

Inflammatory Bowel Disease: Epidemiology, Pathogenesis, and Therapeutic Opportunities

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Abstract: Ulcerative colitis (UC) and Crohn's disease (CD), the primary constituents of inflammatory bowel disease (IBD), are precipitated by a complex interaction of environmental, genetic, and immunoregulatory factors. Higher rates of IBD are seen in northern, industrialized countries, with greater prevalence among Caucasians and Ashkenazic Jews. Racial gaps are closing, indicating that environmental factors may play a role. IBD is multigenic, with the most clearly established genetic link between certain *NOD2* variants and CD. Regardless of the underlying genetic predisposition, a growing body of data implicates a dysfunctional mucosal immune response to commensal bacteria in the pathogenesis of IBD, especially CD. Possible triggers include a chronic inflammatory response precipitated by infection with a particular pathogen or virus or a defective mucosal barrier. The characteristic inflammatory response begins with an infiltration of neutrophils and macrophages, which then release chemokines and cytokines. These in turn exacerbate the dysfunctional immune response and activate either T_H1 or T_H2 cells in the gut mucosa, respectively associated with CD and, less conclusively, with UC. Elucidation of immunological and genetic factors indicate multiple points at which the inflammatory cascade may be interrupted, yielding the possibility of precise, targeted therapies for IBD.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, immunoregulatory defects, commensal bacteria

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Inflammatory bowel disease (IBD) comprises primarily 2 disorders: ulcerative colitis (UC) and Crohn's disease (CD). The hallmark of IBD is chronic, uncontrolled inflammation of the intestinal mucosa,¹ which can affect any part of the gastrointestinal tract. Diagnosis is based on the presence of architectural distortion (e.g., transmural or superficial patchy granulomatous infiltration) and/or acute inflammatory cells. However, chronic inflammation without any diagnostic abnormality can also be a feature of the normal gut. What distinguishes IBD from

inflammatory responses seen in the normal gut is an inability to down-regulate those responses. In healthy people, the intestine becomes inflamed in response to a potential pathogen, then returns to a state of tolerance once the pathogen is eradicated from the gut. In individuals with IBD, however, inflammation is not down-regulated, the mucosal immune system remains chronically activated, and the intestine remains chronically inflamed.

Although UC and CD are generally accepted as clinically distinct conditions with distinguishing clinical, anatomical, and histological findings, a diagnostic gold standard remains elusive.² In fact, these conditions probably represent a continuum of diseases, with UC and CD at opposite ends. Moreover, there may be a spectrum of illnesses within each disorder, making it likely that "ulcerative colitides" and "the Crohn's diseases" will be the terms used to describe these illnesses in the future.

Underscoring this hypothesis is the fact that about 10% of patients have indeterminate features between UC and CD that cannot be clearly categorized.³ There is no established definition for this subset of patients; their condition is simply termed "indeterminate colitis" until the diagnostic features of UC or CD become apparent later on.³

The great diversity of symptoms within UC and CD suggests distinct underlying pathogenetic mechanisms. It is hoped that a better understanding of the environmental, genetic, and immunological mechanisms that produce UC and CD will lead to improved therapy for IBD.⁴

EPIDEMIOLOGY

In regions with a high prevalence of IBD, such as North America, the incidence was seen to increase between the 1960s and 1980s, reaching the current plateau.^{5–7} In the United States specifically, an estimated 1 million individuals have IBD,⁸ with about 30,000 new cases reported each year. The incidence is evenly divided between UC and CD.⁸

The peak age of onset for IBD is 15 to 30 years old, although it may occur at any age. About 10% of cases occur in individuals <18 years old. Both UC and CD have a bimodal age distribution, with a second, smaller peak occurring in individuals ages 50 to 70 years.^{6,8} Ulcerative colitis is slightly

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more common in males, whereas CD is marginally more frequent in women (female-to-male ratio range, 1:1 to 1.8:1). Both diseases tend to occur in higher socioeconomic groups.^{5,6}

Breakdowns by racial and ethnic subgroups indicate that higher rates of IBD occur in people of Caucasian and Ashkenazic Jewish origin than in individuals from other backgrounds.^{5,9} The distribution of IBD among ethnic and racial groups remains dynamic. In past decades, it was thought that IBD occurred less frequently in ethnic or racial minority groups compared with whites. This gap has been closing, with an increased incidence in African Americans⁵ and in second-generation south Asians who have migrated to developed countries.^{5,10}

