REVIEW ARTICLE

MECHANISMS OF DISEASE

Inflammatory Bowel Disease

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The idiopathic inflammatory bowel diseases comprise two types of chronic intestinal disorders: Crohn's disease and ulcerative colitis. Accumulating evidence suggests that inflammatory bowel disease results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host. Genetic studies highlight the importance of host–microbe interactions in the pathogenesis of these diseases.[1-13] Prominent among these genetic findings are genomic regions containing nucleotide oligomerization domain 2 (NOD2),[14] autophagy genes,[4,7,8,10] and components of the interleukin-23–type 17 helper T-cell (Th17) pathway.[2] The NOD2 protein is an intracellular sensor of bacterial peptidoglycan, and autophagy enables cells to regulate and degrade diverse intracellular components, including pathogens.[15] The autophagy gene, *ATG16L1,* has been associated with Crohn's disease but not, thus far, with ulcerative colitis. The interleukin-23–Th17 pathway mediates microbial defense and intestinal inflammation.[16,17] Multiple genes regulating this pathway have been associated with both Crohn's disease and ulcerative colitis. This review summarizes recent progress in studies of intestinal immunity and genetics in inflammatory bowel disease.

Inflammatory bowel disease affects approximately 1.4 million Americans, and its peak onset is in persons 15 to 30 years of age.[18] Crohn's disease generally involves the ileum and colon, but it can affect any region of the intestine, often discontinuously. Ulcerative colitis involves the rectum and may affect part of the colon or the entire colon (pancolitis) in an uninterrupted pattern. In Crohn's disease the inflammation is often transmural, whereas in ulcerative colitis the inflammation is typically confined to the mucosa. Crohn's disease can be associated with intestinal granulomas, strictures, and fistulas, but these are not typical findings in ulcerative colitis. Cigarette smoking affects these two diseases differently: smokers are at increased risk for Crohn's disease and tend to have more severe disease, whereas former smokers and nonsmokers are at greater risk for ulcerative colitis. Patients with inflammatory bowel disease are at risk for primary sclerosing cholangitis, ankylosing spondylitis, and psoriasis.[19]

Familial clustering of cases and twin studies have established a role for genetic factors, which are likely to play a more prominent role in Crohn's disease than in ulcerative colitis.[14] The observation that cases of both these diseases can occur within the same family suggests that some of the genes may be common to both disorders. As with other complex genetic disorders, inflammatory bowel disease entails the interaction of genetic and nongenetic factors. Changes in diet, antibiotic use, and intestinal colonization (e.g., the eradication of intestinal helminths) have probably contributed to the increased prevalence of inflammatory bowel disease during the past century.[20,21]

Our current knowledge of inflammatory bowel disease is based on a combination of gene association studies, clinical investigations, and laboratory experiments in mice. In this review, we first describe homeostasis of the intestinal immune

system in health and then focus on advances in our understanding of how genetic alterations in this system contribute to the development of inflammatory bowel disease.

THE INTESTINAL IMMUNE SYSTEM

THE INTESTINAL MICROBIOME AND INFLAMMATORY BOWEL DISEASE

The intestinal microbiome consists of the microorganisms that inhabit the gut. The intraluminal microbiota affects the development of the intestinal immune system, supplies key nutrients, and modulates energy metabolism.[22] The intestinal microbiota is acquired at birth but changes rapidly during the first year of life. In adults, each person's unique population of fecal microbiota is fairly stable over time, but fluctuations occur in response to environmental and developmental factors and in disease.[21,23,24]

Host–microbiome interactions can be mutually beneficial or can be deleterious, inciting intestinal inflammation. Observations in patients with inflammatory bowel disease and in animal models point to the role of bacteria in such inflammation. For example, antibiotics are effective in some patients with inflammatory bowel disease, and most mouse models of colitis require intestinal bacteria for inflammation to occur.[25] Bacteria that can adhere to and invade the intestinal mucosa may be particularly important, as in the case of *Escherichia coli*.[26] Although a number of specific pathogens have been incriminated in the development of inflammatory bowel disease, none have been confirmed as causal; rather, microbial antigens that are normally present in the intestinal lumen seem to drive inflammation in the gut. As compared with control subjects, patients with Crohn's disease and those with ulcerative colitis have depletion and reduced diversity of members of the mucosa-associated phyla Firmicutes and Bacteroidetes.[21,27] Whether these alterations contribute to the disease or merely reflect secondary changes caused by the inflammation is not known.

