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TOPIC HIGHLIGHT

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# Immunopathology of inflammatory bowel disease

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## Abstract

Inflammatory bowel disease (IBD) results from a complex series of interactions between susceptibility genes, the environment, and the immune system. The host microbiome, as well as viruses and fungi, play important roles in the development of IBD either by causing inflammation directly or indirectly through an altered immune system. New technologies have allowed researchers to be able to quantify the various components of the microbiome, which will allow for future developments in the etiology of IBD. Various components of the mucosal immune system are implicated in the pathogenesis of IBD and include intestinal epithelial cells, innate lymphoid cells, cells of the innate (macrophages/monocytes, neutrophils, and dendritic cells) and adaptive (T-cells and B-cells) immune system, and their secreted mediators (cytokines and chemokines). Either a mucosal susceptibility or defect in sampling of gut luminal antigen, possibly through the process of autophagy, leads to activation of innate immune response that may be mediated by enhanced toll-like receptor activity. The antigen presenting cells then mediate the differentiation of naïve T-cells into effector T helper (Th) cells, including Th1, Th2, and Th17, which alter gut homeostasis and lead to IBD. In this review, the effects of these components in the immunopathogenesis of IBD will be discussed.



**Key words:** Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Microbiome; Autophagy; T helper 17; Innate immune system; Adaptive immune system; Innate lymphoid cells; TL1A

**Core tip:** Inflammatory bowel disease (IBD) results from the complex interactions between susceptibility genes, the environment, the immune system, and the host's microbiome. It is thought that either a mucosal susceptibility or a defect in sampling of gut luminal antigen leads to activation of the innate immune system that then recruits cells of the adaptive immune system leading to inflammation. This review will detail the interaction of these components in the immunopathogenesis of IBD.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflam-

matory disorder that is comprised of both Crohn's disease (CD) and ulcerative colitis (UC), and is characterized by alternating phases of clinical relapse and remission. CD can affect any part of the gastrointestinal tract and classically presents with fatigue, prolonged diarrhea with or without gross bleeding, abdominal pain, weight loss, and fever. UC characteristically involves the colon and presents with symptoms that usually rectal bleeding, frequent stools, mucus discharge from the rectum, tenesmus, and lower abdominal pain. IBD is thought to be the result of a dysregulated immune system in the context of a genetically susceptible individual. Currently, IBD affects 1.4 million Americans and at a prevalence rate of 396 per hundred thousand individuals worldwide[1]. The incidence of CD in the United States is estimated to be 5 per hundred thousand persons and is characterized by focal and transmural inflammation that can occur anywhere along the length of the gastrointestinal system, that may include B2 stricturing (gut luminal narrowing), B3 penetrating (bowel perforation, fistula, inflammatory mass/abscess), and with possible perianal disease[2,3]. UC affects 8-12 per hundred thousand individuals and is characterized by colonic mucosal inflammation along the entire colon and involving the rectum[3,4]. Also, patients with IBD have an increased risk of developing other chronic inflammatory disorders, such as psoriasis and primary sclerosing cholangitis[5,6].

The exact cause of IBD is still unknown, but is thought to be due to a combination of a patient's genetics, microbiome, immune response, and the environment that result in an excessive and abnormal immune response against commensal flora in genetically susceptible individuals. Epidemiological data suggest an association between IBD and a number of environmental factors, such as antibiotic use, microbial exposure both early and late in life, and possibly diet[5,7-9]. The genetics of IBD are complex and thought to be polygenic. Genome-wide association studies (GWAS) suggest that dysregulation in innate and adaptive immunity contribute to the development of IBD. Susceptibility variants have been reported in genes associated with autophagy (*ATG16L1*), the interleukin (IL)-23/Th17 pathway (*IL-12B*), TGF-beta pathway (*SMAD3*), T-cell activation (*TAGAP*), among other immune system genes[10-13].

The identification of these and other loci is only part of a larger picture that aims to understand how polymorphisms in these genes can lead to an increased risk of developing IBD. Here we review the available evidence supporting the role of the microbiome and the innate and adaptive immune responses and their crosstalk in IBD.

## THE MICROBIOME

### Overview

Th interaction of the host with its abundant microbiota is complex. The luminal surface of the small and large intestine, approximately 300-400 $m^2$, is a unique environment where an enormous population of bacteria exists in close proximity to the immune system of the gut mucosa. This roughly translates to the interactions of $10^{12}$ microorganisms per gram of feces with $10^6$ immune cells per gram of enteric tissue[14]. A complex network of interactions exists between gut epithelial cells, immune cells, and foreign bodies that transition along the gut. Functionally, the gut-associated lymphoid tissues generates either an immune response for rejection of pathogens or a clinical immune response of tolerance for dietary and microbial antigens[15]. Data supports the hypothesis that IBD results from a dysregulated immune response to the microbiota. It was found that in CD patients, diversion of feces induces inflammatory remission and mucosal healing in the downstream intestinal segment and infusion of feces reactivates the disease[16]. Furthermore, in UC patients with active disease, treatment with broad-spectrum antibiotics reduced mucosal inflammation[17]. These data support the concept that luminal bacteria provide the stimulus for an inflammatory response leading to mucosal injury. Two main hypotheses have been suggested that might contribute to the loss of tolerance towards the indigenous microbiota in patients with IBD. First, genetic susceptibility leads to a dysregulation of the mucosal immune system that result in excessive immunologic responses to normal flora. Second, an imbalance exists in the composition of the microbiota that elicits a pathologic response from the normal mucosal immune system[18]. In all likelihood, it probably is a combination of both hypotheses.