HEALTH BURDEN

IBD is a chronic condition without a medical cure, which commonly requires a lifetime of care. It can cause significant morbidity, but it is not generally associated with increased mortality. Most patients are able to live normal, productive lives. Each year in the United States, IBD accounts for 700,000 physician visits, 100,000 hospitalizations, and disability in 119,000 patients.¹¹ Over the long-term, up to 75% of patients with CD and 25% to 33% of those with UC will require surgery.^{8,12}

ETIOLOGY

It is likely that a number of factors contribute to the development of mucosal inflammation. Also, variations in influence may account for the clinical diversity seen in UC and CD.⁴ For example, a single family may have multiple affected members, suggesting heightened genetic susceptibility. In contrast, sporadic disease, which accounts for the majority of IBD cases, is more likely to be engendered by a unique environmental trigger or by a more subtle abnormality within the enteric immune system. Current etiologic theories concerning IBD focus on environmental triggers, genetic factors, and immunoregulatory defects and microbial exposure.

Environmental Triggers

“Westernization”

IBD is most prevalent in developed regions, including the United States, United Kingdom, and Scandinavia.^{5,6} The higher incidence of IBD seen in industrialized countries and the dramatic increase in cases during the 20th century support the theory that environmental factors contribute to disease development.^{7,13} This may also account for the north-to-south variation and higher frequency in urban communities compared with rural areas. Interestingly, increases in incidence have recently been noted in southern countries and Asia and among migrants to first-world countries.^{5,6} It is postulated that this is the result of “westernization” of lifestyle, such as

changes in diet, smoking, and variances in exposure to sunlight, pollution, and industrial chemicals.⁵

Sanitation and exposure to infection

IBD is a disease of cleanliness. In common with diseases such as asthma, multiple sclerosis, and rheumatoid arthritis, it demonstrates an inverse relationship with the degree of sanitation: poor sanitation appears to protect against IBD. The propensity for infection associated with overcrowding may also be a factor. For example, children raised in more spacious conditions (i.e., reduced sharing of sleeping accommodation and bathrooms) have a higher risk of developing CD.¹³ It is postulated that improved hygiene alters the intestinal flora by decreasing exposure to certain critical bacteria. There is also an increased frequency of UC and CD in higher socioeconomic groups.^{13,14}

Occupation

Both UC and CD are more prevalent in white-collar compared with blue-collar occupations.^{13,15–17} Higher mortality from IBD has been noted in managerial, clerical, and sales positions, which typically involve sedentary, indoor work. In contrast, mortality resulting from IBD is low among farmers and construction workers.^{7,17} Sonnenberg suggests that employment involving outdoor air and physical activity is protective against IBD, whereas work in artificial venues confers an increased risk.¹⁶ This theory could explain the higher risk for IBD in northern climates (e.g., more indoor exposure) and in immigrants to developed countries, as well as the varying rates among ethnic groups in different regions.⁶

Diet

Studies seeking to link diet and IBD are generally inconclusive. There is some evidence that a higher intake of fatty acids increases the risk for IBD.¹³ Similarly, Persson et al¹⁸ suggests that frequent fast-food intake confers a 3- to 4-fold greater risk for IBD.

Tobacco smoking

The strongest environmental risk factor for IBD is tobacco smoking, particularly among consumers of cigarettes. The relationship between IBD and smoking is complex, suggesting unique pathophysiological factors for both UC and CD. Numerous case-control studies have shown that current smoking is protective against UC (relative risk [RR], 40% of that of nonsmokers), with results that are consistent across diverse geographic regions.⁷ The decreased risk for UC in smokers appears to be dose dependent.¹⁹ Current smoking also is protective against sclerosing cholangitis^{15,20} and pouchitis.²¹ Paradoxically, ex-smokers are approximately 1.7 times more likely to develop UC than those who never smoked.⁷ Ex-smokers also have a poorer disease course, with more frequent hospitalization than current smokers; as a group they are twice as likely as current smokers and those who have never smoked to require colectomy.²²

