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Animal models of IBD: linkage to human disease

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Abstract

Spontaneous development of intestinal inflammation in many different kinds of genetically engineered mice as well as the presence of numerous susceptibility genes in humans suggests that inflammatory bowel disease (IBD) is mediated by more complicated mechanisms than previously predicted. The human genetic studies implicate some major pathways in the pathogenesis of IBD, including epithelial defense against commensal microbiota, the IL-23/Th17 axis, and immune regulation. Murine IBD models, which are genetically engineered to lack some susceptibility genes, have been generated, and have provided useful insights into the therapeutic potential of targeting the susceptibility genes directly or their downstream pathways indirectly for IBD. This review summarizes current information related to the function of IBD-associated genes as derived from genetically engineered mouse models.

Introduction

Inflammatory bowel disease (IBD), which affects approximately 1.4 million individuals in the United States alone, is a chronic intestinal inflammatory condition caused by multifactorial conditions in a genetically predisposed host. IBD is characterized by two major forms, Crohn's disease (CD) and ulcerative colitis (UC), which are mediated by both common and distinct mechanisms and exhibit distinct clinical features [1,2,3]. Many kinds of knockout (KO) and transgenic mice spontaneously develop intestinal inflammation [4] and recently numerous different IBD susceptibility genes have been identified in humans [5,6,7,8,9,10,11,12–15]. The linkage of human genetic studies and animal models of IBD is a multigenetic disorder whose fundamental mechanisms are still unclear.

Many animal models, including genetically engineered mice, congenic mouse strains, chemically induced models, and a cell-transfer model have been established for studying IBD (Figure 1). The majority of animal models exhibit Th1-dominant immune responses, and they have been used widely for studying CD. Although CD affects both small (ileitis) and large (colitis) intestines, only some CD models develop inflammation in the small intestine. In contrast to Th1-mediated models, mouse models developing Th2-mediated colitis for the study of UC are limited. Animal models cannot fully reflect human diseases, but they have provided important opportunities to more closely examine the mechanisms of IBD. Indeed, animal models have not only contributed during the last decade to our

understanding of the mechanisms of IBD but also provided useful interventions for developing novel therapeutic strategies for this disease [16]. In addition, recent advances on genetic engineering technology have allowed the discovery of previously unrecognized functions of some molecules in IBD. For example, X-box binding protein (XBP1) and T-box transcription factor (T-bet), which were generally thought to play crucial roles primarily in adaptive immune responses, recently have been revealed in T/B cell-deficient T-bet and epithelial cell-specific XBP1 KO mice to actively participate in innate immune responses and to suppress the development of colitis [7•,17]. Another example is the role of autophagy in IBD. Autophagy pathways, which are currently well implicated in the innate defense against enteric microorganisms in IBD, are required for adaptive immune response involved in the protection against IBD, as indicated by spontaneous development of colitis in mice that lack an autophagy gene (Atg) 5, specifically in the thymic epithelial cells [18•].

The employment of cell-specific gene KO systems has also demonstrated conflicting functions of some signaling molecules in the pathogenesis of IBD depending on the cell types involved. For example, canonical NFκB (NFκB1) and signal transducer and activator of transcription (STAT) 3 pathways have been implicated in the activation of adaptive immune responses involved in the pathogenesis of IBD. Indeed, inhibition of these signaling is beneficial in suppressing colitis in some IBD models [19]. In contrast, recent studies show that a specific deletion of either NFκB essential modulator (NEMO) or STAT3 in the epithelial cells of mice induces the spontaneous development of colitis [20•,21,22]. These findings suggest dual functional abilities (deleterious versus protective) of some signaling pathways in the pathogenesis of IBD, depending on the cell types involved. Therefore, careful attention should be made when these signalings are targeted directly or indirectly (through neutralization of cytokines) for treatment of IBD [21].

