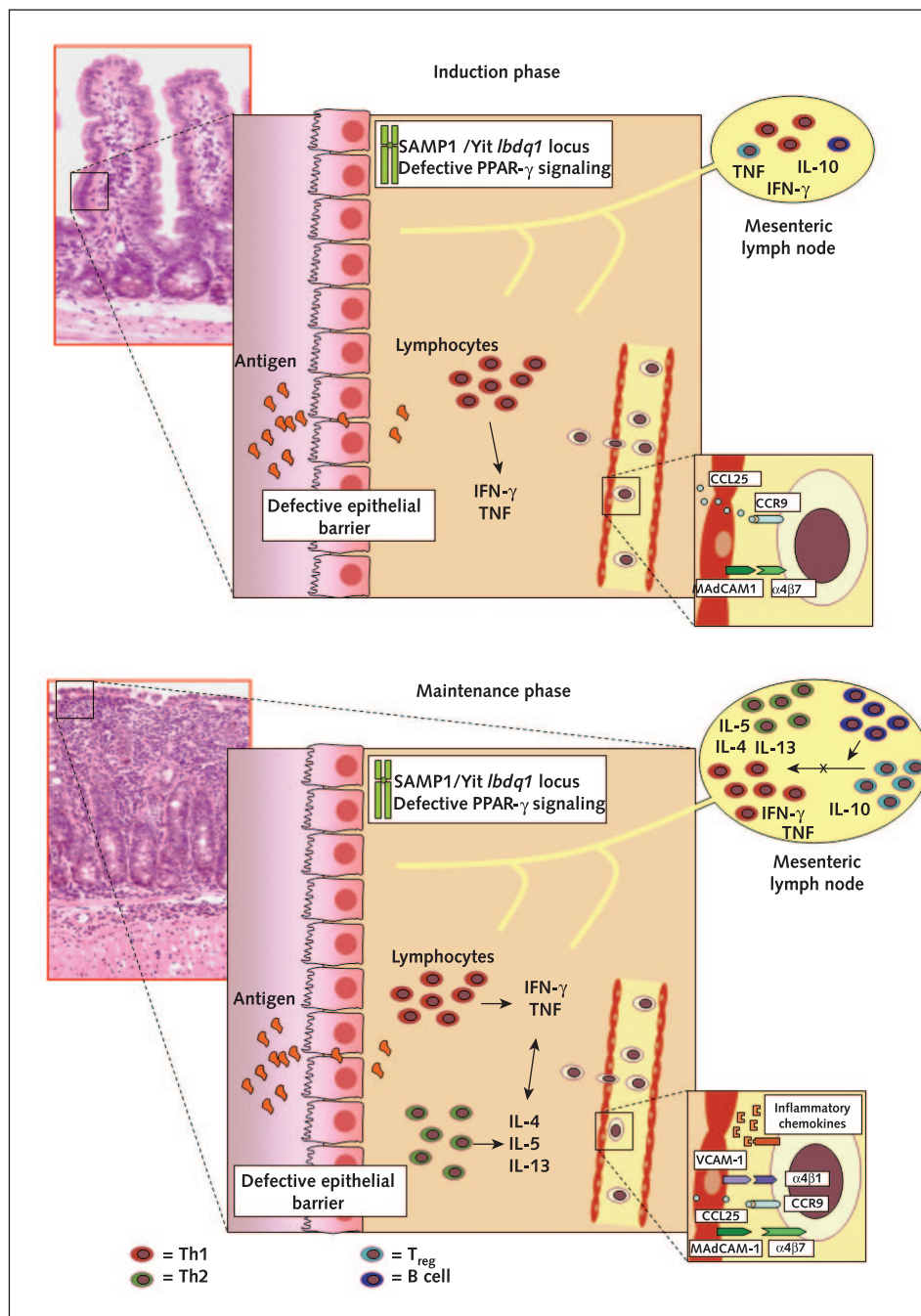
Environmental factors unquestionably play a major role in the pathogenesis of IBD. The major environmental factors implicated in the pathogenesis of IBD are listed in Table 2. The commensal bacterial flora are the environmental factor most frequently implicated in the development of IBD (57–59). The association was primarily established in animal models (Table 3), because intestinal inflammation does not develop when mice are kept under sterile (germ-free) conditions. This led to the current theory of “no bacteria, no IBD.” In other words, in the ab-