In contrast to UC, cigarette smoking is a significant risk factor for the development of CD (RR, 1.15–3.9).^{13,19} Smokers with CD have a poorer disease course than nonsmokers, with higher disease recurrence, more frequent surgical interventions, and a greater need for immunosuppressive agents.¹³ An exception is provided by Jewish patients living in Israel, in whom smoking is not associated with an increased risk of developing CD. Interestingly, smoking continues to protect this group against UC, suggesting that genetic factors may override environmental influences.²³

Genetic Factors

Epidemiological and family studies demonstrate that genetic factors play a role in the susceptibility to IBD.²⁴ The disease is, however, genetically complex and cannot be explained by a single gene model alone.²⁴ It is thought that UC and CD may be heterogeneous polygenic disorders sharing some but not all susceptibility loci. Most likely, the disease phenotype is determined by several factors, including interaction between allelic variants at a number of loci, as well as genetic and environmental influences.²⁴ Consequently, the presence of a mutated gene does not guarantee that IBD will develop, nor does it predict who will develop it,⁴ underscoring the importance of cofactors in precipitating the disease.

Familial and ethnic syndromes

There is an increased prevalence of IBD in first- and second-degree relatives and a higher relative risk among siblings. The familial frequency of IBD ranges from 20% to 30% in referral-based studies and between 5% and 10% in population surveys.²⁵ The higher risk for IBD in the Jewish population²⁶ suggests that genetic factors may play a larger role in some subgroups.²⁴

In families with a high incidence of IBD among first-degree relatives, 75% of those affected are concordant for either UC or CD, whereas 25% are not concordant, with some members having UC and others having CD.²⁵ This finding indicates that multiple, overlapping genetic factors may contribute to disease pathogenesis. Further support for a genetic susceptibility comes from the finding of an association between IBD and other syndromes with a genetic predisposition.²⁴

Heritability studies indicate that there is a higher rate of concordance in monozygotic versus dizygotic twins for both UC and CD. These studies also show that the concordance rate for UC is much lower than for CD, suggesting that the genetic penetrance in CD is greater. For UC, reported concordance rates for monozygotic and dizygotic twins ranges from 6% to 17% and 0% to 5%, respectively, which is about the same as for nontwin siblings.^{24,27–29} For CD, the concordance rate for monozygotic twins ranges from 37% to 58%,^{24,27} whereas that for dizygotic twins ranges from 3.9% to 12%. These findings indicate that there is genetic susceptibility for IBD, particularly

CD, and that IBD is not inherited as a Mendelian trait but rather has a complex genetic basis with many contributing genes.³⁰

IBD-1 locus and *NOD2/CARD15* gene

Genomewide scanning with microsatellite DNA markers has identified several genetic sites as being potentially associated with UC or CD.²⁴ Significant linkages have been reported on chromosomes 1, 3, 6, 7, 12, 14, 16, and 19.³¹

One of the clearest linkages is for *IBD-1*, a susceptibility locus in the pericentromeric region of chromosome 16.³⁰ Detailed analysis has resulted in the identification of the nucleotide-binding oligomerization domain 2 (*NOD2*) gene and protein. *NOD2* is also known as caspase activation and recruitment domain 15 (*CARD15*). This is a polymorphic gene, the product of which is involved in the innate immune system. It is the first gene to be clearly associated with IBD,^{32,33} and >60 mutations have been recognized, 3 of which have been linked to the development of CD.³⁴ *NOD2* is a member of a large family of intracellular proteins widely distributed in nature. Its leucine-rich region is strongly homologous to similar regions of plant disease-resistance genes involved in the defense against Gram-negative bacteria.^{24,30}

It is estimated that defects in *NOD2* account for 17% to 27% of cases of CD.^{32,34} Individuals who are homozygous for variant *NOD2* comprise <20% of those with the disease³; they have a >20-fold increased risk of developing CD, particularly ileal disease.³⁵ Heterozygous individuals are also at greater risk,^{35–37} especially as the number of mutations increases.³² Abreu et al⁴ suggests that the absolute risk of developing CD in an individual with 2 *NOD2* mutations (1 from each parent) is about 3%.

