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# Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies

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Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disorder with an unknown etiology. IBD is composed of two different disease entities: Crohn's disease (CD) and ulcerative colitis (UC). IBD has been thought to be idiopathic but has two main attributable causes that include genetic and environmental factors. The gastrointestinal tract in which this disease occurs is central to the immune system, and the innate and the adaptive immune systems are balanced in complex interactions with intestinal microbes under homeostatic conditions. However, in IBD, this homeostasis is disrupted and uncontrolled intestinal inflammation is perpetuated. Recently, the pathogenesis of IBD has become better understood owing to advances in genetic and immunologic technology. Moreover, new therapeutic strategies are now being implemented that accurately target the pathogenesis of IBD. Beyond conventional immune-suppressive therapy, the development of biological agents that target specific disease mechanisms has resulted in more frequent and deeper remission in IBD patients, with mucosal healing as a treatment goal of therapy. Future novel biologics should overcome the limitations of current therapies and ensure that individual patients can be treated with optimal drugs that are safe and precisely target IBD.

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## INTRODUCTION

The entire surface of the human intestine reaches 200~400 $m^2$ (1). Moreover, it occupies a central position as the frontier of the innate immune system. The inner cell lining of the intestine works not only as a barrier to protect the host from harmful pathogens but also as a place where interactions with commensal microorganisms occur. These interactions are delicately modulated by the intestinal immune system and contribute to immune homeostasis. For various reasons, idiopathic intestinal inflammations such as inflammatory bowel disease (IBD) can occur when this homeostasis is disrupted (2,3).

IBD is a multifactorial immune disorder characterized by chronic relapsing inflammation of the intestine (4). It is classified into two different disorders: Crohn's disease (CD) and ulcerative colitis (UC). Clinically, CD and UC share similar symptoms, including diarrhea, hematochezia, and abdominal pain, whereas the location and depth of inflammation, as well as complications and prevalence can differ. Currently, the exact etiology of IBD is unclear. However, it is believed that disturbance

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of the immune system and/or imbalanced interactions with microbes leads to development of chronic intestinal inflammation when certain environmental factors trigger genetically susceptible hosts. Traditionally, Th1 cells have been thought to play an important role in pathogenesis related to the chronicity of intestinal inflammation, especially in CD, whereas Th2 cells have been thought to play an important role in UC (5). Recently, however, activation of Th17 cells and imbalance of Th17/regulatory T (Treg) cells are recognized to be an important component in the development of intestinal inflammation (6). Since tumor necrosis factor (TNF)-α has been identified as a key cytokine in IBD pathogenesis, the introduction of anti-TNF-α treatment has led to the development of disease-modifying drugs (7-9). Compared to conventional therapies, anti-TNF agents have higher rates of remission induction and maintenance. Moreover, these drugs have been able to obtain mucosal healing through targeted immune suppression. However, about a third of patients with IBD still do not show an appropriate response to existing therapies. This high rate of treatment failure suggests that there are still unknown aspects regarding the mechanism of IBD. Encouragingly, however, dozens of novel agents based on recent advances in our understanding of the mucosal immune system for IBD pathogenesis have been developed and are now in clinical trials worldwide. In this review, we will describe our current knowledge of the mucosal immune system in terms of IBD pathogenesis and discuss its therapeutic implications.

## THE INTESTINAL EPITHELIUM AND MICROBIOTA

The intestinal epithelial cell (IEC) layer consists of several different cells, including enterocytes, goblet cells, neuroendocrine cells, Paneth cells, M cells, and epithelial resident intestinal stem cells. These cells structurally constitute crypts and villi, with a single columnar cell lining with a tight junction, and secrete mucus containing anti-microbial peptides; these cells separate intra-luminal pathogens from the subepithelial lamina propria (3,10,11).

### Mucus layer

To protect mucosa, a mucus layer covers the outer epithelial surface. The mucus layer is composed of glycosylated mucin from goblet cells as well as defensins from Paneth cells and IECs. A major component of mucin is encoded by *Muc2*, and spontaneous colitis develops upon deletion of *Muc2* in mice (12). A study showed that aberrant mucin production was accompanied by endoplasmic reticulum (ER) stress (13). Goblet cell depletion and a reduced mucus layer are characteristic findings in patients with UC (14). In addition to mucin, Paneth cells secret α-defensin, whereas most IECs produce β-defensin. Paneth cells are known to play an important role in the homeostasis of the intestinal epithelium. Genetic alterations or ER stress causing Paneth cell dysfunction or depletion result in dysbiosis of commensal flora and increased susceptibility to intestinal inflammation (15). It is known that IBD patients often have this Paneth cell dysfunction (16). Paneth cell abnormalities are thought to be a very early event in IBD development, particularly in CD. Therefore, there are studies examining the effects of applying ER-stress-reducing methods to IBD treatment. A study showed that the chemical chaperones tauroursodeoxycholate (TUDCA) and 4-phenylbutyrate (PBA)—small molecules that can reduce ER stress by facilitating protein folding—prevented the induction of intestinal inflammation in mice (17).

