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Review

Inflammatory bowel disease: past, present, and future

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Crohn's disease and ulcerative colitis, collectively known as the inflammatory bowel diseases (IBD), are largely diseases of the twentieth century, and are associated with the rise of modern, Westernized industrial society. Although the causes of these diseases remain incompletely understood, the prevailing model is that the intestinal flora drives an unmitigated intestinal immune response and inflammation in the genetically susceptible host. A review of the past and present of these diseases shows that detailed description preceded more fundamental elucidation of the disease processes. Working out the details of disease pathogenesis, in turn, has yielded dividends in more focused and effective therapy for IBD. This article highlights the key descriptions of the past, and the pivotal findings of current studies in disease pathogenesis and its connection to medical therapy. Future directions in the IBD will likely explicate the inhomogeneous causes of these diseases, with implications for individualized therapy.

Key words: Crohn's disease, ulcerative colitis, inflammatory bowel diseases, medical therapy, pathogenesis

Past: the era of description

In the beginning, medical science was capable of describing the features of inflammatory bowel disease (IBD), and medical therapeutics were guided by trial and error, misguided hypotheses about disease pathogenesis, and some measure of serendipity. Crohn's disease and ulcerative colitis—the two major forms of idiopathic IBD—have been recognized as distinct disease entities for over a century. As early as 1761 Morgagni described intestinal inflammation that in modern times we would recognize as Crohn's disease.[1] After the identification of the causative agent of tuberculosis by Koch in 1882, it became clear that some individuals had a disease similar to intestinal tuberculosis but did not bear the tubercle bacillus. Reports by Fenwick in 1889, Dalziel in 1913, Weiner in 1914, Moschowitz and Wilensky in 1923 and 1927, and Goldfarb and Suissman in 1931 predated the landmark publication of Crohn, Ginzburg, and Oppenheimer in 1932 describing terminal ileitis.[1,2] Later, Lockhart-Mummery and Morson[3] described granulomatous colitis, and the disease process was understood to potentially affect the large bowel as well. Thus, phenotypic distinction from ulcerative colitis was established. The historical origins of ulcerative colitis are less clear, with descriptions of bloody diarrhea and dysentery dating back to antiquity. Generally, however, Wilkes is credited with the first pathologic description of what was called simple ulcerative colitis in 1859.[1] Subsequently, in 1875, Wilkes and Moxon described a syndrome of simple ulcerative colitis in greater detail.[1]

With the recognition of the nosologic distinctions of these diseases came attempts to treat them surgically and medically (Table 1). Depending upon the etiologic concept of the disease, various therapies were attempted. For example, many conceived of the disease as being caused by an as yet unrecognized pathogen. Accordingly, treatments have included potassium permanganate, Dakin's solution, antidysentery serum, *Escherichia coli* vaccine, antiamoebic drugs, and sulfonamides.[1] These treatments did not prove to be durable or effective, and have all been abandoned over time. Sulfasalazine, the first truly effective agent used in IBD, was discovered serendipitously when this antirheumatic agent was observed to produce resolution of both diarrhea and arthralgias in patients with ulcerative colitis being treated with this agent for their joint disease.

Further experimentation revealed that the active moiety of sulfasalazine was 5-aminosalicylate (5-ASA),

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Table 1. Inflammatory bowel disease landmarks of the past

- Distinction of Crohn's disease and ulcerative colitis from infectious colitis made possible by the development of bacteriologic techniques
- Distinction between Crohn's disease and ulcerative colitis drawn
- The inflammatory bowel diseases are understood to be immune-mediated diseases
- Sulfasalazine and hydrocortisone used to treat ulcerative colitis
- Thiopurine agents (mercaptopurine and azathioprine) used to treat IBD
- Methotrexate used to treat Crohn's disease and cyclosporine used to treat severe, steroid-refractory ulcerative colitis
- Familial clustering implicates genetic factors in IBD
- Bowel-sparing understood to be a key principle of surgical therapy, and the technique of stricturoplasty developed
- Ileal pouch–anal anastomosis developed as an alternative to ileostomy after total proctocolectomy for ulcerative colitis

IBD, inflammatory bowel disease

whereas the sulfa moiety was responsible for many of the untoward effects of the drug.[4] Furthermore, delivery of the active 5-ASA molecule was finally understood to rely upon the presence of the diazo bond between the sulfapyridine and 5-ASA moieties for the delivery of the 5-ASA to the distal bowel upon cleavage of the bond by the colonic flora.[5] Subsequently, a host of second-generation 5-ASA agents were developed that utilized a variety other mechanisms to deliver the drug topically to the distal bowel. These have included time-released and pH-dependent agents, as well as non-sulfa-containing diazo-bonded agents such as olsalazine and balsalazide.

The descriptive histology of IBD suggested that immune activation could also be targeted by therapeutic agents. The observation of acute and chronic inflammatory cells, and the common occurrence of extraintestinal immune-mediated manifestations eventually led to the use of adrenocorticotropic hormone[6] and corticosteroids,[7] which have proven to be highly effective in treating these diseases. The first randomized controlled trial of hydrocortisone in ulcerative colitis proved the agent to be remarkably effective,[8] and finally produced effective therapy for severe ulcerative colitis, which previously had been associated with a considerably high case fatality rate.

Nevertheless, the corticosteroids have proven to be a double-edged sword in the treatment of IBD. Evidence from population-based cohorts suggests that although less than half of patients with IBD require treatment with these agents, the need for corticosteroids is associated with a worse prognosis, including increased risk of surgery and risk of disability.[9] In all, slightly more than half of individuals treated with glucocorticoids will be well and off steroids at 1 year after beginning these agents.