The mechanism whereby defects in the *NOD2* gene lead to the development of IBD remains unclear. The *NOD2* gene is expressed mainly in monocyte/macrophage cell lines, where it has a role in host-signaling pathways. One effect is the activation of nuclear factor (NF)- κ B, a transcription factor involved in cellular inflammatory responses^{24,33} and macrophage apoptosis.^{3,24} Activation leads to production of a wide variety of nonspecific mediators of inflammation. These include cytokines, growth factors, and metabolites of arachidonic acid and reactive oxygen, all of which facilitate the inflammatory process and ultimately lead to tissue destruction.³ The trigger for NF- κ B appears to be the presence of lipopolysaccharide, a cell wall component found in Gram-negative bacteria.³¹

Mutations in the *NOD2* gene paradoxically reduce macrophage activation of NF- κ B (Fig. 1).⁴ Consequently, one may expect diminished inflammation rather than the increase seen in IBD. Why this should be true remains unclear. It has been suggested that the initial abnormality in the innate immune response precipitates a secondary, compensatory up-regulation of the adaptive immune response. Alternatively, the *NOD2* mutation may increase susceptibility to chronic

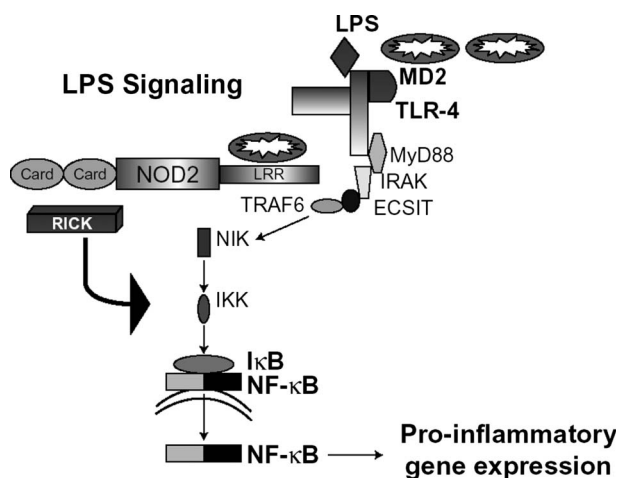


FIGURE 1. Model of *NOD2* gene mutation in the pathogenesis of CD. Mutations in *NOD2* result in diminished immune cell NF- κ B activation in the presence of lipopolysaccharide (LPS). The *NOD2* gene consists of 2 CARD, amino-terminal effector domains, a central NOD, and multiple leucine-rich repeat (LRR) domains that function as sensors of bacterial infection. Normally, stimulation of *NOD2* with bacterial proteins activates the NF- κ B pathway via RIP-like interacting CLARP kinase receptor interacting protein 21 (RICK), a serine-threonine kinase that phosphorylates the inhibitor of NF- κ B kinase (IKK), thus allowing transport of NF- κ B to the nucleus. In this model, NF- κ B is down-regulated, which, paradoxically, up-regulates inflammatory mechanisms. ECSIT = evolutionary conserved signaling intermediate; IKK = inhibitor of NF- κ B degradation; IRAK = interleukin-1R-associated kinase (a serum kinase); MD2 = myeloid differentiation protein-2; MyD88 = myeloid differentiation factor 88, an adapter molecule that mediates apoptosis and NF- κ B activation; NIK = NF- κ B-inducing kinase; TLR-4 = toll-like receptor-4, TRAF6 = TNF receptor-associated factor 6. Adapted from *Curr Gastroenterol Rep.* 2002;4:481.

intracellular infection or prevent the development of tolerance to commensal microflora.⁴ In the absence of *NOD2* expression by epithelial cells, microbial products that normally induce these cells to secrete chemokines fail to do so, leading to proliferation of bacteria and potential loss of barrier function.³⁰ A third theory focuses on disruption of mucosal homeostasis resulting from the absence of *NOD2*-mediated conditioning of antigen-presenting cells to induce regulatory and effector T cell responses.³⁰

Immunoregulatory Defects and Microbial Exposure

In healthy gut epithelium, the presence of potentially proinflammatory luminal bacteria is tolerated without neutrophil recruitment into the epithelial surface. This may be caused in part by the unique phenotype of the resident macrophage population within the intestine. Triggering the receptor expressed on myeloid cells (TREM-1) is a cell surface molecule

present on neutrophils, monocytes, and macrophages that amplifies the inflammatory response by enhancing degranulation and secretion of proinflammatory cytokines. Fewer than 10% of macrophages found within the intestinal lamina propria express this molecule, suggesting that this may be a mechanism that prevents excessive inflammatory responses.³⁸

IBD is characterized by immunoregulatory defects in the mucosa, which appear to be associated with microbial exposure. A number of theories have been advanced concerning the pathogenesis of this process: dysfunctional immune host response to normal luminal components, infection with a specific pathogen, and/or defective mucosal barrier to luminal antigens.