THE INTESTINAL EPITHELIUM

The intestinal epithelium at the interface between the intestinal microbiome and the lymphoid tissue associated with the gastrointestinal system plays a critical role in shaping the mucosal immune response. Intestinal epithelial cells are a physical barrier against excessive entry of bacteria and other antigens from the intestinal lumen into the circulation. An intact mucosal barrier depends on intercellular junctions, which help to seal the space between adjacent epithelial cells (the paracellular space), and tight junctions, which are the key elements of the seal.[28] In inflammatory bowel disease, the paracellular space has increased permeability, and the regulation of tight junctions is defective.[28] These abnormalities may be due to a primary defect in barrier function or may be an outcome of inflammation.[28-32]

Additional defenses against bacterial invasion consist of specialized epithelial cells, including goblet cells and Paneth cells. Goblet cells regulate the production of mucus and factors that contribute to epithelial repair and regulation of inflammation.[33,34] Paneth cells secrete antimicrobial peptides such as α-defensins. Intestinal mucus overlies the epithelium, thereby limiting contact between bacteria and epithelial cells. Epithelial regeneration and repair serve to control and ultimately resolve the inflammatory response to injury. In inflammatory bowel disease, however, the inflammatory response often results in continued epithelial injury, which causes erosions, ulcerations, and a decrease in the production of defensin.[35,36] The result is increased exposure to intestinal microbiota and amplification of the inflammatory response.

In mouse models of inflammatory bowel disease, several types of epithelial dysfunction can cause intestinal inflammation. These include defects in epithelial-cell development or proliferation, barrier function, cell-matrix adhesion, endoplasmic reticulum stress, and epithelial restitution after injury.[28,37,38] Prostaglandin E receptor 4 (EP4) contributes to mucosal repair and barrier function; in mice that are deficient in EP4, the colitis that develops in response to chemical injury is more severe than that in wild-type animals.[39] Polymorphisms in proximity to the gene encoding EP4 (*PTGER4*) were recently implicated in Crohn's disease in humans[6] (Table 1). In mice in which the gene encoding MUC2, a major mucin component, has been deleted, intestinal inflammation develops[41]; moreover, a variant in a genomic region that includes the gene encoding MUC19 has been associated with Crohn's disease.[2] Endoplasmic reticulum stress (a cellular response to various environmental changes) is increased in inflamed intestinal epithelial cells,[42]

Table 1. Genetic Associations with Crohn's Disease and Ulcerative Colitis.*

Gene	Genomic Region	No. of Genes in Region†	Associated with Crohn's Disease	Associated with Ulcerative Colitis	Function
Innate immune responses					
NOD2 (nucleotide-binding oligomerization domain 2)	16q12	1	Yes	No	Senses bacterial peptidoglycan to activate cell signaling
ATG16L1 (autophagy-related, 16-like)	2q37	1	Yes	No	Component of autophagy complex
IRGM (immunity-related GTPase M)	5q33	3	Yes	Equivocal	Role in autophagy; required for interferon-γ–mediated clearance of intracellular pathogens
Interleukin-23–Th17 pathway					
IL23R (interleukin-23 receptor)	1p31	1	Yes	Yes‡	Unique component of heterodimeric interleukin-23 receptor
IL12B (interleukin-12B, p40 subunit)	5q33	1	Yes	Yes‡	Component of interleukin-23 cytokine; common to interleukin-12
STAT3 (signal transducer and activator of transcription 3)	17q21	4	Yes	Yes‡	Major STAT downstream of various cytokines, including interleukin-6, 10, 17, 21, 22, and 23
CCR6 (chemokine [C-C motif] receptor 6)	6q27	3	Yes	No	Cell-membrane protein mediating migration and recruitment of inflammatory cells
Other genes in association regions					
PTGER4 (prostaglandin E receptor 4)	5p13	0	Yes	No	One of the receptors for the inflammatory mediator *PGE2*
ZNF365 (zinc finger protein 365)	10q21	1	Yes	No	Reported role in mitosis
SLC22A4 (solute-carrier family 22, organic-cation transporter)	5q31	7	Yes	Equivocal	Plasma membrane polyspecific organic cation transporter
PTPN2 (T-cell protein tyrosine phosphatase)	18p11	1	Yes	No	Multiple interactions with STAT proteins; also associated with type 1 diabetes
Major histocompatibility complex (MHC)	6p21	—	Yes‡	Yes	Distinct MHC class II associations between ulcerative colitis and Crohn's disease
NKX2-3 (NK2–transcription-factor–related, locus 3)	10q24	1	Yes	Yes‡	Homeodomain-containing transcription factor affecting lymphoid and spleen development

MST1 (macrophage stimulating 1)	3p21	35	Yes	Yes‡	Involved in macrophage chemotaxis and activation following proinflammatory signals
PLA2G2E (secretory phospholipase A_2)	1p36	0§	No	Yes	Releases arachidonic acid from membrane phospholipids
IL10 (interleukin-10)	1q32	1¶	Equivocal	Yes	Immunosuppressive cytokine with a central role in regulating intestinal inflammation
IFNG (interferon-γ)	12q15	2§	No	Yes	Critical cytokine in innate and adaptive immunity against intracellular pathogens

* Each genomic region listed in the table has been reported to be highly associated with either Crohn's disease or ulcerative colitis ($P<10^{-11}$). Because epidemiologic studies predict that some genetic loci will demonstrate similar association trends in Crohn's disease and ulcerative colitis, loci strongly associated in one disease have been tested for association in the converse phenotype. Because in this situation the multiple testing burden is reduced, less stringent thresholds for association in the converse phenotype provide evidence for disease association.