Advancements in genetic technology, such as 16S ribosomal RNA (rRNA) gene and metagenomic sequencing have allowed researchers to determine the composition of the microbiome[19]. Recently, a number of studies have profiled the "normal" human gut microbiota. Briefly, it is thought that greater than 90% of all phylotypes belong to two divisions, *Bacteroidetes* and *Firmicutes*[20]. Other divisions that have consistently been recovered from "normal" individuals include *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia*. It is believed that the composition of fecal microbiota remains relatively constant over time, termed resilience, with temporary changes occurring after exposure to food, medicine, and physical environment[21]. In 2010, whole-genome shotgun sequencing revealed 3.3 million nonredundant microbial genes in fecal samples from an adult European cohort[22]. It was found that up to 98% of the genes were bacterial with the rest belonging to archaea, yeasts, viruses, and protists. The three most abundant genera in the fecal samples were *Bacteroides*, *Faecalibacterium*, and *Bifidobacterium*, however the percent composition was found to be highly variable between individuals[23]. Three main enterotypes (independent of gender, age, race, body mass index, or country and continent of residence) were created that are classified based upon the prominent genera represented: enterotype 1-*Bacteriodes*; enterotype 2-*Prevotella*; enterotype 3-*Ruminococcus*[23].

Individuals with IBD have been shown to have changes in the bacterial composition of feces with less bacterial

diversity, having fewer numbers of non-redundant bacterial genes, as compared to healthy controls[24,25]. Adding to the complexity, the bacterial profile also differs between individuals with UC and CD. In a twin study, twins with UC were found to have less *Bacteroides* and more *Actinobacteria* and *Proteobacteria* than their healthy twin counterparts. The decrease in Bacteroides was made up for by an increase in the Prevotellaceae family[26]. Also, it has been found that *Escherichia coli* (*E. coli*) is to be increased in fecal samples from individuals with UC, with some isolates expressing virulence factors and invading properties[27,28]. Dysbiosis also exists in CD. Many studies have shown a decrease in the abundance of several bacterial species of the phylum *Firmicutes* in patients with CD[29,30]. Also, the microbiome of individuals with CD predominantly in the ileum was found to differ from those whose disease was found predominantly in the colon. Those with ileal CD had decreased *Faecalibacterium* and *Roseburia* and increased amounts of *Enterobacteriaceae* and *Ruminococcus gnavus*[31]. Consistent with what is seen in UC patients, *E. coli* also has been observed in patients with CD[27].

Recently a new pathogenic group called adherent-invasive *E. coli* (AIEC) has been isolated from the ileum of CD patients[30,32]. Darfeuille-Michaud[33] have accumulated a large body of data showing that AIEC is able to invade epithelial cells and to survive and replicate within macrophages and is associated with ileal mucosal CD pathogenesis. They found that AIEC was present in the inflamed ileum of 22% of chronic CD patients, as compared to only 6% of control patients, as well as 36% of the newly formed terminal ilea of postsurgical CD patients[34]. However, AIEC was found in only a small percentage of affected colons of CD patients and in zero percent of UC patients, suggesting that AIEC strains are associated specifically with ileal mucosa in CD[34]. AIEC facilitate binding and invasion into epithelial cells *via* type 1 pili and flagella[35]. This interaction is dependent upon epithelial expresseion of CEACAM6, which is a carcinoembryonic antigen upregulated by inflammatory cytokines and possibly by AIEC itself[36]. Furthermore, transgenic mice overexpressing CEACAM6 in epithelial cells are colonized by AIEC and manifest gut inflammation with marked neutrophil infiltration and ulceration[37]. In the lamina propria, AIEC is taken up by macrophages and can survive and proliferate within macrophage vacuoles, which suggest that the bacteria is not readily cleared from the site and may represent a defect in autophagy[38,39].

Also, recently an important role of fungi in gut homeostasis has been found. Besides the massive amount of bacteria known to make up the intestinal microflora, the mammalian gut also contains a rich fungal community that interacts with the immune system *via* Dectin-1, which is a pattern-recognition receptor expressed by innate immune cells, such as: macrophages, dendritic cells (DCs), and neutrophils[40]. It was found that mice deficient in Dectin-1 exhibited increased susceptibility to dextran sulfate sodium (DSS) colitis that was the result of an altered response to the host's fungi[41]. Furthermore, polymorphisms in the gene for Dectin-1 have been shown to be strongly linked to a severe form of UC[41]. This data suggests that the interactions between fungi and the innate immune system are important in the development of IBD. Viral infections also impact the gut microflora. In mice, virus-plus-susceptibility gene interactions have been shown to induce colitis that mimics CD. When mice with a specific mutation in a CD susceptibility gene for autophagy (*ATG16L1*) were infected with murine norovirus they displayed abnormal Paneth cell structure and granule packaging similar to those seen in CD patients homozygous for the risk allele of *ATG16L1*[42]. These changes were not seen in control mice nor in CD patients homozygous for the nonrisk allele of *ATG16L1*. Furthermore, when these mice were treated with DSS they displayed worse colitis than control animals[42]. These results demonstrate how a genetic factor and an environmental agent can contribute to the pathogenesis of CD. Also, HIV infection of humans and simian immunodeficiency virus (SIV) infection of rhesus monkeys is known to cause systemic immune activation and associated with damage to the intestinal epithelium and translocation of antigens into the blood[43-45]. Pathogenic SIV infection has been associated with significant expansion of the enteric virome, including adenovirus and parvovirus, that can lead to enteritis without changes in the microbiome[46]. This data suggests that the enteric virome might contribute to AIDS pathogenesis by damaging the intestinal epithelium to allow translocation of microbes and viral antigens into the circulation.