Consequently, more potent immunomodulatory agents were explored for the treatment of IBD. Mercaptopurine and azathioprine were initially disappointing in clinical trials in Crohn's disease until appropriate dosing and duration of therapy were more fully explicated. With the landmark study of Present et al.,[10] mercaptopurine and azathioprine assumed their place in the IBD armamentarium as treatments primarily for patients who were steroid-refractory or steroid-dependent. These agents are also thought to be effective in fistulizing Crohn's disease.[11] More recently, these agents have been more fully accepted as appropriate therapies for the treatment of steroid-dependent to -refractory ulcerative colitis, as well.[12] A second-line agent shown to be effective in steroid-dependent Crohn's disease is methotrexate. This agent is effective both in the short term, to induce steroid-free remission,[13] and in the long term, to maintain remission.[14]

Immunosuppressive therapy progressed further as increasingly potent agents became available. The introduction of cyclosporine for treatment of severe, steroid-refractory ulcerative colitis has provided an alternative to total proctocolectomy for some individuals.[15] However, the narrow therapeutic margin of this agent has precluded widespread application, and in the United States its use remains confined largely to tertiary-care referral centers. Cyclosporine appears to be most effective when used as a bridge to maintenance therapy with mercaptopurine or azathioprine.[16] The continued role of this agent becomes less certain with the advent of potent biologic agents effective in severe ulcerative colitis.

Surgical advances have also advanced the field significantly. The earliest surgeries for Crohn's disease often sought to divert the fecal stream by bypassing surgery, rather than resection. Although effective, this technique has long been out of favor, with resection and primary anastomosis possible for the majority of patients with Crohn's disease. More directly applicable to the optimum care of patients was the appreciation that wide margins of resection were not effective in preventing disease recurrence.[17] The important principle of bowel preservation in Crohn's disease became favored in an effort to prevent short-bowel syndrome from repeated small-bowel resections. This principle of sparing the small bowel was carried further with the development of stricturoplasty techniques.[18] Finally, the development in the 1980s of ileal pouch–anal anastomosis for patients

Table 2. Landmarks of the present

- Controlled physiologic inflammation is understood to result from the normal state of immune tolerance in the intestine
- Development of genetic animal models of colitis demonstrate diverse disturbances of immunity and intestinal barrier function capable of inducing a phenotype of gut inflammation
- Animal models demonstrate the central role of gut flora as a necessary factor in colitis, with the flora further implicated in serologic studies in humans
- *NOD2/CARD15* demonstrated as the first disease-associated gene in Crohn's disease after IBD1 localized to chromosome 16 by genomewide scanning
- Defective innate immune response implicated in Crohn's disease by NOD2 physiology
- Biologic agents developed through monoclonal antibody technology and molecular biology techniques
- Infliximab, the first of a new class of anti-TNF biologics, shown to be effective in Crohn's disease and ulcerative colitis
- The heterogeneity of Crohn's disease and ulcerative colitis demonstrated in genetic and serologic studies

TNF, tumor necrosis factor

with ulcerative colitis who required total proctocolectomy was a revolutionary surgical advance that has provided a much needed alternative to permanent endileostomy.[19]

Present: the era of explanation

At present, key concepts regarding the pathogenesis of inflammatory bowel disease are as follows (Table 2). First, it is recognized that immune tolerance is the normal state of the intestinal immune system. Second, it is apparent that a wide variety of cell types are orchestrated in a tightly regulated fashion to maintain immunologic tolerance. At the same time, the capacity to mount an immune and inflammatory response within the mucosa is maintained. Third, the luminal flora is a key ingredient in the abnormal immune response of IBD. Fourth, genetic factors predispose individuals to an abnormal immune response to the flora. Finally, it is recognized that both the innate and adaptive immune responses play integrated roles in the homeostasis of the intestinal mucosal immune response.

For many years it has been recognized that the intestinal mucosa contains a resident population of inflammatory cells. These cells are poised at the interface between the intestinal lumen and the systemic circulation in readiness for enteric infection and other insults to the mucosa. When such an incursion occurs, the inevitable response is inflammation. The key factor that differentiates individuals with IBD from normal individuals is the ability to downregulate that inflammatory state and return it to a condition of normal, controlled gut inflammation. By contrast, individuals susceptible to IBD will tend to enter a state of uncontrolled and chronic inflammation with failure to downregulate the inflammation caused by the insult.

Genetics have long been known to play a role in the susceptibility to IBD. Historically, it has been recognized that approximately one in five individuals newly diagnosed with IBD will report a family history. In addition, first-degree relatives, in particular siblings, are at increased risk of IBD, and this risk is somewhat higher in individuals of Ashkenazi Jewish background.[20] Third, there is a high concordance for Crohn's disease among monozygotic twins, whereas a somewhat lesser concordance is observed in monozygotic twins with one affected individual with ulcerative colitis.[21] These clues have long suggested that genetics play an important role in susceptibility to the inflammatory bowel diseases.

Environmental contributions to the pathogenesis of IBD have also long been suspected. For many years, predominant theories have surrounded the notion that the mucosal inflammation of IBD is an appropriate response to pathogenic microbiota.[22] Candidates for pathogenic agents have been diverse over the years, and have included *Diplostreptococcus*, *Entamoeba histolytica*, and, most persistently, *Mycobacterium paratuberculosis.*[23] More recently, lines of evidence suggest that normal, nonpathogenic flora (at least in the conventional sense of pathogenicity) are a necessary though not sufficient factor in the pathogenesis of IBD, whereas firm evidence of a pathogenic agent has been lacking.