### Integrity of the intestinal epithelium

Epithelial integrity is maintained by tight junctions between IECs. When the permeability of the intestinal epithelium is increased, external pathogens are easily introduced, which is known to affect the pathogenesis of IBD (18). Several lines of evidence showed that single-nucleotide polymorphisms in the organic cation transporter (OCTN), which mediates the transport of organic cations across the cell membrane, were associated with CD susceptibility (19,20). IECs also play a role as communicator between pathogens and lamina propria. Only small amounts of bacteria are generally capable of moving into the intestinal epithelium. This translocation is a method of antigen sampling and immune surveillance for the intestinal mucosal immune system that is essential for the host's immune homeostasis (21). However, when the integrity of the intestinal epithelial layer is broken, a high influx of intestinal contents and/or a high burden of microorganisms is thought to initiate and maintain a sustained inflammatory response, which is considered to be one of the mechanisms underlying IBD (22). For example, in an animal model in which the barrier function of the intestinal epithelial layer is reduced, such as in mice with a dominant negative N-cadherin mutation (23) or mice lacking NOD1 and NOD2 (24), the mice develop IBD-like enteritis. Moreover, several genetic studies have identified several candidate genes in patients with UC (25,26), such as *CDH1* and *LAMB1*, which are involved in regulation of the epithelial barrier. Therapeutic attempts to restore mucosal barrier function have also been attemp-

ted. Phosphatidylcholine (lecithin) is abundant in the mucus of healthy colons, whereas reduced lecithin levels were observed in UC patients (27). A phase IIA, double-blind, randomized, placebo-controlled study showed that oral administration of lecithin was effective for achieving clinical remission in patients with chronic active UC (28).

### Intestinal microbiota

Generally, there are approximately $10^{11}$~$10^{14}$ enteric commensal microorganisms from 300~500 bacterial species (29,30). Under normal circumstances, most commensal bacteria play an essential role in protecting intestinal homeostasis. They affect crucial nutrient provision, development of the immune system, and modulation of energy metabolism (5,31). The majority of commensal bacteria consist of gram-negative bacteria, such as *Bacteroidetes*, and gram-positive bacteria, such as *Firmicutes* (32). Other minor divisions are comprised of *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* (32). Those mucosa-associated phyla are reduced in diversity and amount in patients with IBD compared to that in healthy humans (5,33,34). However, commensal microorganisms can be noxious for intestinal inflammation under certain circumstances (35). There are some clues that commensal bacteria play an important role in the development of IBD. First, empiric antibiotic treatment has been effective in some IBD patients (36). Second, IBD patients have increased titers against indigenous bacteria (37). Third, genetic variants that are associated with bacterial detection, such as *NOD2* (38), and T cell immunity, such as *IL23R* (39), are implicated in IBD. Fourth, most animal models of colitis require commensal bacteria for the initiation of intestinal inflammation (40). In addition, recent studies have focused on the contribution of other enteric microorganisms, such as viruses or fungi, for IBD development. For example, a study (41) revealed that altered amounts and compositions of enteric virus were related to experimental colitis. In particular, mice without Toll-like receptor (TLR) 3 and TLR7 were more susceptible to the induction of colitis. Likewise, Iliev *et al*. reported that mice deficient for Dectin-1, which is an innate immune receptor responsible for interacting with commensal fungi, showed increased susceptibility to colitis (42).

To date, several pathogens have been proposed as causative microorganisms for IBD development. Recent studies showed *Proteobacteria*, especially adherent-invasive *Escherichia coli* (AIEC), as one of the candidates. AIEC has been detected more frequently in patients with CD than in healthy subjects (43-45). AIEC is known to be able to invade epithelium and replicate within macrophages (46). Some investigators isolated AIEC from the ileum of patients with CD (47,48). However, AIEC was rarely found in the colon tissues of CD patients and was not identified in UC patients (49), suggesting that AIEC performs an important role in the occurrence of small bowel inflammation (18).