The consequences of these shifts in microbiota are unclear, particularly whether it is cause or effect. Regardless of the inciting cause of IBD, it is apparent that the host-microbiome interaction plays a large part in disease pathogenesis.

### Host-microbial interactions

Host-microbe interactions are crucial in the development and modulation of the immune system and protection from pathogenic bacterial invasion. The first line of defense to pathogenic organisms is the innate immune system, which in the gut consists of mucin, the epithelium, and cells of the innate immune system [*i.e.*, neutrophils, DCs, monocytes/macrophages, and innate lymphoid cells (ILCs)]. Interestingly, mice lacking an adaptive immune system, but that have an intact innate immune system, such as recombinase activation gene deficient ($RAG^{-/-}$) and severe combined immunodeficient (SCID) mice, do not develop spontaneous colitis and co-exist with the microbiota. However, these mice can develop colitis when induced by DSS, anti-CD40 antibody, and *Heliobacter hepaticus* infection[47-49]. These data suggest that in the absence of an adaptive immune system, the innate immune system is sufficient for the development of IBD. However, the adaptive immune system is still thought to play an important role in the development of IBD, as RAG deficiency can prevent the development of spontaneous

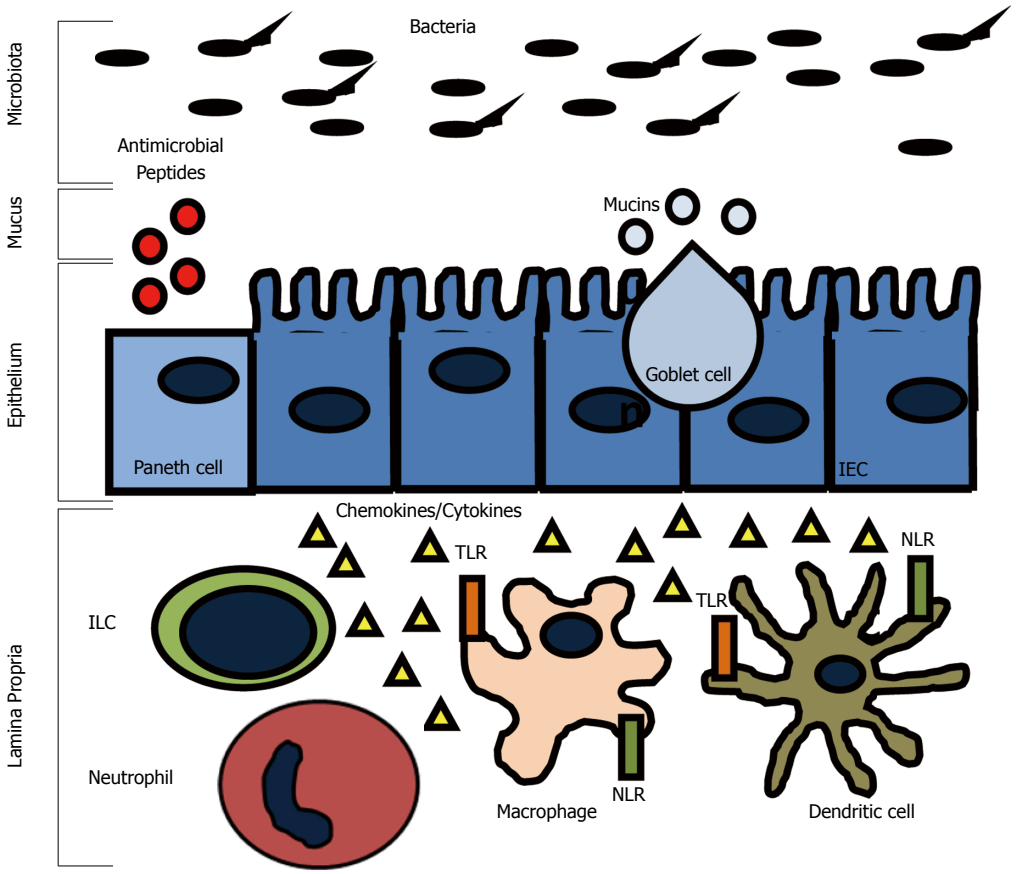


**Figure 1 Innate immune system responses in the gut.** The intestinal epithelial barrier is equipped with several layers of defense mechanisms to limit luminal antigen translocation. Goblet cells, Paneth cells, and enterocytes secrete mucins and antimicrobial peptides that assemble into a mucus layer. Innate immune system cells, such as macrophages and dendritic cells, can sense invading bacteria through extracellular and intracellular pattern recognition receptors (Toll-like receptors-TRLs and NOD-like receptors-NLRs) and initiate rapid inflammatory reponses mediated by the secretion of cytokines and chemokines. Innate lymphoid cells (ILCs) are also found in the lamina propria where they contribute to cytokine production and inflammatory cell recruitment.

colitis that are seen with certain mutant mouse strains[50].