† The number of genes in the associated region was obtained from Barrett et al.[2] unless otherwise specified. In some cases, the association signal identified in genomewide association studies is confined to a genomic region containing only one gene, strongly implicating that gene in the pathogenesis (e.g., chromosomes 16q12, 2q37, 1p31, and 5p33). In other cases, the association signal encompasses multiple genes and the causal gene or genes are unknown, most notably the chromosome 3p21 association signal encompassing 35 expressed transcripts. At the other extreme, the association can be confined to a region containing no genes (e.g., chromosome 5p13). However, in the case of the chromosome 5p13 association signal, *PTGER4* is the closest gene to the association signal and is a compelling functional candidate gene; polymorphisms in this region that are associated with Crohn's disease regulate PTGER4 messenger RNA levels.[6]

‡ There is less significant evidence for an association in the converse phenotype.

§ The number of genes in the associated region was obtained from Silverberg et al.[40]

¶ The number of genes in the associated region was obtained from Franke et al.[11]

and deletion from murine intestinal epithelium of the *XBP1* gene, which encodes X-box binding protein 1, a key component of the endoplasmic reticulum stress response, results in inflammation in the small intestine.[38]

THE INFLAMMATORY RESPONSE IN INFLAMMATORY BOWEL DISEASE

The intestinal lamina propria contains a complex population of immune cells that balance the requirement for immune tolerance of luminal microbiota with the need to defend against pathogens, the excessive entry of luminal microbiota, or both (Fig. 1 and 2A). The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells). Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α (TNF-α), interleukin-1β, interferon-γ, and cytokines of the interleukin-23–Th17 pathway (Fig. 2B).

The initial immune response to intestinal microbiota is tightly regulated, and this regulation determines whether immune tolerance or a defensive inflammatory response ensues. Disturbance of the balance of these responses can lead to inflammatory bowel disease: in mouse models, perturbation of the proteins essential to immune function can incite intestinal inflammation.[25] In experimental colitis, some intestinal lymphocytes respond to microbial antigens, but the extent to which specific intestinal microbial antigens drive intestinal lymphocytes in inflammatory bowel disease is unknown.

INNATE IMMUNE RECOGNITION

The innate arm of the immune system provides an initial, rapid response to microbes. Cells of the innate system display receptors that recognize general microbial patterns (pattern-recognition receptors), in contrast to antigen-specific recognition by receptors of the adaptive immune system. The intestinal epithelial layer expresses various types of innate immune receptors (Fig. 1) that mediate defenses against luminal microbiota but also condition epithelial and antigen-presenting cells for inducing the tolerance mechanisms that maintain immune homeostasis in the intestine.[43-46] The expression of plasma-mem-