In contrast, *Clostridium* cluster *XIVa* and *IV* are thought to be a crucial part of gut homeostasis through Treg cell accumulation (50). $Foxp3^{+}CD4^{+}$ Tregs are known to be abundant in the colonic lamina propria and are the most important immune-regulating cells (51). Several studies showed that Treg cells were strongly affected by intestinal microbiota (52). In particular, Treg cells stimulated by CBir1, a microbiota flagellin, induce $IgA^{+}$B cells in the intestine. As a result, decreased pathogenic loading by IgA leads to down-regulation of systemic T cell activation (53). An experimental murine model with an increased *Clostridium XIVa/IV* population was resistant to allergy and intestinal inflammation (50). Conversely, patients with IBD showed a reduced *Clostridium XIVa/IV* compared to that in controls (34,54,55).

Observations of dysbiosis in IBD patients led to efforts to restore microbiota to a normal composition. Fecal microbial transplantation (FMT) has emerged as a novel treatment in patients with IBD. One randomized control trial involving 75 UC patients showed a significantly higher remission rate (24%) in patients receiving FMT from unrelated donor enemas than that in the placebo group (5%) (56). However, a second randomized control trial with 48 UC patients reported a negative result (57). Currently, there are no randomized control trials comparing FMT with placebo treatment in CD patients. A meta-analysis using four case series data in 38 CD patients revealed a 60.5% pooled response rate (58). However, their outcome was not that of mucosal remission but of clinical response. Therefore, the effectiveness of FMT as a therapeutic application for IBD remains unclear. Furthermore, optimal donor selection, delivery methods, and donor feces processing have not yet been standardized. Probiotics are nutritional supplements that contain microorganisms that benefit the host's health when administered in the proper amount. Attempts have also been made to treat IBD by improving intestinal microbial balance through probiotics. In an experimental colitis model, probiotics showed an anti-inflammatory effect through TLR9 signaling (59). A recent meta-analysis using 23 randomized controlled trials showed that administration of probiotics was associated with benefits regarding induction and maintenance of remission in

patients with UC but not in CD (60). Further studies are warranted to draw a concrete conclusion in terms of the therapeutic effects of probiotics in IBD.

## INNATE AND ADAPTIVE IMMUNITY IN IBD TREATMENT

### Innate immune recognition

The innate immune system is at the forefront of defending against external pathogens in the human immune system. The innate immune system provides rapid and non-specific protection to the host through pattern-recognition of pathogens, whereas the adaptive immune system mediates highly selective and long-lasting immunity. The innate immune system of the intestine is composed of intestine epithelia, macrophages, monocytes, neutrophils, eosinophils, basophils, dendritic cells (DCs), and natural killer cells. Intraluminal pathogens continuously communicate with innate immune cells through diverse innate immune receptors such as TLRs, NOD, leucine-rich repeat receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene 1-like receptors (RLRs) (61). When intestinal macrophages and DCs sense pathogen-associated molecular patterns (PAMPs) of microbes, activated signal pathways, such as NF-κB, produce proinflammatory cytokines, chemokines, and anti-microbial peptides (62). Activation of macrophages by these cytokines and chemokines plays a role in the direct elimination of pathogens through free radicals and proteases and also results in antigen presentation to the adaptive immune system. Antigen presenting cells (APCs), such as DCs and macrophages, have a key role in connecting the innate and adaptive immune system. Comparing that macrophages perform antigen presentation and have a phagocytic function, activated DCs present intraluminal pathogens to naïve $CD4^+$ T cells at secondary lymphoid organs of the gut and modulate the polarization of naïve $CD4^+$ T cells to Treg cells and helper T cells, including Th1, Th2, and Th17 cells.