Dysfunctional immune host response to normal luminal components

The normal relationship between commensal bacteria and the host is symbiotic.⁴ It is hypothesized that exposure to commensal bacteria down-regulates the inflammatory genes and blocks activation of the NF- κ B pathway, thus inhibiting the inflammatory immune response of the gut to the myriad microbes and food antigens to which it is constantly exposed (Fig. 2).^{3,39,40} In IBD, this tolerance is lost. Exposure to luminal microflora now triggers an inflammatory response by the cells lining the mucosa,⁴⁰ leading to a chronic, destructive immune response.⁴¹

Mouse models demonstrate that colitis does not develop in mutant strains maintained in a germ-free environment.⁴² When a single commensal or mixed gut bacterial load is introduced, this rapidly results in mucosal inflammation.⁴³ In patients with UC, the triggers are possibly epithelial antigens or functionally altered aerobes; in CD, the antigens seem to be anaerobic bacteria and cell wall bacterial components.⁴² Contributory factors may include the continued presence of the pathogen in the intestine resulting in a chronic inflammatory response or the persistence of an immune dysfunction after resolution of the acute infection.³¹ Dysregulation may also occur as a result of alteration in bacterial function and composition.

Research suggests that genetic alterations result in varied immunoregulatory responses to the same bacteria. For example, exposure to *Bacteroides vulgatus* in an IL-10-deficient mouse results in only minimal inflammation, whereas the same bacterium causes a high expression of inflammation in a human leukocyte antigen-B27 β_2 transgenic model.^{4,14,44,45} Thus, in patients with IBD, it is likely that different bacteria are responsible for the inflammatory effect in different individuals.

Infection with a specific pathogen

To date, no single organism has been conclusively associated with the development of IBD.^{31,43} Implicated pathogens include *Mycobacterium paratuberculosis*, *M paramyxovirus*, *Listeria monocytogenes*, and *Helicobacter hepaticus*.⁴¹ A