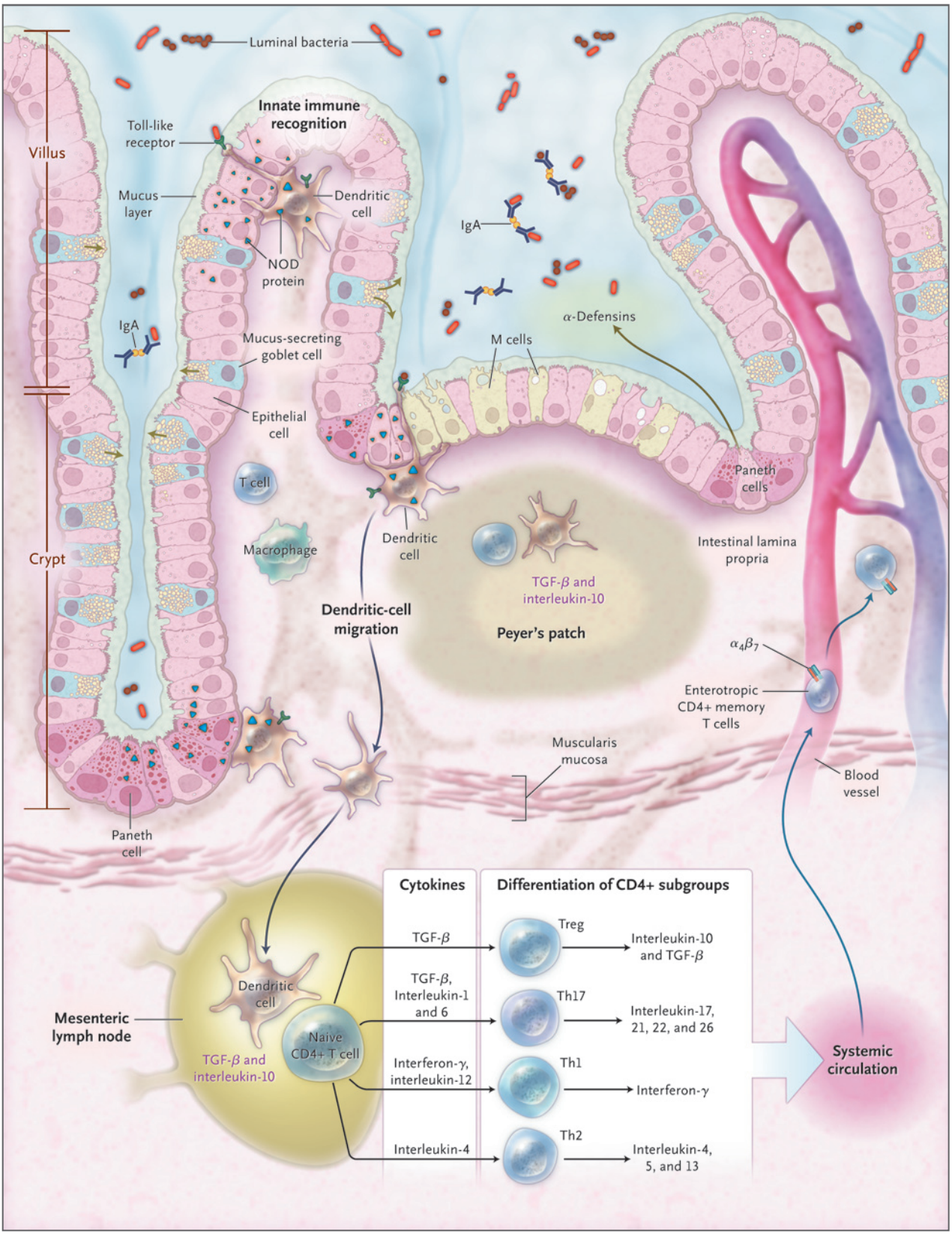

Figure 1 (facing page). The Intestinal Immune System.
In the healthy state, the goblet cells secrete a layer of mucus that limits exposure of the intestinal epithelial cells to bacteria. Both the secretion of antimicrobial peptides (e.g., α-defensins) by Paneth cells and the production of immunoglobulin A (IgA) provide additional protection from luminal microbiota. Innate microbial sensing by epithelial cells, dendritic cells, and macrophages is mediated through pattern-recognition receptors such as toll-like receptors and nucleotide oligomerization domain (NOD) proteins. Dendritic cells present antigens to naive CD4+ T cells in secondary lymphoid organs (Peyer's patches and mesenteric lymph nodes), where factors such as the phenotype of the antigen-presenting cells and the cytokine milieu (transforming growth factor β [TGF-β] and interleukin-10) modulate differentiation of CD4+ T-cell subgroups with characteristic cytokine profiles (regulatory T cells [e.g., Treg] and helper T cells [e.g., Th1, Th2, and Th17]), and enterotropic molecules (e.g., $\alpha_4\beta_7$) are induced that provide for gut homing of lymphocytes from the systemic circulation. These activated CD4+ T cells then circulate to the intestinal lamina propria, where they carry out effector functions.

brane toll-like receptors — either intracellularly or basolaterally — and the down-regulation of the expression and responses of pattern-recognition receptors limit activation of intestinal epithelial cells by luminal microbes.[45,47-50]

Continual sampling of intestinal microbiota is important in regulating the intestinal immune response. In laboratory animals, microbial sampling occurs by translocation of microbes across epithelial cells and the M cells of the epithelium of Peyer's patches, by immunoglobulins,[51] and by dendritic cells[52,53] (Fig. 1). Activated antigen-presenting cells, notably dendritic cells, then present peptide antigens to T cells in secondary lymphoid organs of the gut, such as Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles[54,55] (Fig. 1). This interaction initiates an adaptive immune response, after which memory lymphocytes develop. One characteristic of adaptive immunity is a rapid and robust response to subsequent challenge by antigen — that is, immunologic memory.

CD4+ T CELLS

Certain helper T cells (Th1, Th2, and Th17) and regulatory T cells (e.g., forkhead box P3 [Foxp3+] Treg), which are subgroups of CD4+ T cells, secrete characteristic types of cytokines (Fig. 1). Regulation of these subgroups must be continually fine-tuned to maintain intestinal immune homeostasis.[56,57] Effector subgroups (Th1, Th2, and Th17 cells) are critical for defenses against pathogens and excessive entry of luminal microbiota (Fig. 2A), but expansion and overactivity of these cells relative to the regulatory CD4+ T cells can lead to intestinal inflammation (Fig. 2B).[25,57-64] Studies of inflammatory bowel disease in mice and humans implicate dysregulation of intestinal CD4+ T-cell subgroups in the pathogenesis of these diseases. In Crohn's disease, for example, there is increased production in the intestinal mucosa of the Th17 cytokine interleukin-17 and the Th1 cytokines interferon-γ and TNF-α.[60,65] In ulcerative colitis, by contrast, there is usually an increase in interleukin-17 and Th2 cytokines.[60,65,66] The interleukin-23 pathway is central to the function of Th17 cells. Polymorphic variants of multiple genes involved in this pathway and in Th17 cell function have been associated with both Crohn's disease and ulcerative colitis.[2]