In addition to the host flora, other environmental factors have been noted to affect the expression of IBD. These factors may be considered to be disease modifiers, and most prominently include smoking,[24] nonsteroidal anti-inflammatory drugs,[25] and prior appendectomy.[26] In particular, both smoking and appendectomy have been recognized to be distinct risk factors with dichotomous outcomes for Crohn's disease and ulcerative colitis. Smoking has been associated with increased risk of Crohn's disease as well as worse outcomes over the course of the disease,[27] whereas for ulcerative colitis, smoking has been recognized as having a protective effect.[28–30] The effects of tobacco smoke are complex and poorly understood. The role of smoking does not appear to be as simple as the presence or absence of nicotine, which may be an effective therapy for ulcerative colitis but is poorly tolerated.[31] Current investigation focuses on the role of carbon monoxide in

smoke as a factor capable of modifying the expression of inflammation in the gut.[32]

Circumstantial evidence has long pointed to the critical role of the luminal flora in IBD. The evidence is strongest in Crohn's disease and relatively sparse in ulcerative colitis. In clinical practice antibiotics are widely used to treat perianal disease in Crohn's disease.[33] Evidence from clinical trials suggests some effect of antibiotic therapy as a treatment for Crohn's disease, primarily in disease with colonic localization.[34] In addition, imidazole antibiotics such as metronidazole[35] and ornidazole[36] have been demonstrated reproducibly to have a prophylactic effect for disease recurrence after ileal resection. Furthermore, as noted above, a time-honored, though outmoded technique to treat refractory Crohn's disease has been to surgically divert the affected segment. Experiments carried out in the 1980s demonstrated that the luminal contents contained factors, most likely bacterial factors, capable of reinducing inflammation in quiescent diverted bowel.[37] In addition, elemental diet has been demonstrated to be an effective therapy for Crohn's disease.[38] Effects of elemental diet may be complex, but are thought to include a favorable effect on the bowel flora composition that may minimize immunologic stimulation of the host immune response. Another line of research being vigorously pursued is the potential role of probiotic therapies as treatments for IBD. Thus far, clinical trials in humans have not demonstrated a robust effect of these agents in IBD. The clearest demonstration of benefit has been with a preparation known as VSL#3 in the treatment and prophylaxis of pouchitis occurring in ileal pouches created as curative therapy for ulcerative colitis.[39,40] Other studies have suggested modest benefit in ulcerative colitis and Crohn's disease for a variety of probiotic agents, including Nissle 1917 and VSL#3.[41,42] Finally, one intriguing study demonstrated excessive responsiveness of lamina propria mononuclear cells to autologous gut bacteria among patients with IBD.[43]

Animal models of colitis have also provided essential clues to the role of the luminal flora in the pathogenesis of IBD. The list of genetic and acquired aberrations that culminate in phenotypic manifestations of intestinal inflammation is strikingly long and diverse.[44] These models include animals with disturbed immune regulation, such as the interleukin (IL)-2, T-cell receptor α and IL-10 knockouts, as well as models where disruption of the epithelial barrier function is paramount, such as the G2αi knockout mouse. The sheer diversity of abnormalities that drive intestinal inflammation reminiscent of human IBD suggests that the gut has a limited phenotypic repertoire and is capable of expressing such disturbances in only a limited number of ways. The corollary is that human IBD may also be two phenotypic syndromes driven by diverse genetic abnormalities. This is clearly suggested by observations of genetic and serologic heterogeneity among individuals diagnosed with ulcerative colitis or Crohn's disease.[45–48]

In addition, the role of the intestinal flora in driving gut mucosal inflammation has been clearly demonstrated in these diverse models. In every model thus far explored, it is clear that removing intestinal flora from the equation by raising animal lines in gnotobiotic conditions greatly diminishes or prevents the onset of gut inflammation. With the introduction of nonpathogenic bacteria, each of these models then proceeds to manifest their typical phenotype of colonic inflammation. It does not appear to be the case that pathogenic microbiota are necessary to drive the disease. Furthermore, it has become clear that the characteristics of the intestinal flora also shape the phenotypic characteristics of the gut inflammation. For example in the HLA B27 transgenic rat, monoassociation experiments with single, nonpathogenic bacterial species have been performed. The introduction of *Bacteroides vulgatus* results in a moderately severe colitis, whereas the introduction of *E. coli* results in no colitis whatsoever. Colonization with the entire mixture of the usual bacterial flora present in the cecum culminates in an aggressive colitis, whereas the introduction of cecal bacteria plus the probiotic species *Lactobacillus GG* results in protection from colitis altogether.[49] These experiments suggest that specific nonpathogenic bacteria may shape the expression of disease severity in profound ways.

Surprisingly, it also appears that specific nonpathogenic bacteria may also be a determinant of anatomic disease localization. IL-10 knockout mice grown in germ-free conditions do not typically manifest colitis. With the introduction of commensal flora, the typical colonic inflammatory phenotype ensues. However, when monocolonization with *Enterococcus faecalis* occurs, a left-sided colitis ensues. Alternatively, upon colonization with *E. coli*, a distinctly right-sided colitis occurs.[50] Together, these findings suggest that the composition of the commensal flora may have a major impact on the phenotypic expression of IBD.