Table 2. Environmental Factors That Have Been Associated with Inflammatory Bowel Disease\*

Factor	Epidemiologic Association	Pathophysiologic Association
Smoking	Active smoking decreases risk for UC Former smoking increases risk for UC Active smoking is associated with milder clinical course of UC Active smoking increases risk for CD Active smoking is associated with more severe clinical course of CD	Altered mucosal cytokine profile Decreased intestinal IgA secretion Altered bactericidal activity Altered eicosanoid pathway Altered generation of free oxygen radicals
Appendectomy	Appendectomy decreases risk for UC	Alteration of the balance between effector and regulatory factors
Perinatal events	Breastfeeding decreases risk for CD Early infection increases risk for IBD	Unknown
Socioeconomic factors	Higher economic status increases risk for IBD IBD is more prevalent in western countries than in developing countries IBD is more prevalent in northern regions compared with southern regions	“Hygiene theory”: Higher socioeconomic status is associated with less frequent helminthic infections during childhood. This results in a lack of mucosal Th2/anti-inflammatory or regulatory cytokines or both and leaves proinflammatory effector mechanisms unopposed.

\* CD = Crohn disease; IBD = inflammatory bowel disease; Th = T-helper; UC = ulcerative colitis.

Figure 3. Immunopathogenesis of chronic ileitis in SAMP1/YitFc mice.



Ileitis in SAMP1/YitFc mice develops through 2 distinct phases. **Top.** During the induction phase, which takes place between 4 and 8 weeks of age, there is little or no evidence of histologic injury in the terminal ileum. Defective epithelial barrier function with augmented intestinal permeability occurs early and leads to increased invasion of the lamina propria by intraluminal antigens. The original effector response is T-helper (*Th1*)-polarized, as indicated by increased production of intestinal interferon- $\gamma$  (*IFN*- $\gamma$ ) and tumor necrosis factor (*TNF*) by mucosal lymphocytes. During this phase, recruitment of leukocytes into the bowel is dependent on a single adhesion molecule pathway. **Bottom.** At approximately 10 weeks of age, severe ileitis is established in SAMP1/YitFc mice and various immunologic pathways drive the maintenance of inflammation. The effector response that is mounted during this phase bears a mixed Th1/Th2 phenotype, with a substantial increase in Th2 cytokine production. Also, expansion of a B-cell population blocks the function of regulatory T cells (*T<sub>reg</sub>*) and allows the unopposed expansion of Th1 and Th2 clones. During the maintenance phase, multiple redundant adhesion pathways direct recruitment of leukocytes into the inflamed bowel. CCR9 = chemokine receptor 9; CCL25 = chemokine ligand 25; IL = interleukin; PPAR- $\gamma$  = peroxisome proliferator-activated- $\gamma$ ; VCAM-1 = vascular cell adhesion molecule-1.

sense of live intraluminal microorganisms, the mucosal immune system is deprived of the antigenic material responsible for its activation. In addition, development of

IBD requires a breakdown of the mechanisms responsible for tolerance against intestinal flora, which prevent intestinal inflammation in healthy persons. Evidence of an asso-

ciation of bacterial factors with IBD derived from both human and animal studies is shown in **Table 3**.