B CELLS

The role of B cells in inflammatory bowel disease has not been as extensively studied as that of T cells. Intestinal B cells produce IgA antibodies, which contribute to immune protection without provoking inflammation. In animal models of colitis, both antiinflammatory[67] and proinflammatory[68] roles of B cells have been described. The presence of circulating antimicrobial antibodies in patients with inflammatory bowel disease (e.g., anti-flagellin antibodies and anti–*Saccharomyces cerevisiae* antibodies)[69] but not in healthy controls indicates B-cell reactivity.

INTESTINAL VASCULATURE AND LEUKOCYTE MIGRATION

The intestinal vasculature and endothelium regulate the entry of leukocytes into the gut and maintain an adequate blood flow. Entry of cells into intestinal tissues is modulated by adhesion molecules (selectins, integrins) and chemokines (secreted cell attractants). T cells that become activated in mesenteric lymph nodes and Peyer's patches become "gut-tropic" cells by expressing the integrin $\alpha_4\beta_7$ and the chemokine receptor CCR9[70,71]; this change requires retinoic acid.[72] The relative specificity in cellular migration to the intestine is the basis for targeting these molecules for the treatment of inflammatory bowel disease.

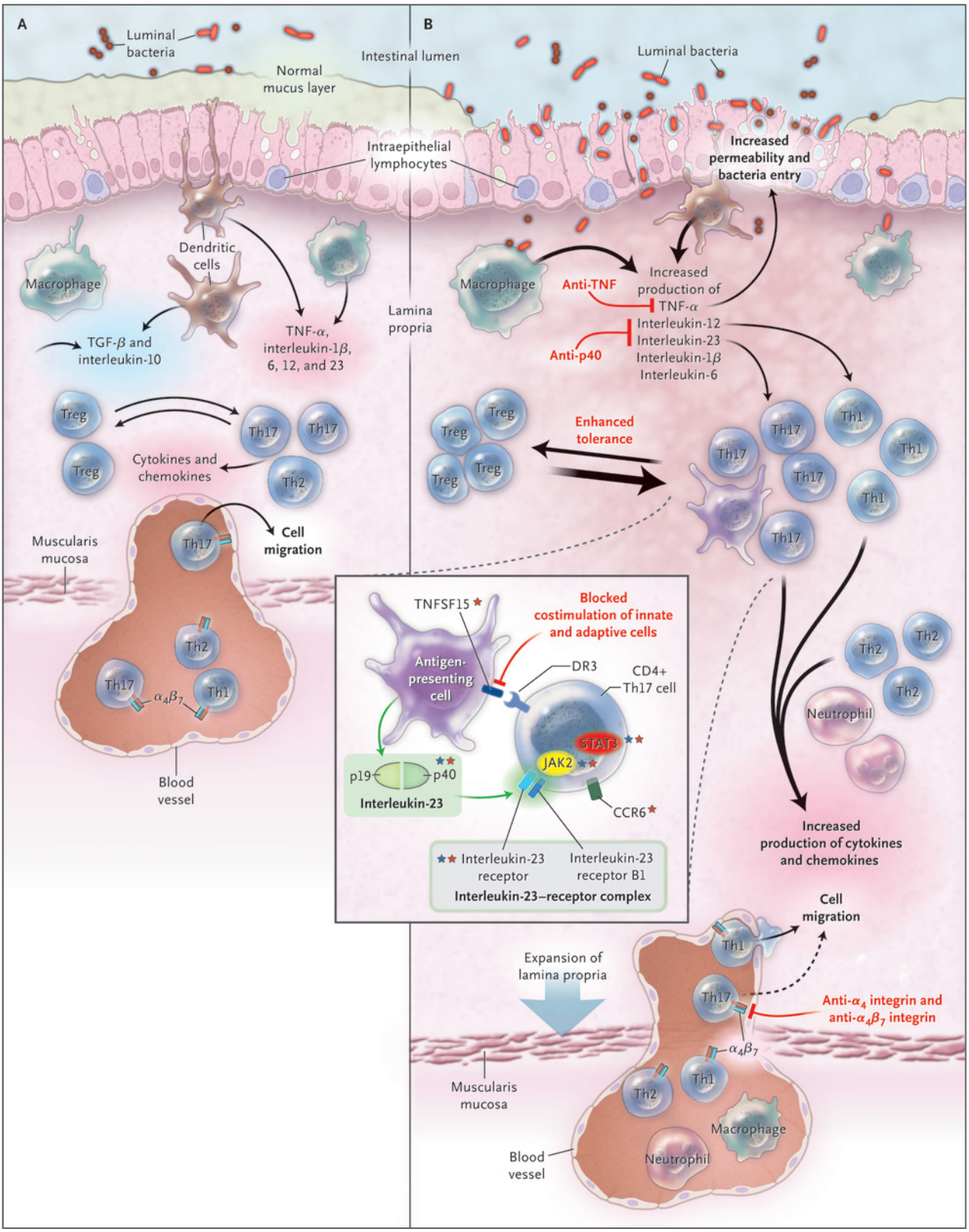

Figure 2 (facing page). The Intestinal Immune System in Health and Disease.