It cannot be assumed that the genetic aberrations in gene knockout or knock-in models of colitis are reflective of the actual genetic polymorphisms that cause human disease. However, great strides have been made in the identification of genetic defects associated with Crohn's disease and ulcerative colitis. The inflammatory bowel diseases have long been understood to be complex polygenic diseases. The greatest progress has been made to the application of genomewide scanning, which has been greatly facilitated by the development of microsatellite markers and more recently single-nucleotide polymorphism (SNP) haplotype maps of the human genome. With the collaboration of numerous genetics research groups across the globe, specific genetic loci with

strong associations with IBD have been discovered.[51] This approach is distinct from the candidate gene approach, which explores genetic polymorphisms in a gene that is predicted to be of particular interest by virtue of its known function. Rather, the greatest progress has been made by an unbiased appraisal of the human genome afforded by genomewide scanning. Using these techniques, the first such IBD gene identified was the *NOD2/CARD15* gene on chromosome 16, associated with the IBD1 locus found on genomewide scanning.[52–54] Specific disease associated polymorphisms included the R702W, G908R, and Δ33 mutations associated with relative risks for Crohn's disease of 14.3, 34.1, and 17.64 for homozygous recessive individuals over control populations.[52–54]

Explication of the cellular function of NOD2 has shed light on the nature of the underlying immune defects of Crohn's disease. NOD2 (nuclear type binding oligomerization domain 2) consists of two CARD domains, followed by a NOD domain, and ending in a leucine-rich repeat. It is within the leucine-rich repeat domain that the disease-associated mutations have been noted. These are loss-of-function mutations, which appear to prevent the binding of muramyl dipeptide, which is ubiquitously present in virtually all bacterial cell walls.[55] Downstream events lead to the activation of NFκB through an interaction with the CARD domains.[56] Thus, it appears that NOD2 is intimately involved in intracellular bacterial sensing and generation of the innate immune response.[57]

Less certain is how a loss-of-function mutation in the leucine-rich repeat causes the inflammation of Crohn's disease. Although many hypotheses have been generated regarding the mechanism of disease, none have been conclusively proven. One hypothesis is that with the loss of binding of muramyl dipeptide to NOD2, there is a compensatory response with failure to inhibit the activation of c-Rel and p50 by binding of peptidoglycan to the toll-like receptor 2.[58] This results in the downstream activation of IL-12 and consequent inflammation.

Regardless of the precise mechanism through which NOD2 polymorphisms generate a Crohn's disease phenotype, this discovery has brought the role of the innate immune responses to the fore. The innate immune responses are the hardwired and immediate responses to pathogens that occur through binding of pathogen-associated molecular patterns to cell-bound receptors. The critical cellular elements in this response include macrophages, NK cells, and nonprofessional antigen-presenting cells. By contrast, much research of the last 20 years has focused on the adaptive immune system. The adaptive immune responses require priming and the generation of antigen-specific responses by B and T cells, and therefore may not be immediate. Although cell-to-cell surface interactions may occur, soluble factors may also play a role in adaptive immune responses.

The dendritic cells of the gut have become a focal point in our understanding of intestinal immune responses.[59] Elegant immunofluorescent microscopic techniques have demonstrated large populations of dendritic cells localized just beneath the intestinal epithelial cells.[60] These arborized cells project long podocytes through the interstices of the intestinal epithelial cells and out to the intestinal lumen. Here, extensive sampling of luminal antigens occurs. It is believed that the dendritic cells process these antigens, and then present them to the cells in the Peyer's patches as well as in the mesenteric lymph nodes. Depending upon the nature of the antigen and the activation state of the dendritic cell, the end result may be immune activation or tolerization. Enterocytes may also present antigen, also likely leading to tolerization,[61] whereas pathogenic microbes traversing M cells to the underlying Peyer's patches are likely to trigger immune activation.[62]

In parallel to the growing importance of the innate immune system came the first studies of therapies intended to enhance the innate immune responses, rather than to suppress adaptive immune responses. Korzenik and Dieckgraefe[63] reexamined data from the 1970s and 1980s that suggested that neutrophil responses were diminished in patients with Crohn's disease. In addition, they noted that varied conditions characterized by neutrophil defects are also commonly associated with Crohn's disease or a Crohn's disease-like phenotype. They reasoned, therefore, that individuals with Crohn's disease may also have neutrophil defects, and that stimulating neutrophils may be beneficial in the treatment of Crohn's disease. This hypothesis led them to test granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage (GM)-CSF in open-label pilot trials in Crohn's disease, with promising early results.[64,65] A subsequent phase 2 study of sargramostim (GM-CSF) in Crohn's disease demonstrated evidence of activity of this agent in decreasing symptoms of active disease.[66] Unfortunately, a phase 3 study failed to demonstrate efficacy over placebo, although a separate study demonstrated efficacy of this agent in steroid sparing.[67]

More detailed descriptions of the immunologic pathways of the adaptive immune responses in Crohn's disease and ulcerative colitis have also led to new and specific therapeutic agents. In the early 1990s, animal models of immunologic disease demonstrated that T helper (Th) cell populations segregated according to distinct cytokine profiles.[68] Th_1 cells are characterized by the expression of IL-2, interferon-γ, IL-12, and tumor necrosis factor (TNF) α. Th_1 responses are most closely associated with the cell-mediated immune responses that characterize Crohn's disease.[69] By contrast, Th_2 responses are associated with humoral immunity and with

a cytokine profile comprising IL-4, IL-5, IL-6, and IL-13. The cytokine profile expressed in ulcerative colitis tissues is most consistent with a variation on Th_2-like immune responses, lacking in the expression of IL-4.[69]

Understanding the role of cytokines has been a critical advance in IBD therapeutics, along with the advent of monoclonal antibody technology, which made possible the targeted inhibition of specific disease-related cytokines. Furthermore, it has been possible to give inhibitory cytokines as therapeutic agents. Clearly, the greatest advance in this area has been the advent of anti-TNF biologic therapies.