Antibodies against intestinal bacteria are frequently detected in the serum of patients with IBD (60, 61). Indeed, in 1 study, patients whose serum was reactive against multiple bacterial antigens frequently had localization of disease to the small intestine, fibrostenotic and perforating phenotypes, and an increased likelihood of needing surgery (62). This subgroup of patients with an “aggressive” serologic profile was defined by the presence of circulating antibodies against *Saccharomyces cerevisiae* and the bacterial proteins outer membrane protein C and I2 (63, 64). Subsequent studies from the same group reported that patients in the “high-reactivity” group responded well to antimicrobial therapy but not as well to the corticosteroid budesonide, although the opposite effect was observed in the group with no bacterial reactivity (64). It was therefore proposed that subdivision of patients with Crohn disease according to the presence or absence of circulating antibacterial antibodies may facilitate the selection of appropriate treatment strategies.

Taken together, these studies raise the possibility that intestinal inflammation may be mediated by both bacteria-dependent and bacteria-independent pathways. Two authors of this review lend further support to this hypothesis by the recent finding that ileitis in SAMP1/YitFc mice can develop under bacteria-free conditions, although with less severity. These data indicate that a concept of “more bacteria, more IBD” may be more accurate than the “no bacteria, no IBD” theory.

### IMPLICATIONS FOR FUTURE MANAGEMENT

It is hoped that the elucidation of well-defined pathogenic mechanisms will lead to new therapeutic approaches for IBD (**Figure 4**). The realization that multiple factors contribute to the pathogenesis of IBD, with additional complexity as the disease progresses, has driven the search for therapeutic strategies that can be tailored to the needs of individual patients. Factors such as the patient’s genetic background, disease stage, and environmental influences have all been shown to play important roles in disease development and responsiveness to treatment (3, 4).

Once the role of genetic determinants is fully understood, early interventions can be designed to prevent disease in predisposed individuals. Gene therapy or modification of bacterial flora with probiotics or antibiotics or both for specific pathogens is expected to be central to this approach. For early clinical disease, defined-target approaches will probably prevail, because induction of disease seems to follow single immunologic pathways. This includes blockade of single adhesion molecule pathways with monoclonal antibodies and small molecules. In addition, biological therapies aimed at blocking specific Th1 or Th2 cytokines (for Crohn disease and ulcerative colitis, respectively) may prove to be effective. Finally, stimulation of the innate

immune response—for example, treatment with granulocyte macrophage colony-stimulating factor—may also have efficacy in early disease.

By contrast, long-lasting disease represents a generalized dysregulation of multiple variables of the immune response. It is possible that successful management at this stage will require combination therapies that target numerous pathways sequentially or concomitantly. Examples of therapies that may be beneficial at this stage of disease are combined adhesion molecule blockade, antibiotics or probiotics combined with antiblockade, and biological therapies that simultaneously target both the Th1 and Th2 pathways.