A major recent advance in the field of IBD has been made by human gene association studies that have identified many IBD-associated genes specific for either CD or UC or both [5,6,7•,8,9,10•,11•,12–15]. Several KO mouse strains, which are genetically engineered to lack IBD-associated genes, have already been developed. Among them, some mouse strains including IL-10 KO [23], STAT3 KO [24,25], XBP1 KO [7•], and GPX1/2 KO [26] mice and human HLAB27 transgenic [27] rats spontaneously develop colitis or ileitis. In contrast, the remaining IBD-associated gene KO mice fail to develop intestinal inflammation spontaneously, suggesting the requirement of additional factors such as immune and environmental factors to fully elicit the development of IBD. Of note, major IBD-associated genes are classified into at least three groups based on the biological function, including host defense, IL-23/Th17 axis, and regulatory immunity. This review summarizes current knowledge from animal models on the role of host defense, the IL-23/Th17 axis, and regulatory immunity in the pathogenesis of IBD.

NOD2

The NOD2 gene, which encodes an intracellular receptor of muramyl dipeptide (a moiety of bacterial cell wall peptidoglycan), has the first definitive genetic risk factor identified for CD [5]. Three different mouse models harboring nonfunctional NOD2 have been developed. The first mouse model, which carries a NOD2^{2939insC} mutation similar to the human CD-associated NOD2^{3020insC} frameshift mutation, is susceptible to dextran sodium sulfate (DSS) induced intestinal injury [28]. Unlike chronic IBD models that do not develop disease under germ-free conditions, DSS-induced acute intestinal injury is exacerbated in the absence of commensal flora [29]. Therefore, the increased susceptibility of NOD2 mutant mice to DSS-induced intestinal injury suggests the involvement of NOD2 in commensal flora-mediated protective immunity, particularly during the acute inflammatory phase. The second model is a NOD2 KO mouse strain that was generated by a deletion of exon 1. This

mouse strain is characterized by altered toll-like receptor (TLR) 2 signaling. The production of IL-12p70 by antigen-presenting cells (APCs) in this model is increased in response to TLR2 stimulation, suggesting an inhibitory role of NOD2 in TLR2-mediated Th1 responses [30]. The third model is another NOD2 KO mouse strain that was generated by deletion of exon 3. This mouse strain is more susceptible to a *Listeria monocytogene* infection because of impaired Paneth cell function and a reduced production of antibacterial peptides such as cryptidin and defensins [31,32]. The importance of Paneth cell function in the suppression of IBD is further supported by recent data from a conditional KO mouse strain deficient of another CD susceptibility gene, XBP1, in epithelial cells. This epithelial cell-specific XBP1 deletion results in an impaired Paneth cell development and consequent development of ileitis [7•]. Indeed, abnormally low production of antibacterial peptides such as α -defensins by Paneth cells is proposed to be a primary defect in CD particularly ileal CD [33,34].

Interestingly, none of the mouse strains carrying nonfunctional NOD2 develop ileitis or colitis spontaneously. In contrast, a genetically engineered mouse strain lacking an ubiquitin-modifying enzyme A20, which restricts signals induced not only by NOD2 but also by TNFR and IL-1R, develops colitis spontaneously [35]. Therefore, it is possible that dysregulation of the NOD2 pathway alone is insufficient to fully induce intestinal inflammation and additional contributing factors are required for the development of CD in patients carrying a NOD2 mutation [1•].

Autophagy

Autophagy is a cellular pathway involved in protein and organelle degradation. Although autophagy was thought to be primarily a response to starvation, recently accumulating data indicate that it affects diverse physiological functions ranging from microbial infections to aging [36]. An autophagy-related gene (Atg) 16L1 has been identified as a CD susceptibility gene [12] and a deletion polymorphism upstream of IRGM, a gene essential for autophagy, is also associated with CD [9], highlighting the significance of autophagy in CD pathogenesis. Two different mouse strains lacking functional Atg16L1 have been developed [37,38]. Both of the Atg16L1 KO mouse strains did not develop intestinal inflammation spontaneously, but one mouse strain with gene trap-mediated disruption of Atg16L1 showed an impaired Paneth cell function particularly the granule exocytosis process [37]. In addition, the CD-associated Atg16L1 coding variant results in the impairment of capture of internalized pathogenic bacteria (*Salmonella*) within autophagosomes of epithelial cells [39]. These findings suggest that both NOD2 and Atg16L1 actively participate in epithelial cell defense against commensal flora. Indeed, the direct association between NOD2 and autophagy signals has recently been identified [40•]. This study shows that a CD-associated NOD2 frameshift mutation impairs the recruitment of Atg16L1 to the plasma membrane of bone marrow-derived macrophages, resulting in the inhibition of the autophagosome process against invading bacteria [40•].