## INNATE BARRIERS OF PROTECTION

### *Mucus*

The surface of the intestine is protected by a layer of mucus that is generated by goblet cells in the epithelium (Figure 1). The inner mucus layer is approximately 100 μm thick, firmly adherent, rich in antimicrobials and mucin, and has a low bacterial density. The outer layer of mucus is comprised of mucin, diluted antimicrobials, and some bacteria. A variant in the *Muc2* gene, which is the major intestinal secretory mucin, confers susceptibility in humans to IBD and *Muc2* deficient mice develop spontaneous colitis[51]. Furthermore, some patients with CD have been found to have goblet cell depletion and an impaired mucus layer, which allows bacteria to adhere directly to epithelial cells, and may contribute to disease progression[52]. It is believed that the ability of commensal bacteria to adhere to the epithelial layer *via* oligosaccharides helps deter invasion by displacing pathogenic bacteria. *FUT2* is a gene that encodes a type alpha (1, 2) fucosyltransferase, which regulates the secretion of the H1 antigen of the ABO antigens into the mucosa. People are either associated as H1 antigen secretors or non-secretors. Twenty percent of the population are non-secretors, which has been associated with a variety of illnesses including recurrent norovirus and encapsulated bacterial infections, duodenal ulcerations, and susceptibility to CD[53-59]. The inability to secrete H1 into the mucosa is thought to affect how commensal and pathogenic flora interact with the epithelial layer and may interfere with the ability of the commensal flora to adhere, which could result in increased susceptibility to infection, invasion, and activation of the immune system.

### *The epithelium*

The epithelium of the intestine has many functions, including absorption, secretion, and digestion. There are four main types of epithelial cells: one, absorptive enterocytes; two, mucus producing goblet cells; three, hormone producing enteroendocrine cells; and four, antimicrobial and growth factor producing Paneth cells (Figure 1). The epithelium forms a mucosal barrier with tight junctions between enterocytes that can exclude the entry of most substances. The epithelial layer is renewed every 2-3 d with a balance of proliferation of epithelial cells in the crypts and migration down the villi in the small intestine or onto the surface of the colon and apoptosis and shedding of the enterocytes. Disruption of this process im-

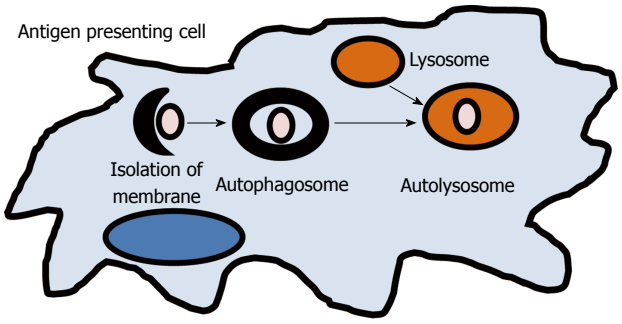


**Figure 2 Autophagy.** A small volume of cytoplasm is enclosed by the autophagic isolation membrane, which forms the autophagosome. The outer membrane of the autophagosome then fuses with the lysosome where the cytoplasm derived materials are degraded.

pairs the epithelial integrity and can result in chronic inflammation. Defects in epithelial integrity may contribute to IBD pathogenesis by allowing free passage of organisms across the epithelial layer where they can incite an immune response. For example, mutations in the *organic cation transporter* (*OCTN*) gene, which is involved in the transport of cationic proteins, such as amino acids and nutrients, lead to an increased susceptibility to CD[60]. The susceptibility is thought to result from impaired fatty acid oxidation, which can cause colitis in experimental models in the setting of bacterial antigen exposure[61].

The epithelium lies between the immune cells in the lamina propria and the microbiota in the gut lumen and functions to communicate with both. For example, the microbiota signals enterocytes as well as innate cells in the lamina propria *via* pattern recognition molecules signal receptors, such as toll like receptors (TLRs) and cytosolic NOD-like receptors (NLRs) (Figure 1). These signals have been shown to be necessary for normal homeostasis and resistance to injury[62]. Cytokines, such as interferon (IFN)-γ, interleukin (IL)-17, and IL-22, pathogens, and commensal bacteria have substantial effects on the epithelium by regulating barrier integrity and function[63-66]. Expression of pattern recognition receptors is highly regulated to prevent an inappropriate immune response, but still allow for constant surveillance. Mutations in genes coding for these receptors have been found to be IBD susceptibility genes. Haplotypes of the *TLR8* gene can confer protection (H1) or risk (H4) to the development of IBD[67]. Agonists of TLR8 have been shown to cause downstream activation of proinflammatory cytokines such as IFN-γ, IL-12, and tumor necrosis factor (TNF)-α in peripheral blood mononuclear cells[68]. The *TLR9* gene is also a CD and UC susceptibility gene[69]. It has been shown that mice infected with *Campylobacter jejuni* (*C. jejuni*) or TLR9 agonists have increased susceptibility to mild DSS colitis *via* a mechanism involving secretion of CXCL8[70].

Defects in the intestinal barrier can lead to persistent immune activation and has been suggested to play a role in IBD[71]. Normally, translocation allows small amounts of luminal antigens to pass transcellularly across the epithelium either through receptor-mediated endocytosis or non-selective endocytosis. A small amount of bacteria is normally allowed to translocate and allows for physiologic sampling of luminal content by the host's immune system[72]. Animal models that lack components of a healthy epithelial barrier have been shown to develop IBD. Expression of dominant-negative N-cadherin in mouse intestinal epithelium has been shown to lead to CD like symptoms[73]. NOD2 is a protein that acts as an intracellular pattern recognition receptor for muramyl dipeptide (MDP), a component of the bacterial wall peptidoglycans. Mice lacking intracellular pattern recognition receptors, NOD1 and NOD2, were shown to have decreased E-cadherin expression with increased epithelial permeability and decreased antimicrobial production[74]. *NOD2* was one of the first CD susceptibility genes, with homozygous mutations found in 15% of patients with CD[75]. Mutations in NOD2, as well as other pattern recognition receptors, might impair the ability of the mucosal immune system to sense organisms thereby leading to defective microbial clearance and persistent antigenic stimulation. This in turn may result in mucosal inflammation and loss of regulatory control over proinflammatory pathways, which could possibly lead to the development of IBD.