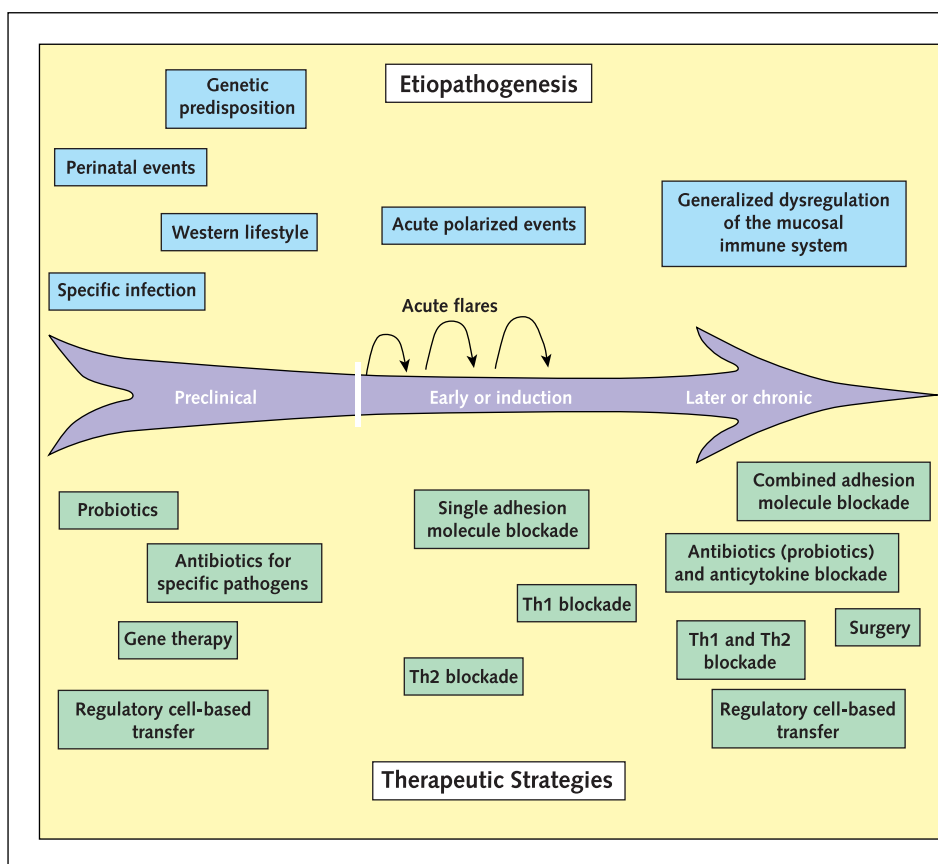
Every experimental finding must be analyzed for applicability to disease management in humans. With such an abundance of new research, the importance of translational studies cannot be overemphasized. Although the identification of the *nod2* gene was an important advance in our understanding of Crohn disease, it has yet to affect our management of the disease. The successful introduction of anti-tumor necrosis factor therapies is proof of the principle that clarification of immunologic pathways can translate to effective treatments. Finally, identification of highly predictive and easily obtained markers that identify defined subgroups within the spectrum of IBD is distinctly lacking at this time. Advances in our understanding of the

**Table 3. Bacterial Factors in the Pathogenesis of Inflammatory Bowel Disease\***

Variable	Evidence for Association
Pathogenic bacteria	Overall weak evidence; may be important in subsets of patients
<i>Mycobacterium avium</i> paratuberculosis	Epidemiologic data are inconsistent May be the causative factor in a subset of patients with CD
Adherent or invasive	Increased prevalence in UC in some but not all studies
<i>Escherichia coli</i>	Increased incidence in postoperative CD recurrence
<i>Helicobacter</i> species	The presence of <i>H. bilis</i> and <i>H. hepaticus</i> results in more severe colitis in mice
Measles	No association has been established for measles infection or vaccination against measles virus
Commensal bacteria	Overall, very strong evidence has led to the “no bacteria, no IBD” theory
Human studies	IBD develops in areas of high bacterial concentration, such as the terminal ileum and the colon Diversion of the fecal stream prevents intestinal inflammation; reestablishment of flow leads to recurrence Antibiotics and probiotics have beneficial effects on IBD Antibodies against bacterial components are detected in IBD Lymphocytes from patients with IBD show reactivity against fecal antigens
Animal models of IBD	Experimental colitis does not develop under germ-free (sterile) conditions Lymphocytes that are reactive to bacterial antigens induce colitis after transfer to immunologically naive recipients

\* CD = Crohn disease; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Figure 4. Future therapeutic approaches in inflammatory bowel disease.



On the basis of the new concepts that researchers have developed, future therapeutic strategies can be tailored to individual characteristics. In the preclinical stage, before the development of disease, strategies can be used that will prevent the onset of disease in predisposed persons (*left*). Strategies that address single pathways will be effective in the early or induction phases of disease development (*center*). Combined strategies that target multiple pathways or mechanisms will probably be required in the later or chronic phases of the disease (*right*). Th = T-helper.

diversity underlying IBD will therefore prove invaluable, not only in the development but also in the selection of future therapeutic interventions.

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