Under non-inflammatory conditions, TLR signaling leads to tolerance towards luminal pathogens through down-regulation of pattern-recognition receptors and promotes mucosal wound healing. In IBD patients, impaired TLR signaling often leads to increased intestinal permeability and inappropriate mucosal healing. For example, TLR2-deficient mice showed an increased mortality rate after damage was induced to the colon mucosa via chemicals. TLR2 signaling stimulates the production of trefoil factor (TFF) 3 and restores damaged mucosa. In mice lacking TLR2, mortality was reduced when TFF3 was administered (63). Likewise, genetic studies showed the association between CD and the nucleotide oligomerization domain (*NOD*) 2 gene. *NOD2* polymorphisms lead to an impaired response to bacterial peptidoglycan sensing. While the exact mechanism between CD and impaired NOD2 function is still unclear, NOD2-mediated chronic stimulation is thought to be one of the factors controlling proinflammatory cytokine production. Recent genome-wide association studies (GWAS) showed relationships between a variety of single-nucleotide polymorphisms (SNPs) and IBD risks: microbial sensing (*NOD2*, *IRF5*, *NFKB1*, *RELA*, *REL*, *RIPK2*, *CARD9*, and *PTPN22*), microbial elimination (*ATG16L1*, *IRGM*, and *NCF4*), and integration of antimicrobial adaptive immune responses (*IL23R*, *IL10*, *IL12*, *IL18RAP/IL1R1*, *IFNGR/IFNAR1*, *JAK2*, *STAT3*, and *TYK2*) (64-66). Recent studies have shown that autophagy plays an important role in the innate immune system. Autophagy is a biological process that activates cellular autodigestion of the cell's own cytosolic materials, including intracellular microbes. Additionally, autophagy enables antigen presentation by major histocompatibility complex class II. Repeated GWAS studies consistently showed the association between CD and autophagy-related genetic polymorphisms, such as *ATG16L1* and *IRGM* (67-71). The accumulation of both macrophages and DCs is observed in the lamina propria of IBD patients and in experimental colitis models (3). If interactions between DCs and T cells are interrupted, experimental T cell-mediated colitis is prevented (72). Moreover, DCs and macrophages also play a role in maintaining gut homeostasis against the inflammatory conditions of the intestine. A study showed that a pro-resolution mediator, prostaglandin D (2), was specifically up-regulated in UC patients with long-term remission (73). Likewise, another study revealed that a SNP associated with low levels of CD39/ENTPD1, which hydrolyzes proinflammatory nucleotides and generates adenosine, was related to an increased risk of developing CD (74). Taken together, an impaired innate immune response might promote IBD development via inappropriate stimulation of adaptive immunity through failure to control microorganisms (66). Therefore, researchers have focused on enhancing innate immunity as a therapeutic target of IBD. For example, certain growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), which are critical for modulation of cellular proliferation, differentiation, angiogenesis, and inflammation, have been evaluated for

treatment of intestinal inflammation (75).

### Adaptive immunity

Chronic inappropriate activation of the adaptive immune system against commensal microorganism has been thought to be the main pathogenesis of IBD. Increased production of IFN-γ from Th1 cells and cytokines related with Th17 cell, such as IL-17A/F, IL-21, IL-22, and CXCL8, are observed in the intestine of CD patients, while T cells from the lamina propria of UC patients highly produce Th2 cell-related cytokines, such as IL-5 and IL-13 (3,76,77).

Classically, immune-modulating treatments of IBD have focused on adaptive immunity. Corticosteroids have been widely used to treat acute flares of IBD since Truelove and Witts reported the effectiveness of oral corticosteroids in patients with UC in 1955 (78). Suppression of pro-inflammatory cytokines, such as TNF-α and IL-1β, is known to be the primary mechanism underlying how corticosteroids control IBD (79). In addition, recent studies highlighted that corticosteroids play an important role in regulation of T helper cell differentiation and type I interferon (IFN) production (79). Clinically, corticosteroids are effective for remission induction of IBD. A study observed that the first course of oral corticosteroid treatment achieved 89.5% of therapeutic response after 1 month, 69.5% after 4 months, and 56.6% after 1 year in patients with CD (80). Likewise, various immunomodulators that down-regulate the proinflammatory cytokines of T cells have been a well-established treatment for IBD. For example, cyclosporine A and tacrolimus are used for remission induction of active UC, and methotrexate is used for chronically active CD (81-83). Of these treatments, the most widely used agent is thiopurines, such as azathioprine and 6-mercaptopurine. Thiopurine inhibits purine nucleotide synthesis and breaking of DNA in leukocytes via 6-thioguanine nucleotides (6-TGNs), which is the effector product of thiopurine metabolism (84). Moreover, thiopurine suppresses $CD4^+$ T cell activity and promotes T cell apoptosis by inhibiting GTPase Rac1 in inflamed intestine (85). Recently, a study showed that autophagy-relate genetic variant, *ATG16L1*, was associated with the good clinical towards thiopurine treatment in patients with CD but not in UC (86). In addition, a study showed that local administration of thioguanine improved murine colitis by promoting autophagy and killing translocated bacteria at the site of the inflamed intestine independently of systemic myelosuppression (87). Therefore, thiopurine probably works by multiple mechanisms to improve IBD. Meanwhile, thiopurine may cause life-threatening leukopenia. The *TPMT* mutation is known to be associated with this complication (88). More specifically, a study involving immunochip genotyping of Asians revealed that *NUDT15* SNP was strongly related to thiopurine-induced leukopenia, and another study showed an association between *FTO* variant and leukopenia by GWAS analysis (89,90). Although non-specific immunosuppression using immunomodulators is generally safe and effective for disease control to an extent, advances in the understanding of the specific mechanisms of IBD led to the development of targeted treatment, i.e., biologics.