Early reports from the Netherlands described two cases of Crohn's disease treated with a chimeric monoclonal anti-TNF antibody called cA2.[70] This was followed by a case series of ten patients with Crohn's disease, who experienced a high rate of response and rapid mucosal healing on endoscopy.[71] The first randomized controlled trial by Targan et al.[72] demonstrated that short-term induction occurred rapidly and in the majority of patients with active disease unresponsive to other therapies. However, the majority of patients relapsed at a median time of 8 weeks. This, in turn, necessitated the investigation of strategies for maintaining response. The ACCENT I[73] and ACCENT II[74] studies demonstrated the ability to maintain a durable response in a subset of patients with nonfistulizing and fistulizing Crohn's disease, respectively, over the course of a year of follow-up.

One of the drawbacks of chimeric monoclonal antibody therapy has been the generation of immune responses against the drug and loss of response. Newer agents have been developed with ostensibly more human protein sequence and structure. These include adalimumab, a fully human anti-TNF antibody,[75] and certolizumab, a pegylated F_{ab} anti-TNF fragment.[76] Whether these agents are less immunogenic than infliximab is as yet uncertain. However, findings of long-term studies lasting from 6 to 12 months suggest that the efficacy of these agents is equivalent to that seen with infliximab.[77,78] Other issues with the anti-TNF biologics relate to weighing the risks and benefits of these agents for specific patients.[79] Described risks include rare occurrence of opportunistic infections, including intracellular infections such as tuberculosis and fungal and viral infections, demyelinating disorders, and rare reports of lymphoma.[80] It will be critical to define populations for whom these risks are appropriate, or alternatively to identify patients at least risk for developing these complications.

Other cytokine-directed therapies are at earlier stages of development. Randomized controlled trials with daily subcutaneous injections of IL-10 provided disappointingly negative results.[81] This result was unexpected after initially promising phase 2 studies, and especially given that the preclinical rationale of using this classic inhibitory cytokine was quite strong. In addition, studies using the humanized anti-IL-2 receptor antibody daclizumab showed this agent to be ineffective as a treatment for ulcerative colitis.[82] Early studies with anti-IL-12 antibody appear to demonstrate some activity in active Crohn's disease.[83] This agent, which binds to epitopes in the p40 subunit of IL-12, may also bind to the same subunit as a component of the heterodimeric proinflammatory cytokine IL-23. Of note, the IL-23 receptor gene was recently associated with Crohn's disease; namely, polymorphisms in this gene appear to confer protection against the disease.[84] This would suggest that agents that inhibit IL-23 may prove to be effective in Crohn's disease.

A second area where understanding of the pathogenesis has led to novel therapies is in the area of cellular adhesion and recruitment. Although a normal state of physiologic inflammation exists in the mucosa of the bowel, it is only through the coordinated expression of specific adhesion molecules that cells are recruited from the peripheral circulation into the mucosa in response to inflammation. In the early 1990s, the details of cellular recruitment and adhesion were explicated in fine detail.[85] When inflammation is present within a tissue, a series of events occur in rapid succession. First, the endothelium becomes activated, and the expression of E- and P-selectins on the endothelial surface expression occurs. L-selectin on the cell surface of leukocytes in circulation binds weakly to the selectins expressed on the endothelium. This, in turn, causes rolling of the leukocyte along the endothelial surface and activation of integrin expression on the leukocyte surface.[85] The integrins then bind tightly to cellular adhesion molecules such as VCAM, ICAM, and MAdCAM[86] on the endothelial surface. Finally, the leukocytes diapedese into the mucosa. Here, chemokines exist in a gradient within the mucosa, guiding the leukocytes further toward the mucosal surface. Thus, adhesion and recruitment of leukocytes is a complex and critical process in inflammation that offers many potential targets for specific interventions against inflammation.

The first agent to have targeted adhesion was the humanized anti-α4 integrin antibody natalizumab. A large phase 2 study of natalizumab in Crohn's disease appeared to demonstrate short-term activity but failed to meet its primary end point in a statistically significant way.[87] A follow-up phase 3 study again demonstrated activity of this agent, but missed its primary end point, in large part owing to a high placebo response rate.[88] However, a follow-on study demonstrated robust maintenance efficacy with natalizumab.[88] An additional short-term study finally confirmed the efficacy of natalizumab among patients with elevated C-reactive protein.[89] Unexpectedly, however, three cases of progressive

multifocal leukoencephalopathy (PML), an otherwise extremely rare and usually fatal central nervous system disease caused by the JC virus, were found among 3000 patients treated for either multiple sclerosis or Crohn's disease with this agent.[90]

A second selective adhesion molecule inhibitor, MLN-02, has been demonstrated in a phase 2 study to be efficacious in patients with active ulcerative colitis failing treatment with 5-aminosalicylates.[91] A second pilot study was performed in Crohn's disease with promising effect.[92] At this time, it is unknown if the more specific adhesion of this antibody to $\alpha 4\beta 7$ integrin, the ligand of MAdCAM (mucosal addressin cellular adhesion molecule, located only in gut endothelium), will improve the safety profile of this agent and avoid the occurrence of PML.

A third area of interest for therapeutic intervention is the process of T-cell activation. The interactions between antigen-presenting cells and T cells may be conceived of as being analogous to a neurological synapse. As with the neuronal synapse, a variety of stimulatory and inhibitory signals are integrated when the antigen-presenting cell interacts with a T cell, yielding a net overall effect of activation or inhibition of the immune response.[93,94] The basis of the antigen-specific response occurs with the presentation of an antigenic epitope in the context of major histocompatibility complex (MHC) class II. MHC class II/antigen binds to the T-cell receptor CD3 in an antigen-specific fashion. However, this primary signal is not sufficient in itself to activate the na ve T cell. Rather, the presence of a costimulatory signal is necessary for activation to occur. These include binding of TNF receptor to TNF on the cell surface, CD40 ligand to CD40, and B7 to the costimulation receptor CD28.[94] When such costimulatory signals are lacking, the end result is anergy or apoptosis of the T cell rather than activation.