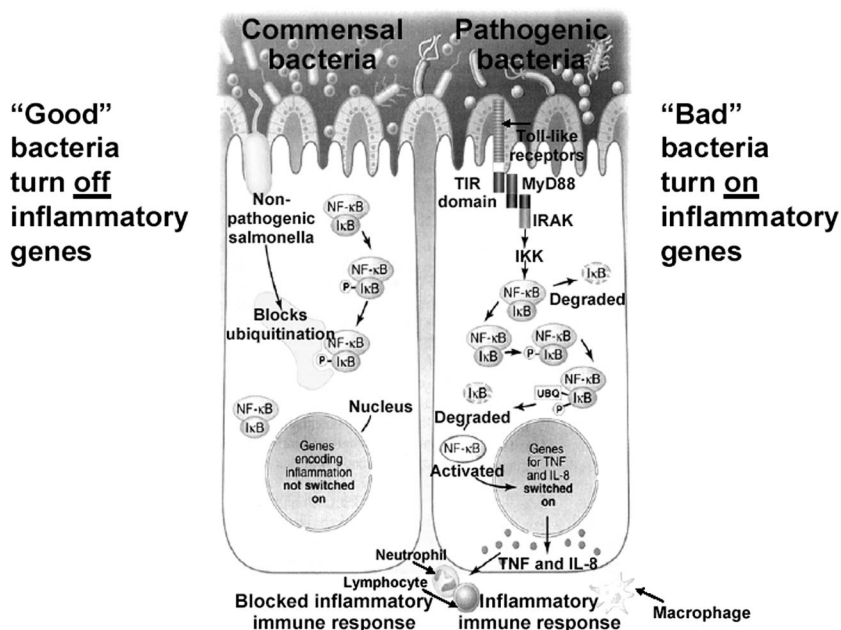


FIGURE 2. Variance in bacterial activation of the inflammatory immune response. (Left) Anti-inflammatory commensal bacteria (nonvirulent *Salmonella* strains) inhibit the NF-κB pathway via blockade of the inhibitor of NF-κB (IκB)-α degradation, which prevents subsequent nuclear translocation of the active NF-κB dimer. Although phosphorylation of IκB-α occurs, the subsequent polyubiquitination required for regulated IκB-α degradation is abrogated.⁴⁰ (Right) Pathogenic bacteria activate the NF-κB pathway. The bacteria bind to a cell-surface receptor, the toll-like receptor (TLR), which generates inflammatory factors connected to the NF-κB pathway. They stimulate intermediate kinases, leading to phosphorylation (P) of the inhibitor of B kinase (IKK) and subsequent dissociation of NF-κB. NF-κB is then able to travel to the nucleus, where it turns on inflammatory genes.³ IRAK = IL-1R-associated kinase; MyD88 = myeloid differentiation factor 88; TIR domain = toll/interleukin-1 receptor; UBQ = ubiquitination. Adapted from *N Engl J Med.* 2002;347:417; *Nature.* 2000;406:768; *Science.* 2000;289:1560.

number of reports suggest a link between CD and early measles infection.³¹

Support for infection by ≥ 1 specific pathogens as being causative of IBD includes seasonal variations in onset and documented flare-ups in conjunction with viral, bacterial, and parasitic infections.¹⁴ The higher incidence of IBD in winter implicates an infectious agent.

Defective barrier function

IBD is associated with increased permeability of the epithelial lining of the gut resulting in continuous stimulation of the mucosal immune system. It has been suggested that this may be the primary defect in individuals with IBD. Animal studies show a tendency for the development of severe inflammation in areas of the intestine lying beneath the permeability defect.³⁰ Luminal bacteria appear to intensify the permeability defect further, establishing a self-sustaining cycle of mucosal inflammation that allows for uptake and translocation of bacteria.¹⁴

In humans, the lumen typically contain 10¹⁴ organisms belonging to 30 known genera and >500 species.⁴⁶ Healthy epithelium, with its highly evolved tight junctions, normally provides an effective barrier against luminal microbes and antigens. Also, the intestinal epithelial cells have developed control mechanisms that limit inappropriate activation of immune responses. If, however, bacterial products are able to cross the mucosal barrier, then they will come into direct contact with immune cells, resulting in a classic adaptive immune response.^{3,4} A variety of inflammatory cytokines are produced, recruiting additional cells into the intestine wall. These include cytokines that reduce the tight junctions between the

endothelial cells in the gut vasculature, which in turn facilitates recruitment of neutrophils to the mucosa from the peripheral blood.³

PATHOLOGY OF MUCOSAL INFLAMMATION

There are many roads to colitis. Whatever the trigger, neutrophils are early responders to all types of insult and play a central role in the inflammatory process. During the initial innate immune response, they are seen passing from the circulation through gaps in the vascular endothelium to infiltrate the tissues. Once there, neutrophils release antimicrobial peptides and reactive oxygen intermediates that may in themselves cause further tissue damage. Neutrophils also recruit and activate other white blood cells (e.g., macrophages) through the production of chemokines and the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8.⁴⁷ In IBD, the characteristic tissue damage and granuloma formation may be in part the end result of neutrophil migration and degranulation.

There is evidence that the cell-mediated arm of the adaptive immune response occurring in IBD may subsequently follow 1 of 2 pathways: an excessive T helper 1 (T_H1) response, which is associated with CD; or an excessive T_H2 phenotype, linked to the development of UC (Fig. 3).^{3,30,48,49} Activation of undifferentiated T cells—the principal conductors of the immune response—is precipitated by antigen-presenting cells such as macrophages and dendritic cells. Secretion of cytokines influences maturation (e.g., to become T_H1 cells); this is presumably under genetic and environmental influence.⁴