## AUTOPHAGY

The term autophagy, or "self-eating," results in the lysosomal degradation of organelles, unfolded proteins, or foreign extracellular material (Figure 2). It is a key process required for maintaining cellular homeostasis after infection, mitochondrial damage, or ER stress. Defects in autophagy have been shown to result in pathological inflammation and GWAS have linked two key genes in autophagy, *ATG16L1* and *IRGM*, to CD[13,76]. An ATG16L1 hypomorphic mouse line that expresses about 1% of the normal level of ATG16L1 was shown to have Paneth cell granule abnormalities that are similar to those found in ileal resections in patients with CD that also carry the *ATG16L1* gene variant[77]. While these hypomorphic *ATG16L1* mice do not develop spontaneous colitis, they were found to have an increased susceptibility to DSS colitis[42]. However, when rederived virus free, these mice lost the Paneth cell pathology and ability to develop DSS induced colitis, which could be reversed by norovirus infection[42]. A recent study has reported that the ATG16L1 and NOD2 pathways may be interrelated[78]. In 2010, Cooney *et al*[78] demonstrated that NOD2 stimulation is capable of initiating autophagy in DCs and that for effective autophagy to occur, both intact NOD2 and ATG16L1 functions are required. *IRGM* belongs to a family of interferon-inducible immunity related GTPases (IRGs) that encodes a protein involved in multiple autophagocytic pathways including intracellular clearance of pathogens[79]. IRGM has been shown to play a role in autophagy during both *Salmonella typhimurium* and *Mycobacterium bovis* infections[79,80]. Another study in CD patients has demonstrated that autophagy is also important in the clearance of AIEC and that *IRGM* and *ATG16L1*

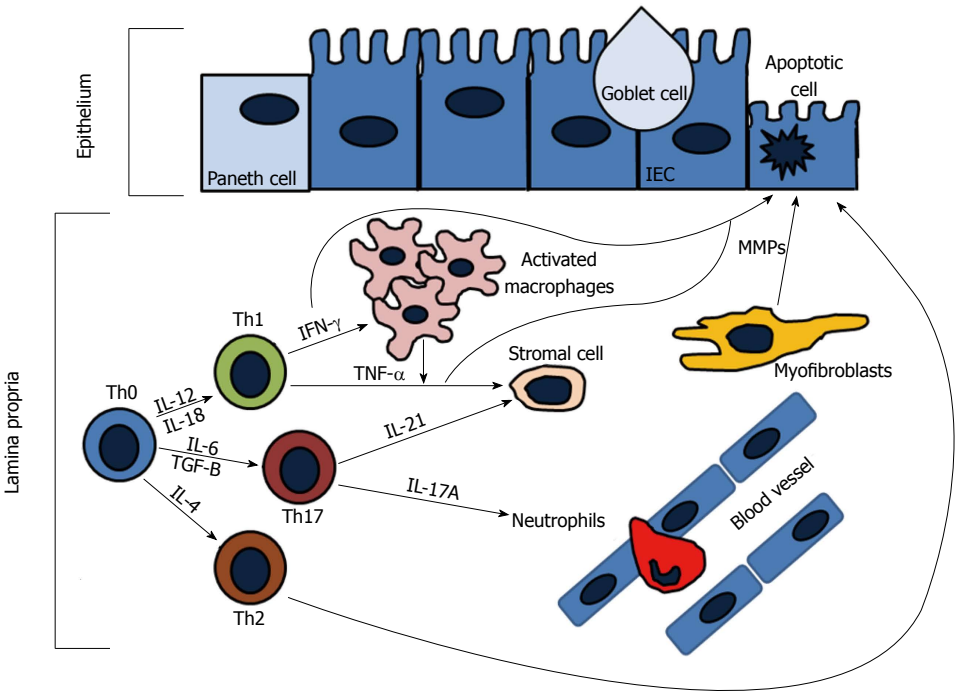


**Figure 3 Adaptive immune responses in the gut.** During active inflammation, naïve T-cells (Th0) differentiate into T helper cell types (Th1, Th2, Th17) under stimulation of different cytokines. Th1 cells produce interferon (IFN)-γ and tumor necrosis factor (TNF)-α. IFN-γ activated tissue macrophages to produce additional TNF-α, which causes epithelial cell apoptosis and differentiation of stromal cells into myofibroblasts. Activated myofibroblasts produce metalloproteinases (MMPs) that cause tissue degredation. Th2 cells produce interleukin (IL)-13 that can increase intestinal permeability and induce epithelial apoptosis. Th17 cells release IL-17A, which plays a role in recruiting neutrophils to sites of active inflammation, and IL-21 that also induces MMP production that contributes to extracellular matrix degredation.

deficient cells had increased AIEC replication, suggesting that these genes play a significant role in clearance of this organism and intestinal inflammation[39]. These studies implicate that autophagy plays an important role in human inflammatory disorders by direct elimination of intracellular bacteria and activation of pattern recognition receptor signaling which is involved in gut homeostasis and CD pathogenesis.