Cellular degradation systems such as the proteasome and the lysosome are not only used for the elimination of intracellular bacteria but also used as an alarm in adaptive immune responses. Autophagy is no exception to this rule, and its substrates can be processed for antigen presentation [41]. Indeed, autophagy plays a critical role in adaptive immune responses through MHC class II-dependent antigen presentation [41,42]. Of note, MHC is an IBD susceptibility gene [1•,11•]. The importance of autophagy in adaptive immune responses for suppressing IBD is highlighted by spontaneous development of colitis in mice engineered to lack Atg5 specifically in thymic epithelial cells [17]. In addition, mice lacking Atg16L1 in hematopoietic cells are highly susceptible to DSS-induced acute intestinal injury [38]. A linkage of NOD2 and autophagy in adaptive immune responses is also highlighted

by a recent study showing that the NOD2 signal induces autophagy in dendritic cells (DCs) for bacterial handling and consequent induction of effector CD4⁺ T cell responses [43••].

IL-23

In addition to a previously well appreciated Th1/Th2 paradigm, recently accumulating data has unveiled a critical involvement of the IL-23/Th17 pathway in the pathogenesis of IBD [1•,2,3]. IL-12p70 (p40/p35) has generally been believed to represent a crucial factor involved in the development of CD because of the beneficial effect of anti-IL-12p40 treatment on CD patients [44] and in experimental models [16]. However, most of the previous studies tested the biological role of IL-12p70 using anti-IL-12p40 mAbs or IL-12p40 KO mice, making it unclear whether IL-12 (heterodimer of p40 and p35 subunits) or IL-23 (heterodimer of p40 and p19 subunits) or both participate in the pathogenesis of IBD. A series of studies using IL-23p19 KO mice or neutralizing anti-p19 mAbs have recently revealed the critical pathogenic role of IL-23, but not IL-12, in different types of experimental colitis, which are mediated by either adaptive or innate immunity [45–50]. In addition, studies of IL-12p35 KO mice has indicated a rather protective role for IL-12 in Th2-mediated colitis in TCR α KO mice [51] and some organ-specific autoimmune diseases [52,53]. The clinical relevance of data from animal models is well supported by gene association studies in humans. Polymorphisms of the IL-23 receptor are negatively associated with the development of IBD [8] and IL-12p40 has been identified as an IBD-associated gene [1•,11•]. These findings highlight IL-23 (p19) rather than IL-12 (p40) as a promising target for treating IBD more effectively and more safely.

Th17

IL-23 is required for maintaining the Th17 T cell subset that is characterized by the production of IL-17 (IL-17A), IL-17F, IL-21, IL-22, and IL-26, but not IFN- γ or IL-4 [54]. Differentiation of Th17 cells is induced through the activation of the orphan nuclear receptor ROR γ t signaling in the presence of proinflammatory cytokines such as IL-6 [54]. The precursor of Th17 cells can also be differentiated into regulatory T (Treg) cells by retinoic acid [55]. A pleiotropic cytokine TGF β is required for the differentiation of both Th17 cells and Treg cells [54,55]. In addition, commensal microbiota has an ability to induce intestinal Th17 development directly and indirectly. Colonization with a segmented filamentous bacterium directly induces the appearance of Th17 cells in the intestine [56] and bacteria-derived adenosine 5'-triphosphate (ATP) activates unique CD70^{high}CD11^{low} APCs to enhance the differentiation of intestinal Th17 cells [57•]. Interestingly, a unique Th17 subset that coexpresses IL-17 and IFN- γ can be observed in the inflamed colon, but not in the peripheral blood, of CD patients [58]. IL-27, which serves as an inhibitor of Th17 differentiation [59], was identified recently as an early-onset IBD susceptibility gene [15]. Although some studies using IL-27R KO mice already have been conducted, the data remain controversial. One study showed that IL-27R KO mice are highly susceptible to DSS-induced intestinal injury [60], whereas other research showed their resistance to this injury [61].