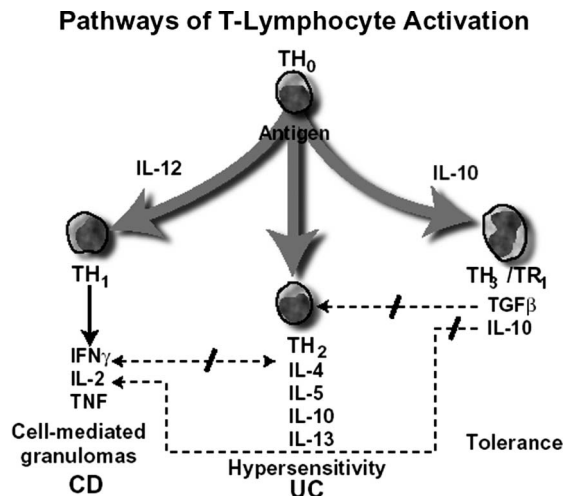


FIGURE 3. Pathways of T-lymphocyte activation. CD is associated with a T_H1 cell phenotype, which is mediated by IL-12 and characterized by production of interferon (IFN)- γ , IL-2, and TNF. UC is associated with an atypical T_H2 phenotype, which is characterized by production of IL-4, IL-5, IL-13, and other cytokines.^{48,49} Activation of both T_H1 and T_H2 cells may be enhanced by concomitant decrease in subgroups of suppressor T cells, T_H3 , or T regulatory cell-1 (T_R1), which are mediated by IL-10. This subgroup, which is associated with oral tolerance, produces down-regulatory cytokines IL-10 and TGF- β , which can act on cytokines released by the effector T cells. Decreases in these suppressor T cells may lead to unchecked inflammatory responses.^{3,30} Adapted from *N Engl J Med.* 2002;347:417; *Nat Rev Immunol.* 2003;3:521; *J Exp Med.* 2002;195:1129; *J Clin Invest.* 2004;113:1490.

T helper cells are mediators of inflammation producing different patterns of cytokines.³¹ Overproduction of IL-12, a macrophage-derived cytokine, shifts the immune response in a T_H1 direction. This response is characterized by increased production of interferon- γ , TNF- α , IL-1 β , IL-2, and IL-6,^{4,30,31,50} resulting in a self-sustaining cycle of activation.³ An excessive T_H2 cell response is associated with increased secretion of IL-4, IL-5, IL-10, and IL-13. T_H2 cells also support a humoral immune response.³¹

It is also speculated that mucosal inflammation may result from a defect in the mature T cells, the T_H3 , and T regulatory 1 (T_R1) cells, suppressor cells that produce transforming growth factor (TGF)- β , IL-10, and other immunoinhibitory cytokines. Such a defect would precipitate loss of tolerance to ordinary antigens in the mucosal microflora, resulting in proliferation and production of inflammatory cytokines. In support of this, experimental studies show that IL-10-deficient mice develop colitis, whereas delivery of TGF- β or IL-10 ameliorates colitis.⁴

THERAPEUTIC IMPLICATIONS

Current treatment of IBD may involve the administration of high-dose steroids, immunomodulators (e.g., azathioprine;

6-mercaptopurine), and surgery. Advances in our understanding of the pathogenesis of IBD introduce the possibility for targeted therapy to interrupt the inflammatory cascade. Emerging therapies focus on controlling the T_H1 or T_H2 cell-response pathway via inhibition of T_H1 - or T_H2 -inducing cytokines or downstream cytokines.³⁰ One possibility is the specific targeting of cytokines using monoclonal antibodies (e.g., the antibody that binds to TNF). Another approach is to block the cell-signaling pathways associated with activation of lymphocytes and macrophages using agents that affect NF- κ B.³

An exciting option now being explored in the United States is the removal of leukocytes from peripheral blood via apheresis in an effort to reduce an excessive inflammatory response. Apheresis, a well-established treatment strategy in Japan and Europe for both UC and CD, filters out many of the circulating inflammatory cell types that are activated in UC and CD. Prevention of neutrophil and macrophage infiltration into the gut mucosa may decrease granuloma formation. More than 90% of peripheral blood monocytes express TREM-1, which renders them capable of a substantial oxidative burst.³⁸ Prevention of any subsequent degranulation of these cells would short-circuit the release of the reactive oxygen intermediates and proteolytic enzymes implicated in tissue damage. This would also have the effect of decreasing the local concentrations of chemokines and proinflammatory cytokines responsible for exacerbating the innate immune response and for stimulating the adaptive immune response.

If IBD develops in response to gut bacteria, then changing the antigenic milieu offers another therapeutic option. The administration of nonpathogenic enteric organisms (probiotics), or genetically engineered bacteria that produce cytokines that down-regulate inflammation, may positively alter the luminal environment. Such agents have been explored in recent animal and human studies.⁵¹⁻⁵³

Advances in understanding the complex interplay of genetic, environmental, and immunological aspects of IBD open up the possibility for an expanded spectrum of novel therapies with targeted efficacy.

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