### Modulation of anti-inflammatory cytokines

The era of biologic therapy began with an anti-TNF agent, infliximab, in patients with CD (91). TNF-α is a proinflammatory cytokine that is produced by activated macrophages, monocytes, and T lymphocytes (7). Intestinal specimens of CD patients were shown to have increased levels of TNF-α protein and mRNA expression (92). Excessive production of TNF-α using experimental deletion of the adenosine-uracil (AU)-rich elements (ARE) from the 38-untranslated region (38-UTR) of the TNF-α gene in mice resulted in development of chronic inflammatory arthritis and CD-like IBD phenotype (93). Another experimental study revealed that inhibiting TNF was able to improve dextran sulfate sodium (DSS)-induced colitis in a mice model (94). Therefore, TNF-α has been thought to play a pivotal role in the development of IBD.

TNF-α has two forms in the human intestine: transmembrane TNF (mTNF) and soluble TNF (sTNF). mTNF is generally expressed on the surface of $CD14^+$ macrophages and targets TNF-R2 of T cells, whereas sTNF is secreted by several immune cells as a signaling molecule and targets TNF-R1 of effector cells (95,96). In IBD, increased levels of both mTNF and sTNF play various pro-inflammatory functions in the inflamed gut, such as angiogenesis, Paneth cell death, matrix metalloproteinase production from myofibroblasts, and the undermining of the barrier function of IECs (77). Recent studies have shown that interaction between mTNF and TNF-R2 is more important for IBD pathogenesis than that of sTNF and TNF-R1 (97,98).

Several anti-TNF-α monoclonal antibodies have been developed since infliximab (chimeric antibody with a murine sequence) and adalimumab (fully humanized antibody) showed effectiveness for induction and maintenance of remission, as well as mucosal healing of

IBD (99-103). A humanized, pegylated anti-TNF Fab fragment, certolizumab pegol, also showed benefits and was approved for CD treatment (104). Moreover, golimumab, a transgenic fully human monoclonal immunoglobulin G1 antibody, was recently launched for the treatment of UC (105). However, another anti-TNF agent that targets sTNF, etanercept, showed no benefits regarding treatment of IBD (106,107). Although there are several limitations of anti-TNF treatment, such as safety issues, relatively high cost, and loss of effectiveness, the potential benefits of anti-TNF agent may outweigh these drawbacks, because blocking the TNF signal in IBD works through various mechanisms, including T cell apoptosis, inhibiting T cell differentiation, induction of Treg cells and macrophages, and barrier improvement (96,108-110). Therefore, efforts to overcome the drawbacks of anti-TNF agents, such as oral formulations, bacteria-producing nanobodies, and therapeutic vaccines against TNF are still in development (111-113).

Other important cytokines in the treatment of IBD are related to Th17 cells (IL-17A, IL21, IL-22, and IL-23) (114). Th17 cells are differentiated from naïve $CD4^+$ T cells that are stimulated with transforming growth factor (TGF)-β and IL-6 in mice models. The inflamed intestinal tissue of IBD patients was shown to contain higher levels of Th17 cells and its cytokines (115). Additionally, a chemoattractant of Th17 cells, CCL20, is also elevated in the intestinal mucosal of IBD patients (116). While the exact role of Th17 cells and their cytokines in regards to intestinal inflammation has not yet been fully understood, the balance between Th17 and Treg cells are thought to be an important aspect in development of IBD (117). Based on those viewpoints, a humanized IFN-γ antibody, fontolizumab, was developed. However, it did not show a satisfactory result in patients with moderately to severely active CD (118). Likewise, an attempt to target IL-17A through a monoclonal antibody, secukinumab, in patients with CD also failed (119). In experimental colitis models, Th17 cells and their related cytokines are thought to play both inflammatory and anti-inflammatory roles in the intestine (114). Anti-inflammatory cytokines such as IL-22 are also produced by Th17 cells. These cytokines are known to promote epithelial proliferation, mucosal healing, and anti-microbial peptides in the mucus (120). Moreover, plasticity reflecting the environmental conditions during the inflammatory process between Th1/Treg and Th17 cells is observed, and these reciprocal alterations are thought to be important for maintaining intestinal homeostasis (121). The contribution of Th17 cells for intestinal inflammation might be controlled by more detailed interactions between immune cells.