Despite the significant increase in Th17 cells in IBD, recently accumulating studies from animal models suggest that the role of Th17 in the pathogenesis of IBD may be much more complicated than previously predicted. Neutralization of IL-17A activity results in the suppression of colitis development in IL-10 KO mice [45], and the absence of the IL-17 receptor causes the mice to become resistant to trinitrobenzene sulfonic acid (TNBS)-induced acute colitis [62]. In addition, the lack of an adaptor protein Act1 for IL-17R signaling protects mice from DSS-induced intestinal injury [63]. In contrast, neutralization of systemic IL-17A activity by administration of anti-IL-17A mAbs has been shown to

exacerbate DSS-induced acute intestinal injury [64•]. No role for Th17-derived IL-17 has been demonstrated in CD45RB model [65], a well-established model for studying CD. A recent study showing that colitis in CD45RB model is mediated by the Th17 cells but not by IL-17 produced by these cells suggest that the biology is complicated [49,66]. In addition, the rather regulatory role of IL-17A in the CD45RB model has been proposed recently [67]. Future studies may be required to determine whether IL-17 can be targeted for the treatment of IBD.

IL-22 and IL-21

A cytokine that is produced by the Th17 subset is IL-22 which belongs to the IL-10 cytokine family and specifically targets innate, but not adaptive, immune responses through the activation of STAT3. The specificity is because of the restricted expression of the IL-22 receptor complex on innate cells, particularly epithelial cells [68,69•]. Of note, IL-22 has been identified recently as a potential susceptibility gene in UC [14] and polymorphisms of the IL-10 receptor (IL-10R) 2 that is shared by both IL-10 and IL-22 receptors are associated with the development of IBD [10•]. Interestingly, the expression pattern of IL-22 seems to differ in the large versus small intestines. Expression of IL-22, which is rarely detectable in the normal colon of both mice and humans, is induced by inflammation, but the expression level is still low in UC as compared to CD [69•,70]. The major sources of IL-22 in the IBD colon is Th17 and NK cells [71•,72], while the major source in an infectious colitis may be DCs [73]. In contrast, IL-22 is constitutively expressed in the small intestine to maintain normal intestinal homeostasis by ROR γ t-dependent NKp46⁺ NK cells that are derived from lymphoid tissue-inducer cells [74]. Although IL-22 can cause skin disease psoriasis and autoimmune myocarditis [75], a series of recent studies have unveiled the protective role of IL-22 against intestinal inflammation. Supplementation of IL-22 levels through colon-specific gene delivery not only attenuates an established Th2-mediated chronic colitis in TCR α KO mice but also enhances the recovery from DSS-induced acute intestinal injury [69•]. This observation is supported by a more recent study showing impaired recovery from this injury in IL-22 KO mice [22]. In addition, a protective role of IL-22 is demonstrated in the CD45RB model of Th1-mediated colitis [71•]. Furthermore, IL-22 KO mice are highly susceptible to an infectious colitis induced with *Citrobacter rodentium* [73]. The protective role of IL-22 against colitis is mediated by the activation of STAT3 in epithelial cells [22,69•]. IL-22-mediated STAT3 activation induces the production of goblet-cell-associated molecules such as mucins capable of strengthening the epithelial barrier function against commensal microbiota [69•,76]. Importantly, STAT3 and a mucin family member MUC19 have been identified as IBD susceptibility genes [1•,11•]. In addition, IL-22 can enhance the production of Reg III γ [73] that serves as an antibacterial peptide against Gram-positive bacteria [33]. These recent findings clearly highlight IL-22 as a promising candidate for biological therapy for IBD. However, unlike its role in the colon, IL-22 also plays a deleterious role in a 'small' intestinal inflammation caused by *Toxoplasma gondii* [77]. In addition, IL-22 can cause psoriasis [78]. Therefore, colon-specific manipulation of IL-22 levels may be a more ideal strategy for treating IBD safely and effectively without affecting systemic levels. The direct accessibility of the colon by colonoscopy or capsule endoscopy would make local therapy possible [69•].