## INNATE AND ADAPTIVE IMMUNITY

### Overview

The immune system has evolved as protection against a wide range of infectious agents. In vertebrates, the immune system is broadly divided into two effector classes, the innate and adaptive immune responses. The innate immune system is the first line of defense and provides an immediate protective response against infections and also helps to initiate the adaptive immune response (Figure 1). The innate immune system is non-specific and does not confer lasting immunity (memory). The innate immune system is comprised of the epithelial barrier, macrophages, monocytes, neutrophils, DCs, and natural killer cells (NK cells), eosinophils, and basophils. These cells act together to initiate inflammation by secreting cytokines, chemokines, and antimicrobial agents. This leads to phagocytosis of infected cells and microorganisms, antigen presentation, and activation of the adaptive immune system.

The adaptive immune response is comprised of lymphocytes (T and B cells) that when activated generate effector responses (cytokines and antibodies). In contrast to the innate immune system, the adaptive immune system is highly specific and confers long lasting immunity (memory). It is generally thought that the adaptive immune system is the main contributor to disease pathogenesis in IBD, either through increased proinflammatory cytokines driven by the T-helper (Th) subsets or by ineffective anti-inflammatory regulatory T-cells (Tregs). Naïve T-cells (Th0) cells after activation are able to differentiate into Th1, Th2, or Th17 cells (Figure 3). In particular, Th1 responses have been thought to drive the pathogenesis of CD, while UC is thought to be driven by Th2 responses. Recent advancements suggest that other cells, such as ILCs and Th17 cells, have emerged as important contributors to IBD pathogenesis.

### Role of innate lymphoid cells in IBD

Until recently NK cells were thought to be the only innate cell derived from a lymphoid progenitor. However, recent developments have classified NK cells as a subset of a new family of hematopoietic effector cells called ILCs. ILCs are an emerging and diverse group of immune cells and are part of the new frontier of immunology research. All ILCs derive from an Id2 expressing progenitor and are defined by three main features: One, they are of lymphoid morphology; two, they are cell lineage negative ($CD3^-$, $B220^-$, $GR1^-$, $CD11b^-$, $Ter119^-$); and three, they lack RAG-dependent antigen receptors (Figure 4)[81]. Recently, a unifying ILC classification system has