Considering the complex interactions between various cytokines that contribute IBD, the targeting of multiple cytokines is thought to be a reasonable approach in the treatment of IBD. Ustekinumab, a human monoclonal antibody against the p40 subunit that is a component of both IL-12 and IL-23, is theoretically relevant for the treatment of CD involving both Th1 and Th17 aspects of CD. IL-12 induces Th1 polarization of naïve $CD4^+$ T cells and IL-23 promotes Th17 cell differentiation (122). In moderate-to-severe CD patients, ustekinumab showed a significant clinical benefit in both remission induction and maintenance (123). Similarly, other biologics targeting the IL-12/23 pathway, such as ABT-874 (124) and apilimod mesylate (125), are under evaluation. IL-10-deficient mice can develop spontaneous T cell-dependent colitis and colitic cancer (126,127). IL-10 is known as an anti-inflammatory cytokine and the UC-related *IL10* gene variation was also noted from a GWAS study. Given this, a study used an interesting approach to treat experimental murine colitis involving the genetically engineered IL-10-secreting bacteria *Lactococcus lactis*. Intra-gastric administration of this bacteria resulted in a 50% reduction of DSS-induced colitis in IL-10- knockout mice (128).

#### Targeting inter-/intra-cellular signaling pathways

Interactions between proinflammatory cytokines and their receptors lead to activation of intracellular signal transduction and production of inflammatory proteins. Janus kinase (JAK)-signaling transducers and activator of transcription (STAT) cytokine signaling pathways are recently thought to be a potential therapeutic target of IBD. Because various key cytokines such as IFN-γ, IL-2, IL-4, IL-7, IL-9, IL-15, IL-12, IL-21, IL-22, and IL-23 depend on the JAK-signaling pathway, inhibiting JAK might result in the downregulation of multiple inflammatory cytokines (129). The JAK family consists of four intracellular proteins, JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2 (130). A JAK1/JAK3 inhibitory small molecule, tofacitinib, showed promising results for the treatment of UC in a phase II study. In 194 moderately to severely active UC patients, 78% of patients who received 15 mg of oral tofacitinib twice a day showed a favorable clinical response (131). However, these clinical responses were not repeated in patients with moderate-to-severe CD in another phase II trial (132). Currently, various kinds of JAK inhibitors are now in development and awaiting clinical results.

In IBD patients, defective tumor necrosis factor (TGF)-β1 activity is related to up-regulation of SMAD7.

Inhibition of TGF-β1 in healthy human intestines results in increased production of proinflammatory cytokines (133). In a double-blind, placebo-controlled, phase 2 trial, an oral SMAD7 anti-sense oligonucleotide, mongersen, showed a better clinical remission rate in patients with CD compared to that in patients who received a placebo (134).

Several approaches involving the targeting of differentiation and activation of T cells have been attempted. However, a cytotoxic T-lymphocyte antigen 4 (CTLA4) agonist, abatacept, which blocks APC and T cell interaction, showed no clinical benefits in regards to either remission induction or maintenance in patients with IBD (135). Similarly, a humanized monoclonal antibody to CD3 on the activated T cell, visilizumab, was shown to have no clinical benefits for treatment of IBD in phase III study (91).

### Inhibition of lymphocyte trafficking

Effector lymphocytes must travel from the periphery to the intestine for development of IBD. In this process, various adhesion molecules act on specific lymphocytes. Different lymphocytes express specific cell surface adhesion molecules targeting specific organs. Therefore, selective inhibition of those adhesion molecules potentially has a therapeutic role for IBD. Natalizumab is a humanized monoclonal antibody that binds the α4 subunit of integrin on T cells. Theoretically, gut homing of T cell results from the interaction between α4β7 integrin and mucosal vascular addressing cell adhesion molecule 1 (MAdCAM-1). Natalizumab showed clinical benefits for remission maintenance (136). However, natalizumab also