Another Th17 cytokine IL-21 [79] is produced not only by Th17 but also by mucosal T follicular helper cells (Tfh) that are differentiated from Foxp3⁺ Treg cells and support the differentiation of B cells to plasma cells [80]. A strong association between the IL-2/IL-21 locus and UC has been found [13]. Interestingly, unlike normal steady state levels, a major source of IL-21 in the inflamed mucosa of IBD patients is CD4⁺ T cells that coexpress IL-21 and IFN- γ [81], suggesting that normal T cell differentiation programming may be impaired under intestinal inflammatory conditions. This possibility may be supported by the impaired

differentiation of monocytes in the inflamed colon, which results in the development of unique myeloid cells sharing properties of both DCs and macrophages in the inflamed mucosa of CD patients as well as in the IL-23-mediated colitis model [50,82]. A study using IL-21 KO mice has observed the protective role of IL-21 against two types of acute intestinal inflammations induced by DSS or TNBS [83].

Regulatory networks

The digestive tract is host to over a trillion viable bacteria consisting of 500–1000 microbial species, which manufacture numerous products that are not only essential for normal intestinal immune homeostasis but also capable of stimulating harmful immune responses [84,85]. Given its anatomical properties and with direct exposure to commensal microbiota, the digestive tract may provide an important environment for inducing the development of immunoregulatory cell subsets. Indeed, Treg cell subsets such as CD4⁺ CD25⁺ Treg cells [86,87], TGFβ-producing Th3 [88], and IL-10-producing Tr1 [89] were all discovered by studies of inflammation within the digestive tract. Interestingly, a breach of the epithelial cell barrier, which enhances host/microbial interaction, stimulates Foxp3⁺ Treg cell development [90]. In addition, a recent *in vivo* imaging study revealed that the number of Foxp3⁺ Treg cells increases during recovery from DSS-induced acute intestinal injury that destroys the epithelial barrier against commensal flora [91]. In contrast, a majority of chronic colitis models except the SAMP1 model (a congenic CD model developing ileitis) fail to develop colitis when housed under germ-free conditions [2,92]. Therefore, it is possible that commensal flora serve as an environmental factor which not only activate effector T cells (e.g. Th17) but also simultaneously induce intestinal Treg development particularly under intestinal inflammatory condition.

Accumulating evidence from animal models clearly indicates the protective role of IL-10 in IBD [2,3]. Indeed, spontaneous development of colitis in IL-10 KO mice has been known since 1993 [23]. The possible clinical relevance of data from animal models is highlighted by a recent identification of the IL-10 as an IBD susceptibility gene [1•,11•]. Recent studies have shown that expression of Foxp3 in Treg cells is unstable *in vivo* and potential autoreactive effector T cells can develop from the Foxp3⁺ Treg cells as a consequence of loss of Foxp3 [93]. Myeloid cell-derived IL-10 is required for maintaining Foxp3 expressions in Treg cells and preserves the regulatory cell's ability to suppress colitis [94•]. In addition to Treg cells, an inducible regulatory B cell subset termed Breg, which appears only under inflammatory condition and limits the progression, but not induction of disease through the production of IL-10, were first identified in mesenteric lymph nodes, a gut-associated lymphoid tissue (GALT) [95]. A recent study using eGFP/IL-10 reporter mice confirms that B cells are one of the major sources of IL-10 in GALT [96•]. Although IL-10 KO mice spontaneously develop colitis [23], specific deletion of IL-10 in B cells does not result in colitis induction [96•], consistent with the ability of IL-10-producing Breg cells to inhibit the progression of established colitis but not the initial induction [97,98]. These findings suggest IL-10 may be a potential biotherapeutic for IBD. However, no apparent beneficial effect of IL-10 therapy has been observed in several human clinical trials [99]. Therefore, it is possible that the polymorphisms of IL-10 receptors [10•] hamper the response of IBD patients to the IL-10 therapy [99]. Alternatively, the instability and short half-life of IL-10 may make the therapy less effective. Engineered lactic acid bacteria have been successfully employed to deliver the biologically active IL-10 into the intestine of animal models of IBD [100] and a phase I clinical trial has suggested the beneficial effect of *Lactococcus lactis*-mediated IL-10 therapy on some CD patients [101].