In healthy persons (Panel A), the lamina propria normally contains a diverse array of immune cells and secreted cytokines. These include antiinflammatory mediators (transforming growth factor β [TGF-β] and interleukin-10) that down-regulate immune responses, as well as proinflammatory mediators from both innate and adaptive immune cells that limit excessive entry of intestinal microbiota and defend against pathogens. Noninflammatory defenses, such as phagocytosis by macrophages, probably assist in defending against bacteria entering the lamina propria while minimizing tissue injury. A homeostatic balance is maintained between regulatory T cells (e.g., Treg) and effector T cells (Th1, Th2, and Th17). In persons with intestinal inflammation (Panel B), several events contribute to increased bacterial exposure, including disruption of the mucus layer, dysregulation of epithelial tight junctions, increased intestinal permeability, and increased bacterial adherence to epithelial cells. In inflammatory bowel disease, innate cells produce increased levels of tumor necrosis factor α (TNF-α), interleukin-1β, interleukin-6, interleukin-12, interleukin-23, and chemokines. There is marked expansion of the lamina propria, with increased numbers of CD4+ T cells, especially proinflammatory T-cell subgroups, which also secrete increased levels of cytokines and chemokines. Increased production of chemokines results in recruitment of additional leukocytes, resulting in a cycle of inflammation. At present, therapeutic approaches to inflammatory bowel disease (labels in red) focus on inhibiting proinflammatory cytokines, inhibiting the entry of cells into intestinal tissues (dashed arrow), and inhibiting T-cell activation and proliferation. Additional investigational biologic therapies include blockade of costimulatory signals that enhance interactions between innate cells and adaptive cells, administration of epithelial growth factors, and enhancement of tolerance through a variety of mechanisms. CD4+ Th17 cells (inset) express surface molecules such as the interleukin-23 receptor (a component of the interleukin-23–receptor complex, which consists of the interleukin-23 receptor and the interleukin-12 receptor B1) and CCR6. Interleukin-23 (comprising subunits p19 and p40) is secreted by antigen-presenting cells, and engagement of interleukin-23 with the interleukin-23–receptor complex results in activation of the Janus-associated kinase (JAK2) signal transducers and activators of transcription (STAT3), thereby regulating transcriptional activation. Interleukin-23 contributes to Th17-cell proliferation, survival, or both, and its actions are enhanced by tumor necrosis factor (ligand) superfamily, member 15 (TNFS15). Of the top 30 genetic associations with Crohn's disease, at least six genes can be implicated in Th17 cells and interleukin-23 signaling. A number of these genes are not unique to interleukin-23–Th17 signaling. Genes in the interleukin-23–Th17 pathway that have been associated with Crohn's disease are designated by red stars, and those with ulcerative colitis by blue stars.

An accumulation of leukocytes in intestinal tissues is characteristic of inflammatory bowel disease. Leukocyte adherence and recruitment are increased in the microvessels in chronic disease,[73] mediated in part by up-regulation of adhesion molecules on vascular endothelial cells by TNF-α and interleukin-1. Moreover, increased levels of tissue-specific and inflammatory chemokines enhance leukocyte migration.[74] Abnormalities in microvascular function probably contribute to inflammation, ischemia, and impaired mucosal healing.[73] Ischemia causes local tissue hypoxia, which in turn regulates factors that contribute to both intestinal injury and protection.[75,76]

INNATE-IMMUNE-RESPONSE GENES AND CROHN'S DISEASE

NOD2 AND CROHN'S DISEASE

The importance of responses to intestinal bacteria in inflammatory bowel disease is highlighted by the association between Crohn's disease and the *NOD2* gene[77] (Table 1), which encodes an intracellular sensor of peptidoglycan, a component in bacterial cell walls.[78,79] The association includes three *NOD2* polymorphisms that change the amino acids in *NOD2*, each impairing responses to peptidoglycan. These three polymorphisms occur with increased frequency in persons of European ancestry but are not present in Asian patients and are significantly less frequent in African Americans with Crohn's disease.[14] Approximately 30% of patients of European ancestry have at least one of the three polymorphisms. *NOD2* carriers are more likely than noncarriers to have ileal involvement and complications related to fibrostenosis and to require intestinal resection.[80] Heterozygosity for a polymorphism confers an increased risk of Crohn's disease (by a factor of 1.75 to 4), whereas homozygosity confers a much greater risk (by a factor of 11 to 27)[81]; these are the highest relative risks observed for any of the genes associated with this disease. *NOD2* polymorphisms alone, however, are not sufficient to cause Crohn's disease, which is indicative of the complexities of a multifactorial disorder.