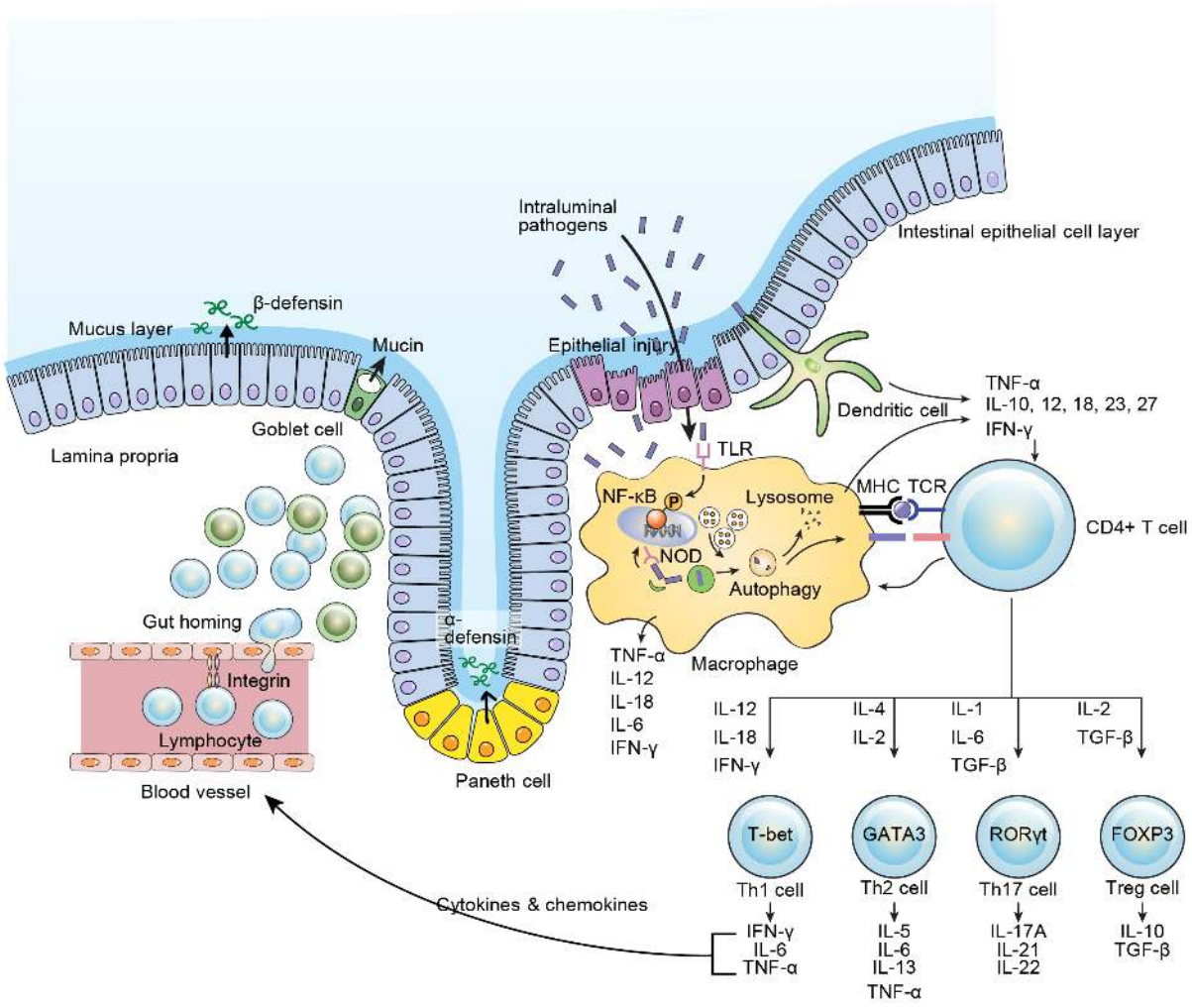


**Figure 1.** Intestinal immune system. IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth factor; Th, helper T cell; Treg, regulatory T cell; TCR, T cell receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; TLR, toll-like receptor; NOD, nucleotide oligomerization domain.

blocks α4β1 integrin, which is important for T cell homing to the central nervous system, and fatal complications such as progressive multifocal leukoencephalopathy have emerged as a result (137). Therefore, using natalizumab for IBD treatment is restricted in some countries such as the USA. A more recently developed intestine-specific, anti-adhesion molecule, vedolizumab (monoclonal antibody against α4β7), showed promising results for inducing and maintaining remission in UC, and clinical remission in CD, with a relatively good safety profile (138,139). Etrolizumab, a monoclonal antibody against the β7 subunit of integrin, is under phase III studies for CD and UC. Etrolizumab acts as dual inhibitor of the α4β7-MAdCAM-1 and αEβ7-E-cadherin interactions. Therefore, etrolizumab prevents both gut homing of lymphocytes and intraepithelial leukocyte retention of intestinal mucosa. A recent phase II trial in UC patients treated with etrolizumab showed a significantly higher clinical remission rate than that in the placebo group (140). Direct inhibition of MAdCAM-1 by its monoclonal antibody, PF-00547659, was also developed and attempted in clinical trials. Recently, mixed results were obtained, with one study showing significantly higher clinical remission rate in UC (TURANDOT study) compared to that in the placebo group, whereas another study yielded negative results for CD (OPERA study) (141,142).