Antigen presentation and regulatory B cells

A growing body of evidence from animal models of IBD indicates that both adaptive and innate immune responses participate simultaneously in the pathogenesis of IBD. Directly linking adaptive and innate immune responses, APCs capable of processing microbial antigens and then stimulating T cells through MHC play a significant role in the disease process. The importance of antigen presentation in the pathogenesis of IBD is highlighted by the identification of MHC loci as a UC-associated gene [1•,11•]. The involvement of autophagy in MHC class II-dependent antigen presentation [18•,41] further supports this concept. DCs are professional APCs that are characterized by high expression of MHC class II molecules. The function and migration of intestinal DCs that determine the differentiation of T cells into effector versus regulatory subsets are controlled by a chemokine CCR6 [102], a CD-associated gene [1•,11•]. In addition, recent studies have unveiled that intestinal basophils, which can be selectively induced by epithelial cell-derived thymic stromal lymphopoietin (TSLP) not by IL-25 or IL-33, serve as a dominant APC to induce Th2 immune responses through MHC class II in intestinal *Trichuris muris* infection [103•].

The intestine has an antigen-independent innate-type B cell subset that is supplied from transitional/naïve B2, but not B1, B cell pools [104]. Interestingly, this B cell subset is characterized by high expressions of MHC class II without costimulatory molecule expression, which is characteristic of tolerogenic APCs capable of inducing oral tolerance [105]. In addition, some regulatory B cell subsets exhibit a transitional stage phenotype, express high levels of MHC class II and contribute to the expansion of Treg cells [106–109]. A homeodomain transcription factor Nkx2-3 is an IBD susceptibility gene [1•,11•]. Nkx2-3 KO mice exhibit aberrant distribution pattern of transitional B cells regardless of normal expressions of homing/chemokine receptors [110]. In addition, the absence of another CD susceptible gene T cell protein tyrosine phosphatase (PTPN2) in bone marrow inhibits the development of B cells [111]. Furthermore, a recent study shows that activation of an IBD susceptibility gene STAT3 is required to fully elicit the regulatory function of transitional B cells in humans [109]. These findings may highlight the potential regulatory role of B cells in IBD [97].

A recent genome-wide association study has identified Fcγ receptor IIb (FcγRIIb) as an IBD-associated gene [11•]. IBD, particularly UC, is characterized by significantly increased productions of autoantibodies [112]. Interestingly, exacerbation and induction of UC by B cell-depletion therapy have been shown in two case reports in humans [113,114]. FcγRIIb contains an immunoreceptor tyrosine-based motif (ITIM) capable of regulating the balance between protective and autoreactive immune responses [115]. Although FcγRIIb has been known since 1977, only limited information on the role of FcγRIIb in the pathogenesis of IBD is currently available. Administration of Fc, but not F(ab)², fragments of IgG contributes to the suppression of a Th2-mediated colitis developing in TCRα KO mice, a model of UC [116]. Alternatively, the absence of FcγRIIb enhances the clearance of an enteric pathogen *C. rodentium* [117]. Since B cell-targeting therapy has already been successfully applied to patients with some autoimmune diseases [118], future studies on B cells are required to produce B cell-targeted therapies safely and effectively applicable to IBD.