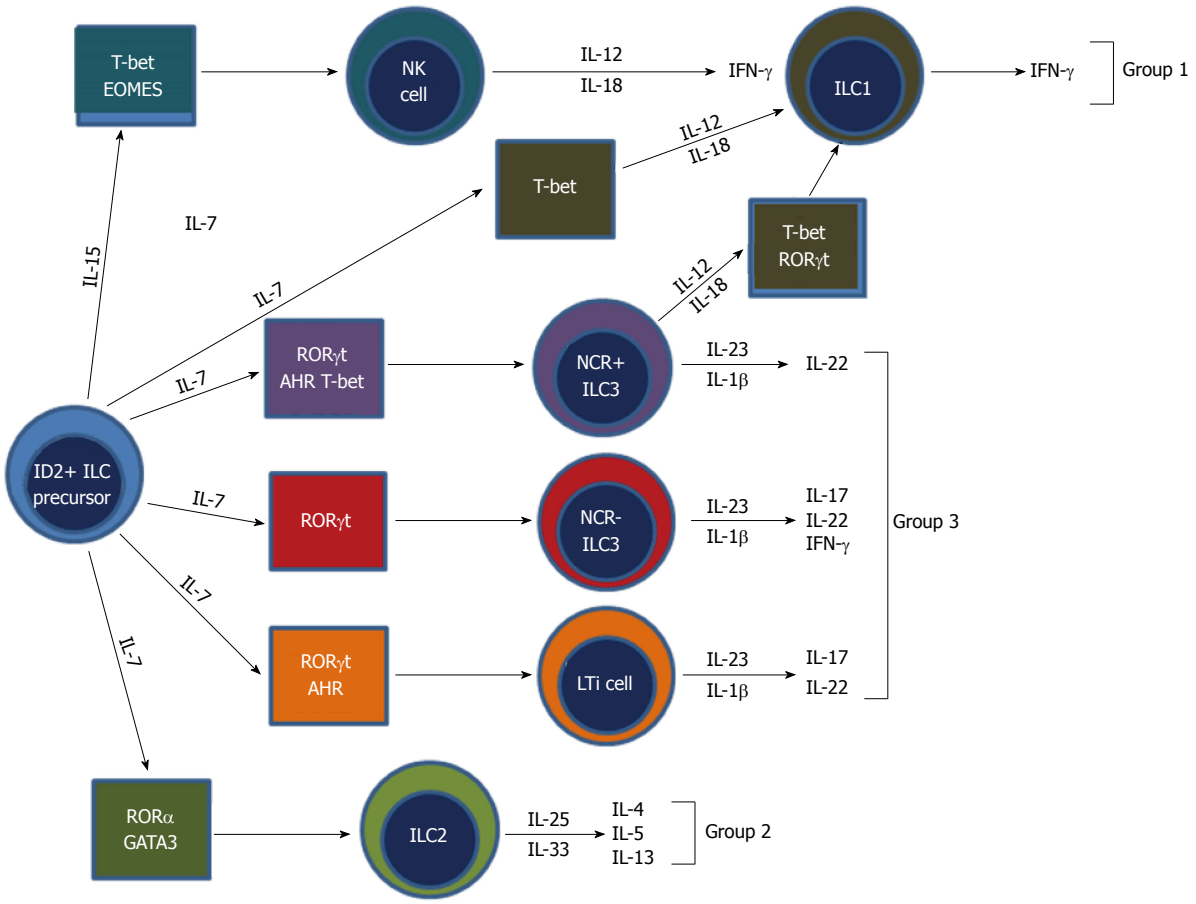


**Figure 4 Development and classification of innate lymphoid cells**[82]. Innate lymphoid cells (ILCs) all derive from an ID2 positive progenitor cell. Group 1 ILCs make interferon (IFN)-γ. Group 2 ILCs produce IL-5 and interleukin (IL)-13. Group 3 ILCs produce IL-17, IL-22, and IFN-γ. NK require IL-15, whereas all other ILCs require IL-7 for development. Group 2 ILCs depend on transcription factors GATA3 and ROR for development. Group 3 ILCs require RORt for development. Also, subsets of group 3 ILCs require additional transcription factors, such as aryl hydrocarbon receptor (AHR) for development. NK cells, which are group 1 ILCs, require both T-bet and eomesodermin (EOMES). The mechanisms of ILC1 development are not fully elucidated, however are known to require transcription factor T-bet for development.

based upon phenotypic and functional characteristics has been proposed (Table 1)[82]. ILCs can be classified into three groups: Group 1 ILCs, which are T-box expressed in T-cells (Tbet) dependent and are comprised of ILC1 and NK cells; group 2 ILCs, which are GATA-binding protein 3 (GATA3) and retinoic acid receptor-related orphan receptor (ROR) dependent, and comprised of ILC2s; and group 3 ILCs, which are RORt dependent and are comprised of ILC3s and lymphoid tissue-inducer (LTi) cells[82].

The key cytokines secreted by ILCs tend to mirror those secreted by the T-helper cells of the adaptive immune system and therefore ILCs have been thought of as the innate counterparts of T-helper lymphocytes (Table 1). Group 1 ILCs are defined by their ability to produce Th1 cell associated cytokines, in particular IFN-γ. Although under debate, the prototypical cell is the NK cell. Group 2 ILCs are defined by their ability to produce Th2 cytokines, in particular IL-5 and IL-13 and the prototypical cells are the IH2 cells or nuocytes[83-86]. These cells have been shown to play a major role in defense against parasites and in allergy and asthma[87,88]. Group 3 ILCs are defined by their ability to secrete Th17 like cytokines such as IL-17 and IL-22 and the prototypical cells are LTi cells[89]. Group 3 ILCs have been shown to play a major role in autoimmune disease and have been shown to mediate colitis in a mouse model of IBD[47].

Since ILCs have been shown to be important in mucosal immunity it was only logical to examine the role of these cells in IBD. Recent data has implicated ILCs, in particular group 3 ILCs in the development of IBD. While most research into IBD has focused on the role of the adaptive immune system, in particular Th1 and Th17 subsets, as well as ineffective regulatory T-cells, new evidence suggests that IBD can be triggered in $RAG^{-/-}$ mice, which lack all components of the adaptive immune system in an IL-23 dependent manner. Buonocore *et al*[47] demonstrated that group 3 ILCs, and not NK cells (group 1 ILCs), were increased and produced large amounts of IL-17A and IFN-γ after *Hepaticus* infection in $RAG^{-/-}$ mice were required for colitogenesis. Accumulating evidence suggests that group 3 ILCs induce colitis *via* an IL-23R-IL-22 dependent mechanism[47,90,91]. $RAG^{-/-}$ mice can also develop colitis after injection of CD40L. Vonarbourg *et al*[92] demonstrated that CD40L induced colitis requires the presence of innate lymphocytes because CD40L

**Table 1 Innate lymphoid cell subsets**

| ILCs | Lineage | Mouse | Human | Cytokines | Function | Disease |
|---|---|---|---|---|---|---|
| Group 1 | ILC1s | Lin$^-$Thy1$^+$Sca1$^+$Tbet$^+$ | Lin$^-$CD56$^+$NKp46$^+$NKp30$^+$NKp44$^+$ IL-7R$^-$ | IFN-γ | Inflammation | IBD? |
| | NK cells | NKp46$^+$NK1.1$^+$CD122$^+$ NKG2D$^+$CD161$^+$CD16$^+$ | CD122$^+$NKG2D$^+$CD161$^+$KIR$^+$ | IFN$^-$, TNF-α, cytotoxic effectors | Immunity to viruses and intracellular pathogens, tumor surveillance | Inflammatory conditions, IBD |
| Group 2 | ILC2s | Lin$^-$ICOS$^+$Thy1$^+$Sca1$^+$ IL-7R$^+$GATA3$^+$ | Lin$^-$IL-7R$^+$CD45$^{hi}$CD161$^+$ CRTH2$^+$ | IL-5, IL-9, IL-13 | Immunity to helminthes, wound healing | Allergy, asthma |
| Group 3 | ILC3s | Lin$^-$Thy1$^+$Sca1$^+$RORt$^+$ NKp46$^+$IL-7R$^+$CCR6$^-$ | Lin$^-$CD56$^-$NKp46$^+$NKp30$^+$NKp44$^+$ IL-7R$^+$ | IL-22 | Lymphoid tissue development, intestinal homeostatsis, immunity to extracellular bacteria | IBD |
| | LTi cells | Lin$^-$Thy1$^+$Sca1$^+$RORt$^+$ NKp46$^-$IL-7R$^+$CCR6$^+$ | Lin$^-$IL-7R$^+$CD45$^+$RORt$^+$ | IL-17A, IL-17F, IL-22 | Homeostasis of epithelia, immunity to extracellular bacteria | IBD |