Epithelial cells, Paneth cells, macrophages, dendritic cells, and endothelial cells all express NOD2.[77] The activation of the NOD2 protein by bacterial peptidoglycan activates the nuclear factor κB (NF-κB) and mitogen-activated protein

(MAP) kinase signaling pathways, which leads to the production of cytokines (e.g., TNF and interleukin-1β) and antimicrobial peptides.[77,82] Decreased secretion of proinflammatory cytokines and decreased activation of NF-κB on acute stimulation of NOD2 with bacterial peptidoglycan components have been detected in *NOD2* carriers.[77] Intestinal inflammation does not develop in NOD2-deficient mice, as is the case with most human *NOD2* risk-allele carriers.[82] Normally, secretion of proinflammatory cytokines by intestinal antigen-presenting cells is minimal,[55,83] yet bacterial killing occurs, implying that the intestinal immune system can defend against luminal microbiota while minimizing tissue injury.[83] In contrast, the gut in inflammatory bowel disease contains an increased number of antigen-presenting cells that secrete proinflammatory cytokines.[84] Various factors within the intestinal environment contribute to the down-regulation of proinflammatory cytokines by intestinal antigen–presenting cells. These include inhibitory cytokines (transforming growth factor β [TGF-β] and interleukin-10) and chronic stimulation through pattern-recognition receptors, such as chronic peptidoglycan stimulation through NOD2.[85,86] The NOD2-mediated mechanisms that down-regulate proinflammatory cytokines during chronic NOD2 stimulation are defective in carriers of genetic variants that impair NOD2 function.[85] How loss-of-function *NOD2* polymorphisms increase susceptibility to Crohn's disease is unknown, but most likely this outcome reflects the myriad functions of NOD2 and the unique features of the intestinal environment.

AUTOPHAGY GENES AND CROHN'S DISEASE

Associations with Crohn's disease have been established for *ATG16L1* and immunity-related GTPase M protein (*IRGM*)[4,7,8,10] (Table 1), two genes involved in autophagy. Autophagy is a mechanism for clearing intracellular components, including organelles, apoptotic bodies, and microbes.[15] In mice with low expression of *ATG16L1*, the morphologic features and gene expression of Paneth cells are abnormal.[87] *ATG16L1* carriers with Crohn's disease also have abnormal Paneth-cell morphology.[87] In mice, ATG16L1 appears to regulate secretion of interleukin-1β and inhibit intestinal inflammation.[88]

ADAPTIVE IMMUNITY AND INFLAMMATORY BOWEL DISEASE

ALTERATIONS IN T-CELL TOLERANCE

The inhibitory cytokines interleukin-10 and TGF-β in Peyer's patches, mesenteric lymph nodes, and lamina propria are involved in T-cell tolerance in the intestine.[25] Regulatory T cells can differentiate in Peyer's patches and mesenteric lymph nodes through the actions of TGF-β and retinoic acid.[89] Defects in the development and function of regulatory T cells, or alterations in the ability to respond to them, can result in intestinal inflammation in mice.[56,90] The autophagy pathway contributes to T-cell tolerance at multiple levels, which suggests that polymorphisms of autophagy genes associated with Crohn's disease could increase a patient's susceptibility to intestinal inflammation through defects in T-cell tolerance.[15,91] Moreover, there is a genetic association between the inhibitory cytokine interleukin-10 and ulcerative colitis.[11] This association corresponds with animal models showing that interleukin-10 participates in down-regulating intestinal inflammation; for example, colitis and intestinal dysplasia develop spontaneously in interleukin-10–deficient mice.[25] The central importance and sufficiency of defective interleukin-10 signaling in the mediation of intestinal inflammation are further highlighted by the finding that uncommon, recessive loss-of-function mutations in either the *IL10RA* or the *IL10RB* component of the interleukin-10 receptor result in Crohn's disease.[92]

TH17 CELLS AND INTERLEUKIN-23 SIGNALING IN INFLAMMATORY BOWEL DISEASE

Interleukin-23 signaling is mediated through the engagement of heterodimeric interleukin-23 (comprising p19 and p40 subunits) with its heterodimeric receptor (comprising interleukin-23R and interleukin-12RB1). The engagement activates the JAK-STAT (Janus-associated kinase–signal transducers and activators of transcription) signaling pathway, which regulates the transcription of several genes. The importance of interleukin-23 signaling in mediating inflammation has been shown in animal models.[17,59,61,64,65,93] Moreover, reports of highly significant genetic associations between *IL23R* and inflammatory bowel disease,[3]

psoriasis,[94] and ankylosing spondylitis[95] indicate that inflammatory bowel disease shares genetic associations with certain other autoimmune diseases. Interleukin-23, secreted by macrophages and dendritic cells, may contribute to TR17 proliferation, survival, or both.[96] Interleukin-23 also contributes to intestinal inflammation through Th17-independent pathways.[93] Levels of interleukin-23 and Th17 cytokines are elevated in the colonic mucosa in both Crohn's disease and ulcerative colitis.[58,60,63]