Both the antigen-specific interaction of MHC class II-CD3 and the costimulatory signals offer opportunities for therapeutic intervention. The humanized anti-CD3 antibody visilizumab has been explored as a treatment for refractory ulcerative colitis.[95] Open-label studies suggest that this agent may be efficacious even in situations where disease is severe and unresponsive to steroids. Visilizumab is highly potent, with activity seen at doses as low as 5 μg per kilogram. A cytokine-release syndrome has been observed with this agent. The long-term safety consequences of lysing activated T cells have yet to be determined, as studies have been relatively small and of short duration.

Other strategies have attempted to target the costimulatory signal rather than the T-cell receptor. An alternative costimulatory interaction of some interest is the binding of CD28 to B7. Abatacept is a fusion molecule of CTL4 and immunoglobulin, known as CTLA-Ig.[96] This agent is approved in the United States for the treatment of rheumatoid arthritis and has been shown to be effective in patients who have not responded to anti-TNF biologic agents in that disease state.[96] In principle, this agent would be of considerable interest as a potential therapy for IBD.

As yet untapped are therapies that might exert therapeutic effect by enhancing regulatory T cells as opposed to inhibiting effector T cells. There is a growing appreciation for various populations of T cells that exert a downregulatory effect on immune responses and do so through a variety of mechanisms. Distinct populations have been recognized as including Tr1 cells, characterized by elaboration of IL-10,[97] Th3 cells,[98] characterized by membrane-bound transforming growth factor β, and CD4+ CD25+ T regulatory cells, which inhibit through direct cell-to-cell contact.[99] The earliest exploration of this therapeutic principle may involve the selection and engineering of T cells to deliver IL-10.[100] The clinical efficacy and safety of this approach is as yet unknown.

In summary, in recent times we have learned that the intestinal flora is critical in generating the immune response of IBD. In Crohn's disease, the innate immune response appears to be defective in some patients. An excess of effector T cells, characterized as either Th1- or Th2-like, is associated with the distinct clinical manifestations of Crohn's disease and ulcerative colitis, respectively. We have teased out cytokine pathways that shape and perpetuate inflammation. The process of leukocyte adhesion and recruitment has been worked out. T regulatory responses have been shown to be deficient in IBD. These detailed explanations of the pathogenesis of IBD have led to more effective and focused treatments for these diseases.

Future: the era of prediction

Increasingly, we are entering a time when high-throughput technologies are revolutionizing the approach to medical discovery. No longer are candidate proteins and genes laboriously discovered and evaluated in isolated systems. High-throughput DNA sequencers are capable of sequencing an individual genome in days rather than years. Gene expression arrays simultaneously represent the expression of thousands of transcripts rather than a handful at a time. Mass spectrometry combined with other techniques permits the simultaneous determination of thousands of proteins in a burgeoning area known as proteomics. Hundreds of metabolites can be determined in biologic specimens through the methodologies of metabolomics. Nonclassical microbiologic techniques based upon molecular biology will facilitate an improved understanding of the role of the gut flora in IBD.

The completion of the Human Genome Project and SNP haplotype mapping[101] have made it possible to examine individual genotypes in relation to disease susceptibility as well as disease characteristics and prognosis. Rather than starting from a prior hypothesis about a single gene, protein, or metabolite playing a role in the disease process, unbiased explorations of all possible biologic variations may be explored. Advances in bioinformatics and the ability to integrate the volumes of data generated by such experiments will be critical in allowing medicine to progress to the point where personalized medicine may become fact rather than aspiration.

When these new techniques have been more fully applied to the problems of patients with IBD, it is likely that we will improve both prediction of individual prognoses for the disease, as well as be able to target therapy to the mechanism of disease. We will no longer blithely talk about curing Crohn's disease or ulcerative colitis; rather, it is very likely that we will talk about very specific cures for each one of the many varied genetic or acquired aberrations that cause the Crohn's disease or ulcerative colitis phenotype. We will also finally elucidate the environmental factors that have contributed to the rise of these diseases in Westernized societies.

In summary, a survey of the past and present advances in the inflammatory bowel diseases provides much cause for optimism. The accelerating pace of discovery in Crohn's disease and ulcerative colitis provides hope that each year will bring a better life to the growing number of individuals who suffer from these curious diseases.

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References

1. Kirsner JB. Historical origins of current IBD concepts. World J Gastroenterol 2001;7:175–84.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. 1932. Mt Sinai J Med 2000;67: 263–8.
3. Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. Gut 1960;1:87–105.
4. Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977;2:892–5.
5. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. J Pharmacol Exp Ther 1972;181:555–62.
6. Kaplan HP, Portnoy B, Binder HJ, Amatruda T, Spiro H. A controlled evaluation of intravenous adrenocorticotropic hormone and hydrocortisone in the treatment of acute colitis. Gastroenterology 1975;69:91–5.
7. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet 1974;1:1067–70.
8. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. BMJ 1955;(4947):1041–8.
9. Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994;35:360–2.
10. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981–7.
11. Korelitz BI, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. Dig Dis Sci 1985;30:58–64.
12. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut 2006;55:47–53.
13. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med 1995;332:292–7.
14. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 2000;342:1627–32.
15. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–5.
16. Arts J, D'Haens G, Zeegers M, Van Assche G, Hiele M, D'Hoore A, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004;10:73–8.
17. Fazio VW, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Ann Surg 1996;224:563–71; discussion 571–3.
18. Deutsch AA, Stern HS. Stapler stricturoplasty for Crohn's disease. Surg Gynecol Obstet 1989;169:458–60.
19. Taylor BM, Beart RW Jr, Dozois RR, Kelly KA, Phillips SF. Straight ileoanal anastomosis v ileal pouch–anal anastomosis after colectomy and mucosal proctectomy. Arch Surg 1983;118: 696–701.
20. Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. Gut 1993;34:517–24.
21. Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut 1988;29:990–6.
22. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002;347:417–29.
23. Hermon-Taylor J, Bull T. Crohn's disease caused by *Mycobacterium avium* subspecies *paratuberculosis*: a public health tragedy whose resolution is long overdue. J Med Microbiol 2002;51:3–6.
24. Odes HS, Fich A, Reif S, Halak A, Lavy A, Keter D, et al. Effects of current cigarette smoking on clinical course of Crohn's disease and ulcerative colitis. Dig Dis Sci 2001;46:1717–21.