## CONCLUSION

As IBD-related research progresses, understanding of these diseases is deepening (Fig. 1). However, it is not believed that only one obvious mechanism of disease will be readily apparent. With the opening of the era of biologics, it has become possible to expect deep remission in IBD patients, unlike in the past; however, about one-third of patients still do not show clinical improvement to the biological agents. A variety of new biologics specific to IBD pathogenesis are now emerging and under clinical investigation (Fig. 2). With this development, more and more patients will benefit from these novel agents. More-

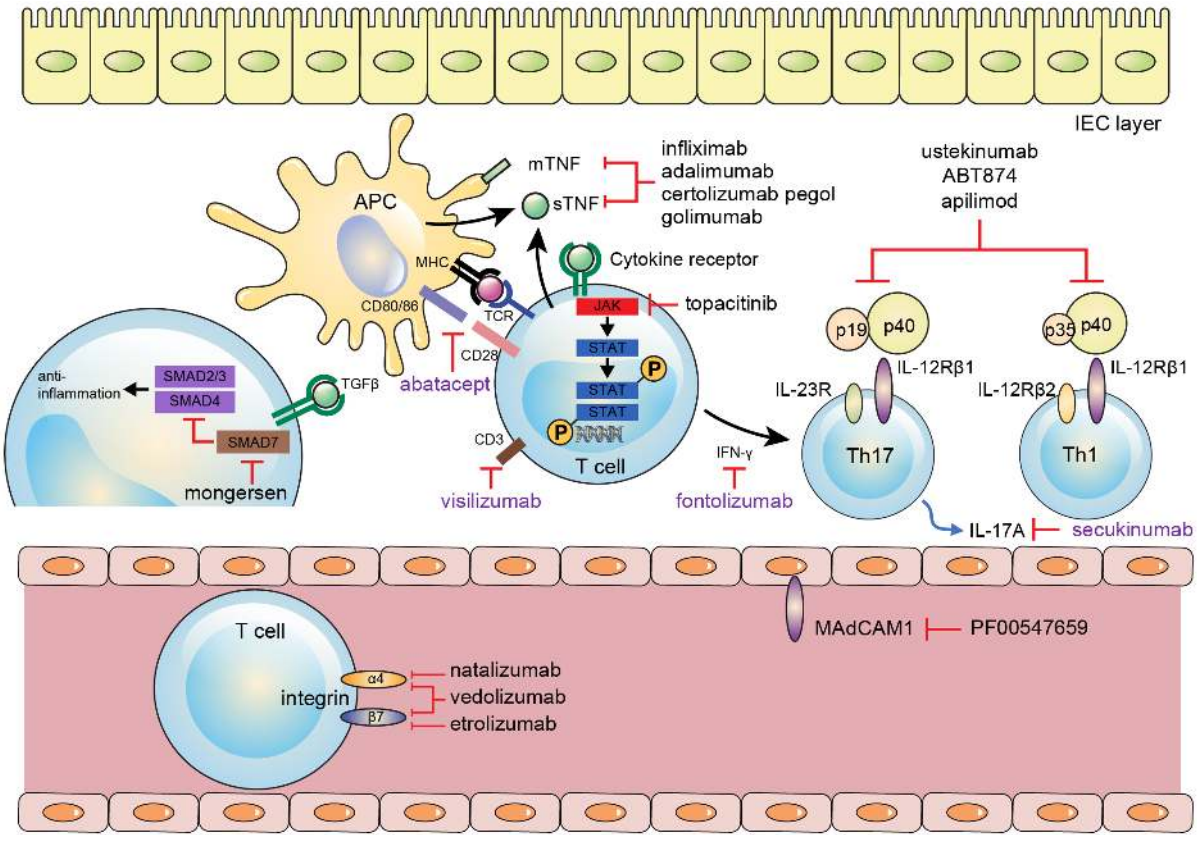


**Figure 2.** Biologics regarding therapeutic targets (black: showed benefits; violet: no benefits). APC, antigen presenting cell; IEC, intestinal epithelial cell; TNF, tumor necrosis factor; MHC, major histocompatibility complex; TCR, T cell receptor; JAK, Janus kinase; TGF, transforming growth factor; IL, interleukin; MAdCAM, mucosal vascular addressing cell adhesion molecule.

over, future IBD therapy should be approached in terms of "patient-customized treatment," and it is anticipated that it will be a great help in clinical practice to have a drug repertoire targeting various mechanisms of the disease.

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## CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

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