Conclusion

As shown in Figure 2, previous and current data from animal models of IBD indicate that the pathways, which are identified in IBD patients through gene association studies, directly or indirectly link together to make an 'IBD immune network'. Therefore, therapeutic strategies targeting the network may be warranted for IBD. Alternatively, data from animal

models also suggest that the fundamental mechanism of IBD is much more complicated than previously and even currently predicted. For example, the role of an individual molecule in IBD distinctly differs depending on several factors such as cell types involved, the tissues targeted, and the environments exposed. Therefore, cell-specific, tissue-specific, or personalized therapy such as through engineered lactic acid bacteria [99], nanoparticle [119], colonoscopy-guiding gene delivery [69•], or capsule endoscopy-mediating delivery systems may be required to improve the lives of patients with IBD more effectively and more safely.

Animal models have tested useful experimental interventions for developing therapeutic strategies for IBD [16]. Indeed, they have identified potential candidate molecules for IBD therapy, and some of them such as IL-12p40 and CD3 are targeted in currently on-going human clinical trials [16]. In addition, recently established genetically engineered mouse models lacking IBD susceptibility gene should be promising tools to develop novel therapeutic measures for IBD. Alternatively, anti- $\alpha 4$ integrin therapy, which was beneficial in some animal models of IBD, has been reported to cause JC-virus-induced multifocal leukoencephalopathy in some CD patients [120]. Therefore, careful attention may be required to translate animal studies to clinical settings by ensuring that both safety and efficacy can be modeled.

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Figure 1.

Animal models of IBD. Many animal models of IBD are currently available to use, including knockout mice (pink), transgenic mice (blue), congenic mice (orange), chemically induced models (gray), and cell-transfer model (green). There are genetically engineered mice that have specific deletion of a target molecule in epithelial cells (**a**), epithelial cells/macrophages (**b**), thymic epithelial cells (**c**), dendritic cells (**d**), or B cells (**e**). Mouse models, which have been used for studying UC, are surrounded by an orange circle. Mouse models, which develop ileitis spontaneously, are indicated by blue stars. Mouse models, which lack an IBD-associated gene, are highlighted by red stars. The abbreviations used in this figure are: A20, also known as TNF-induced protein 3; Atg, autophagy gene; $\alpha\text{v}\beta 8$, integrin $\alpha\text{v}\beta 8$; CBI-b, E3 ubiquitin ligase; DSS, dextran sulfate sodium; Gai2, G protein $\alpha i 2$; GFAP-Hatg, transgenic mice in which entero glia is specifically disrupted; GPX, glutathione peroxidase; HLA/B27, HLAB27/human $\beta 2$ microglobulin transgenic rats; LIGHT, a TNF superfamily member; Mdr, multiple drug resistance; Muc, mucin; NCAD, transgenic mice which overexpress dominant negative N-cadherin in the intestinal epithelial cells; NEMO, NF κ B essential modulator; NFAT, nuclear factor of activated T cells; SAMP, a congenic mouse developing ileitis; STAT, signal transducer and activator of transcription; TAK, TGF β -activated kinase; T-bet, T-box transcription factor; TCR, T cell receptor; Tir8, also known as SIGIRR (single Ig IL-1-related receptor); TLR, toll-like receptor; TNBS, trinitrobenzene sulfonic acid; TNF Δ ARE, mice lacking TNF AU-rich elements; WASP, Wiskott–Aldrich syndrome protein; XBP1, X-box binding protein.

Figure 2.

IBD immune network. Genes specific for both CD and UC (orange ellipses), for CD (green ellipses) and for UC (pink ellipses) have been identified. Genetically engineered mice are currently available for studying these IBD-associated genes. Previous and current data from animal models indicate that IBD-associated genes are positively (blue lines) or negatively (red lines) linked together, making a complicated network. For example, both NOD2 and autophagy, which are primarily involved in epithelial defense against commensal microbiota, can control IL-23/Th17 axis through antigen presentation. The IL-23/Th17 axis can directly activate epithelial defense through IL-22 and also represent a key determinant of differentiation of effector versus regulatory immune responses. Regulatory immunity can modify the IL-23/Th17 axis and also influence epithelial defense. Enteric microorganisms can stimulate not only Th17 but also Treg developments.