TABLE 351-3 EXAMPLES OF GENETIC LOCI ASSOCIATED WITH CD AND/OR UC

Chromosome	Putative Gene	Gene Name	Protein Function	CD	UC
ER Stress and Metabolism					
5q31	*SLC22A5*	Solute carrier family 22, member 5	β carnitine transporter	+	
7p21	*AGR2*	Anterior gradient 2	ER stress	+	+
17q21	*ORMDL3*	Orosomucoid related member 1-like 3	ER stress and lipid synthesis	+	+
22q12	*XBP1*	X-box binding protein 1	ER stress	+	+
1q23	*ITLN1*	Intelectin 1	Bacterial binding	+	
2q37	*ATG16L1*	ATG16 autophagy related 16-like 1	Autophagy	+	
5q33	*IRGM*	Immunity-related GTPase family, M	Autophagy	+	
9p24	*JAK2*	Janus kinase 2	IL-6R and IL-23R signaling	+	+
12q12	*LRRK2*	Leucine-rich repeat kinase 2	Autophagy?	+	
16q12	*NOD2*	Nucleotide-binding oligomerization domain containing 2	Bacterial sensing and autophagy activation	+	
17q21	*STAT3*	Signal transducer and activator of transcription 3	IL-6R, IL-23R, and IL-10R signaling	+	+
Adaptive Immunity					
1p31	*IL23R*	Interleukin 23 receptor	Th17 cell stimulation	+	+
1q32	*IL10*	Interleukin 10	Treg-associated cytokine		+
5q33	*IL12B*	Interleukin 12B	IL-12 p40 chain of IL-12/IL-23	+	+
18p11	*PTPN2*	Protein tyrosine phosphatase, nonreceptor type 2	T cell regulation	+	
Inflammation					
3p21	*MST1*	Macrophage stimulating 1	Macrophage activation	+	+
5p13	*PTGER4*	Prostaglandin E receptor 4	PGE_2 receptor	+	+
6q23	*TNFAIP3*	Tumor necrosis factor, alpha-induced protein 3 (A20)	Toll-like receptor regulation	+	
6q27	*CCR6*	Chemokine (C-C motif) receptor 6	Dendritic cell migration	+	

Abbreviations: CD, Crohn's disease; ER, endoplasmic reticulum; GTPase, guanosine triphosphatase; IL, interleukin; PGE_2, prostaglandin E_2; UC, ulcerative colitis.

Source: Adapted from A Kaser et al: Ann Rev Immunol 28:573, 2010; B Khor et al: Nature 474:307, 2011; and L Jostins et al: Nature 491:119, 2012.

in the intestinal lumen. In IBD this suppression of inflammation is altered, leading to uncontrolled inflammation. The mechanisms of this regulated immune suppression are incompletely known.

Gene knockout ($^{-/-}$) or transgenic (Tg) mouse models of IBD, which include those that are directed at genes demonstrated to be associated with risk for the human disease, have revealed that deleting specific cytokines (e.g., IL-2, IL-10, TGF-β) or their receptors, deleting molecules associated with T cell antigen recognition (e.g., T cell antigen receptors), or interfering with IEC barrier function and the regulation of responses to commensal bacteria (e.g., XBP1, N-cadherin, mucus glycoprotein, or nuclear factor-κB [NF-κB]) leads to spontaneous colitis or enteritis. In the majority of circumstances, intestinal inflammation in these animal models requires the presence of the commensal microbiota. Thus, a variety of specific alterations can lead to immune activation by commensal microbiota and inflammation directed at the intestines in mice. How these relate to human IBD remains to be defined, but they are consistent with inappropriate responses of the genetically susceptible host to the commensal microbiota.

In both UC and CD, an inflammatory pathway thus likely emerges from the genetic predisposition that is associated with inappropriate innate immune and epithelial sensing and reactivity to commensal bacteria that secrete inflammatory mediators together with inadequate regulatory pathways that lead to activated CD4+ and $CD8^+$ T cells within the epithelium and lamina propria that altogether secrete excessive quantities of inflammatory cytokines relative to anti-inflammatory cytokines. Some cytokines activate other inflammatory cells (macrophages and B cells), and others act indirectly to recruit other lymphocytes, inflammatory leukocytes, and mononuclear cells from the bloodstream into the gut through interactions between homing receptors on leukocytes (e.g., α4β7 integrin) and addressins on vascular endothelium (e.g., MadCAM1). Consistent with this, neutralization of tumor necrosis factor (TNF) or α4β7 integrin demonstrate therapeutic efficacy in IBD. CD4+ T helper (T_H) cells that promote inflammation are of three major types, all of which may be associated with colitis in animal models and perhaps humans: T_H1 cells (secrete interferon [IFN] γ), T_H2 cells (secrete IL-4, IL-5, IL-13), and T_H17 cells (secrete IL-17, IL-21). T_H1 cells induce transmural granulomatous inflammation that resembles CD; T_H2 cells, and related natural killer T cells that secrete IL-13, induce superficial mucosal inflammation resembling UC in animal models; and T_H17 cells may be responsible for neutrophilic recruitment. However, neutralization of the cytokines produced by these cells, such as IFN-γ or IL-17, has yet to show efficacy in therapeutic trials. Each of these T cell subsets cross-regulate each other. The T_H1 cytokine pathway is initiated by IL-12, a key cytokine in the pathogenesis of experimental models of mucosal inflammation. IL-4 and IL-23, together with IL-6 and TGF-β, induce T_H2 and T_H17 cells, respectively, and IL-23 inhibits the suppressive function of regulatory T cells. Activated macrophages secrete TNF and IL-6. These characteristics of the immune response in IBD explain the beneficial therapeutic effects of antibodies to block proinflammatory cytokines or the signaling by their receptors (e.g., anti-TNF, anti-IL-12, anti-IL-23, anti-IL-6, or Janus kinase [JAK] inhibitors) or molecules associated with leukocyte recruitment (e.g., anti-α4β7), or the use of cytokines that inhibit inflammation and promote regulatory T cells (e.g., IL-10) or promote intestinal barrier function and may be beneficial to humans with intestinal inflammation.

THE INFLAMMATORY CASCADE IN IBD

Once initiated in IBD by abnormal innate immune sensing of bacteria by parenchymal cells (e.g., IECs) and hematopoietic cells (e.g., dendritic cells), the immune inflammatory response is perpetuated by T cell activation. A sequential cascade of inflammatory mediators extends the response; each step is a potential target for therapy. Inflammatory cytokines such as IL-1, IL-6, and TNF have diverse effects on tissues. They promote fibrogenesis, collagen production, activation of tissue metalloproteinases, and the production of other inflammatory mediators; they also activate the coagulation cascade in local blood vessels (e.g., increased production of von Willebrand's factor). These cytokines are normally produced in response to infection but are usually turned off or inhibited at the appropriate time to limit tissue damage. In IBD their activity is not regulated, resulting in an imbalance between the proinflammatory and anti-inflammatory mediators. Therapies such as the 5-aminosalicylic acid (5-ASA) compounds and glucocorticoids are potent inhibitors