Multiple independent associations within the *IL23R* gene region have been found in inflammatory bowel disease, most notably for an Arg381Gln variant of the gene: carriers of this uncommon glutamine allele are less likely to have inflammatory bowel disease, by a factor of 2 to 3, than persons who carry only the common arginine allele.[3] The effect of the *IL23R* polymorphisms on interleukin-23R function has not been defined. In addition to *IL23R*, associations with Crohn's disease have been observed in genomic regions encompassing multiple genes involved in interleukin-23–Th17 signaling[2] (Fig. 2 and Table 1).

COMPARATIVE GENE ASSOCIATION STUDIES IN CROHN'S DISEASE AND ULCERATIVE COLITIS

It is estimated that known genetic associations account for only about 20% of the genetic variance underlying susceptibility to inflammatory bowel disease; the remaining genetic factors have not been identified. Consistent with predictions inferred from epidemiologic studies, genomewide association studies have identified loci associated solely with Crohn's disease or ulcerative colitis and other loci associated with both disorders (Table 1). For example, multiple genes along the interleukin-23 signaling pathway — notably *IL23R*, *JAK2*, *STAT3*, and *p40* — have been associated with both these diseases.[2,11,40,97] Genomic associations with Crohn's disease alone include *NOD2* and the autophagy gene, *ATG16L1*,[2] but a number of well-powered studies have not shown associations between these genes and ulcerative colitis. Given the broad functional contributions of autophagy, a more general role in either Crohn's disease or ulcerative colitis may eventually be established. Significant associations between ulcerative colitis and a region on chromosome 12q15 encompassing the interferon-γ and interleukin-26 genes have been observed, but no such associations with Crohn's disease have thus far been reported.[40] In the initial genomewide association studies in ulcerative colitis, a highly significant association was observed for a common polymorphism in a region on chromosome 1q32 containing the *IL10* gene, with only a very modest association observed in Crohn's disease.[11] However, the intriguing finding that complete, loss-of-function mutations in the interleukin-10 receptor[92] result in a Crohn's disease–predominant phenotype highlights the complex phenotypic overlap between these two diseases.

Associations within the major histocompatibility complex class II region near HLA-DRA (alpha chain) are the most significant observed in genomewide association studies of ulcerative colitis.[11,40,97] Distinct HLA-DRB1 (beta-chain) alleles have been associated with both diseases.[97]

THERAPEUTIC IMPLICATIONS

Treatment of inflammatory bowel disease includes lifestyle alterations (e.g., smoking cessation for patients with Crohn's disease), medical management, and surgical interventions. A seminal advance was the introduction of treatment with an anti–TNF-α monoclonal antibody, which is particularly effective in Crohn's disease. The efficacy of this therapy alone probably reflects the pleiotropic effects of TNF; however, the therapy is often limited by a loss of efficacy, underscoring the need for novel therapies.

Anti-p40 monoclonal antibodies have been reported to be effective in psoriasis[98] and Crohn's disease.[99,100] The p40 cytokine subunit is common to both interleukin-23 and interleukin-12, and monoclonal antibodies against p40 inhibit both pathways. Selective blockade of interleukin-23 can be achieved by targeting the p19 subunit, and this approach has been reported to be effective in many,[59,64] although not all,[101] animal models of inflammatory bowel disease. Selective inhibition of interleukin-23 may, however, deregulate other, cross-regulated pathways and T-cell subgroups, with unintended consequences.[100] Moreover, some Th17 cytokines may also have protective features; for example, interleukin-22 ameliorates disease in

an animal model of colitis.[102] A major question that remains to be resolved is whether selective interleukin-23 blockade will be more or less effective than combined interleukin-12–interleukin-23 blockade in the treatment of inflammatory bowel disease.

Other treatments under investigation include the infusion of interleukin-10–producing T cells and the administration of interleukin-10–producing bacteria.[103,104] Certain bacterial components, commensal bacteria, and "probiotic" bacteria more generally are also being investigated.[48,105] The increased levels of tissue-specific and inflammatory chemokines that enhance intestinal leukocyte migration[74] are the basis for targeting these molecules in inflammatory bowel disease.[104,106] With the development of new, potent antiinflammatory agents, one must consider balancing therapeutic benefit with side effects resulting from an increased risk of infection or reactivation of infections (JC virus–induced multifocal leukoencephalopathy in the case of natalizumab[107] and tuberculosis in the case of anti-TNF-α monoclonal antibody[108]). Future progress in disease monitoring and therapy will depend on the development of a more refined and integrated understanding of the mechanisms mediating intestinal immune homeostasis.

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