25. Bjarnason I, Zanelli G, Smith T, Prouse P, Williams P, Smethurst P, et al. Nonsteroidal antiinflammatory drug-induced intestinal inflammation in humans. Gastroenterology 1987;93:480–9.
26. Frisch M, Johansen C, Mellemkjaer L, Engels EA, Gridley G, Biggar RJ, et al. Appendectomy and subsequent risk of inflammatory bowel diseases. Surgery 2001;130:36–43.
27. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. Gastroenterology 2001;120:1093–9.
28. Boyko EJ, Perera DR, Koepsell TD, Keane EM, Inui TS. Effects of cigarette smoking on the clinical course of ulcerative colitis. Scand J Gastroenterol 1988;23:1147–52.
29. Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. BMJ Clin Res Ed 1982;284:706.
30. Motley RJ, Rhodes J, Ford GA, Wilkinson SP, Chesner IM, Asquith P, et al. Time relationships between cessation of smoking and onset of ulcerative colitis. Digestion 1987;37:125–7.
31. McGrath J, McDonald JW, Macdonald JK. Transdermal nicotine for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2004 Oct 18;(4):CD004722.
32. Hegazi RA, Rao KN, Mayle A, Sepulveda AR, Otterbein LE, Plevy SE. Carbon monoxide ameliorates chronic murine colitis through a heme oxygenase 1-dependent pathway. J Exp Med 2005;202:1703–13.
33. Dejaco C, Harrer M, Waldhoer T, Miehsler W, Vogelsang H, Reinisch W. Antibiotics and azathioprine for the treatment of perianal fistulas in Crohn's disease. Aliment Pharmacol Ther 2003;18:1113–20.
34. Wild GE. The role of antibiotics in the management of Crohn's disease. Inflamm Bowel Dis 2004;10:321–3.
35. Rutgeerts P, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617–21.
36. Rutgeerts P, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2005;128:856–61.
37. Rutgeerts P, Goboes K, Peeters M, Hiele M, Penninckx F, Aerts R, et al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. Lancet 1991;338: 771–4.
38. Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. Inflamm Bowel Dis 2005;11: 580–8.
39. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial [see comment]. Gastroenterology 2003;124:1202–9.
40. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:305–9.
41. Fedorak RN, Madsen KL. Probiotics and the management of inflammatory bowel disease. Inflamm Bowel Dis 2004;10: 286–99.
42. Rioux KP, Fedorak RN. Probiotics in the treatment of inflammatory bowel disease. J Clin Gastroenterol 2006;40:260–3.
43. Duchmann R, Schmitt E, Knolle P, Meyer zum Buschenfelde KH, Neurath M. Tolerance towards resident intestinal flora in mice is abrogated in experimental colitis and restored by treatment with interleukin-10 or antibodies to interleukin-12. Eur J Immunol 1996;26:934–8.
44. Stadnicki A, Colman RW. Experimental models of inflammatory bowel disease. Arch Immunol Ther Exp 2003;51:149–55.
45. Arnott ID, Landers CJ, Nimmo EJ, Drummond HE, Smith BK, Targan SR, et al. Sero-reactivity to microbial components in Crohn's disease is associated with disease severity and progression, but not NOD2/CARD15 genotype. Am J Gastroenterol 2004;99:2376–84.
46. Landers CJ, Cohavy O, Misra R, Yang H, Lin YC, Braun J, et al. Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. Gastroenterology 2002;123:689–99.
47. Lodes MJ, Cong Y, Elson CO, Mohamath R, Landers CJ, Targan SR, et al. Bacterial flagellin is a dominant antigen in Crohn disease. J Clin Invest 2004;113:1296–306.
48. Mow WS, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology 2004;126:414–24.
49. Dieleman LA, Goerres MS, Arends A, Sprengers D, Torrice C, Hoentjen F, et al. Lactobacillus GG prevents recurrence of colitis in HLA-B27 transgenic rats after antibiotic treatment. Gut 2003;52:370–6.
50. Kim SC, Tonkonogy SL, Albright CA, Tsang J, Balish EJ, Braun J, et al. Variable phenotypes of enterocolitis in interleukin 10-deficient mice monoassociated with two different commensal bacteria. Gastroenterology 2005;128:891–906.
51. Ahmad T, Satsangi J, McGovern D, Bunce M, Jewell DP. Review article: the genetics of inflammatory bowel disease. Aliment Pharmacol Ther 2001;15:731–48.
52. Hampe J, Cuthbert A, Croucher PJ, Mirza MM, Mascheretti S, Fisher S, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet 2001;357:1925–8.
53. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599–603.
54. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603–6.
55. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, et al. Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. J Biol Chem 2003;278:5509–12.
56. Maeda S, Hsu LC, Liu H, Bankston LA, Iimura M, Kagnoff MF, et al. Nod2 mutation in Crohn's disease potentiates NF-kappaB activity and IL-1beta processing. Science 2005;307:734–8.
57. Girardin SE, Hugot JP, Sansonetti PJ. Lessons from Nod2 studies: towards a link between Crohn's disease and bacterial sensing. Trends Immunol 2003;24:652–8.
58. Watanabe T, Kitani A, Murray PJ, Strober W. NOD2 is a negative regulator of Toll-like receptor 2-mediated T helper type 1 responses. Nat Immunol 2004;5:800–8.
59. Bilsborough J, Viney JL. Gastrointestinal dendritic cells play a role in immunity, tolerance, and disease. Gastroenterology 2004;127:300–9.
60. Niess JH, Brand S, Gu X, Landsman L, Jung S, McCormick BA, et al. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. Science 2005;307:254–8.
61. Savidge TC, Newman PG, Pan WH, Weng MQ, Shi HN, McCormick BA, et al. Lipopolysaccharide-induced human enterocyte tolerance to cytokine-mediated interleukin-8 production may occur independently of TLR-4/MD-2 signaling. Pediatr Res 2006;59:89–95.
62. Tyrer P, Foxwell AR, Cripps AW, Apicella MA, Kyd JM. Microbial pattern recognition receptors mediate M-cell uptake of a gram-negative bacterium. Infect Immun 2006;74:625–31.
63. Korzenik JR, Dieckgraefe BK. Is Crohn's disease an immunodeficiency? A hypothesis suggesting possible early events in the pathogenesis of Crohn's disease. Dig Dis Sci 2000;45:1121–9.
64. Korzenik JR, Dieckgraefe BK. An open-labelled study of granulocyte colony-stimulating factor in the treatment of active Crohn's disease. Aliment Pharmacol Ther 2005;21:391–400.

65. Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor [see comment]. Lancet 2002;360:1478–80.
66. Korzenik JR, Dieckgraefe BK, Valentine JF, Hausman DF, Gilbert MJ, Sargramostim in Crohn's Disease Study G. Sargramostim for active Crohn's disease. N Engl J Med 2005;352:2193–201.
67. http://www.schering.de/scripts/en/50_media/2006/pi/Q3/060731_Leukine.php?n=mep accessed on 10 December 2006.
68. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today 1996;17:138–46.
69. Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol 1996;157:1261–70.
70. Derkx B, Taminiau J, Radema S, Stronkhorst A, Wortel C, Tytgat G, et al. Tumour-necrosis-factor antibody treatment in Crohn's disease. Lancet 1993;342:173–4.
71. van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, Jansen J, Tytgat GN, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 1995;109:129–35.
72. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–35.
73. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.
74. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–85.
75. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–33; quiz 591.
76. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005;129:807–18.
77. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab induces and maintains clinical response and remission in patients with active Crohn's disease: results of the CHARM trial. Gastroenterology 2006;131:950.
78. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, McColm JA, et al. Certolizumab pegol administered subcutaneously is effective and well tolerated in patients with active Crohn's disease: results from a 26-week, placebo-controlled phase iii study (PRECiSE 1). Gastroenterology 2006;130:A107.
79. Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1017–24; quiz 976.
80. Colombel JF, Loftus EV Jr, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126:19–31.
81. Schreiber S, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, et al. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. Gastroenterology 2000;119:1461–72.
82. Van Assche G, Sandborn WJ, Feagan BG, Salzberg BA, Silvers D, Monroe PS, et al. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. Gut 2006;55:1568–74.
83. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, et al. Anti-interleukin-12 antibody for active Crohn's disease. N Engl J Med 2004;351:2069–79.
84. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A Genome-Wide Association Study Identifies IL23R as an Inflammatory Bowel Disease Gene. Science 2006;314:1461–3.
85. Springer TA. Adhesion receptors of the immune system. Nature 1990;346:425–34.
86. Berlin C, Berg EL, Briskin MJ, Andrew DP, Kilshaw PJ, Holzmann B, et al. Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. Cell 1993;74:185–95.
87. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, et al. Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24–32.
88. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353:1912–25.
89. Targan S, Feagan B, Fedorak R, Lashner B, Panacionne R, Present D, et al. Natalizumab induces sustained response and remission in patients with active Crohn's disease: results from the Encore trial. Gastroenterology 2006;130:A108.
90. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005;353:362–8.
91. Feagan BG, Greenberg GR, Wild G, Fedorak RN, Pare P, McDonald JW, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med 2005;352:2499–507.
92. Feagan BG. MLN-02 Crohn's disease. Gastroenterology 2003;124:A25.
93. Paul WE, Seder RA. Lymphocyte responses and cytokines. Cell 1994;76:241–51.
94. Seder RA, Germain RN, Linsley PS, Paul WE. CD28-mediated costimulation of interleukin 2 (IL-2) production plays a critical role in T cell priming for IL-4 and interferon gamma production. J Exp Med 1994;179:299–304.
95. Katz S. Update in medical therapy of ulcerative colitis: newer concepts and therapies [erratum appears in J Clin Gastroenterol 2005;39:843]. J Clin Gastroenterol 2005;39:557–69.
96. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114–23.
97. Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature 1997;389:737–42.
98. Weiner HL. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. Immunol Rev 2001;182:207–14.
99. Dieckmann D, Bruett CH, Ploettner H, Lutz MB, Schuler G. Human CD4(+)CD25(+) regulatory, contact-dependent T cells induce interleukin 10-producing, contact-independent type 1-like regulatory T cells. J Exp Med 2002;196:247–53.
100. Van Montfrans C, Hooijberg E, Rodriguez Pena MS, De Jong EC, Spits H, Te Velde AA, et al. Generation of regulatory gut-homing human T lymphocytes using ex vivo interleukin 10 gene transfer. Gastroenterology 2002;123:1877–88.
101. Hurles M. Are 100 000 "SNPs" useless? Science 2002;298:1509; author reply 1509.