Lin$^-$: Lineage marker negative (mouse negative for CD3, CD19, B220, CD11b, CD11c, GR1, Ter11; human negative for CD1a, CD3, CD11c, CD34, CD123, TCR, TCR, CD19, CD14, CD16); IBD: Inflammatory bowel disease; ILC: Innate lymphoid cell; IFN: interferon; TNF: Tumor necrosis factor; NK: Natural killer.

injection into RAG2$^{-/-}$-IL-2Rg$^{-/-}$ mice, which lack both adaptive immune cells and ILCs, did not develop colitis. Furthermore, group 3 ILC involvement in IBD has been further supported by the observation that RORt$^{-/-}$ mice do not develop CD40L induced colitis[47]. In an elegant set of experiments, it was found that LTi cells were the subset of group 3 ILCs that were colitogenic and required for disease onset, suggesting an important role for these cells in IBD pathogenesis[47]. In individuals with CD, a population of innate lymphocytes that were RORt$^+$ and represent human ILCs were found to be increased in the lamina propria compared to controls and this increase was IL-23 dependent[93,94]. Although a young field, data suggests that group 3 ILCs are an important cell type to study for answering questions about the pathogenesis of IBD as well as possible future therapies.

### *Th1 and Th2 cells*

Th1 cells are induced by IL-12 and characteristically secrete copious amounts of IFN-γ, TNF-α, and IL-12, whereas the signature cytokines secreted from Th2 cells are IL-4, IL-5, and IL-13[95]. CD is thought to be a Th1 mediated disease, while UC is believed to be mediated by Th2 responses[96]. Mucosal T-cells from CD patients have been shown to secrete higher amounts of IFN-γ and IL-2 than from T-cells from UC patients[97,98]. Furthermore, it has been demonstrated that UC patients produce increased amounts of IL-5 and have atypical natural killer T (NKT)-cells that secrete higher amounts of IL-13 as compared to CD patients[99-101]. However, recent data has suggested that the CD-Th1 and UC-Th2 paradigms are not so straight forward. Biopsies from both CD and UC patients have demonstrated high *ex vivo* levels of IFN-γ and lower levels of IL-13 have been found in UC patients as compared to CD patients[102,103]. Furthermore, data suggests that Th17 cell production of IL-17 and IL-23 play important roles in the pathogenesis of IBD, with DCs isolated from CD patients producing more IL-23 than UC patients[104]. Understanding the complicated interactions underlying the dysregulated adaptive immune response in IBD will ultimately identify novel therapeutic targets.

### *Th17 cells: Friend or foe*

Th17 cells are a subset of helper T-cells that are induced by IL-6 and TGF-B, expanded by IL-23, and characterized by the secretion of copious amounts of IL-17A, IL-17F, IL-21, and IL-22[105-107]. RORt has been identified as the master transcription factor of Th17 differentiation[108,109]. The IL-17 cytokine family includes six members: IL-17A-F[110]. IL-17A and IL-17F are 50% similar in their amino acid structure, while IL-17B, IL-17C, and IL-17D have less homology[111]. IL-17A and IL-17F signal through the same receptor, the IL-17 receptor A (IL-17RA) and act through activation of the NF-κB and MAPK pathways[112,113]. The major proinflammatory effects of IL-17A and IL-17F are the activation of various cellular targets, including the epithelium, endothelium, monocytes/macrophages, fibroblasts, and neutrophils that cause the induction of TNF-α, IL-1B, chemokines (CXCL8, CXCL9, CXCL10), GM-CSF, G-CSF, IL-6, and metaloproteases[114-117]. There are two major subsets of Th17 cells: Th17 cells producing IL-17 and Th1/Th17 cells producing both IFN-γ and IL-17[104,118-122]. IL-17 has been implicated in various immune mediated diseases, including rheumatoid arthritis (RA), asthma, IBD, and experimental autoimmune encephalitis (EAE)[123,124].

Th17 cells and signature cytokines have been extensively studied in IBD. GWAS have identified several genes involved in Th17 differentiation and expansion, including *IL-23R*, *IL-12B*, *JAK2*, *STAT3*, *CCR6* and *TNFSF15*, as CD susceptibility genes with some overlap in UC[12,58]. As compared to normal, CD and UC patients have increased levels of IL-17A gut mucosal transcripts and the lamina propria contains increased numbers of Th17 and Th1/Th17 cells[102,123,125]. RORt is found to be expressed at higher levels in lamina propria T-cells from CD patients[126].

Th17 pathobiology is complicated by the fact that in different experimental models, Th17 subsets can be distinguished by their function as either "pathogenic" or "nonpathogenic". Pathogenic Th17 cells are thought

to be characterized by their production of IFN-γ and by the expression of specific surface markers, including IL-18R1 and CXCR3[127]. IL-17A deficient mice or those treated with neutralizing antibodies to IL-17A or IL-17RA are resistant to the development of RA and EAE[128,129]. Furthermore, in a trinitrobenzene sulfonic acid (TNBS) mouse model of colitis IL-17RA deficient animals were protected from the development of acute mucosal inflammation[130]. However, in a DSS model of colitis, mucosal inflammation was ameliorated by IL-17F deficiency, but exacerbated by IL-17A deficiency, suggesting an important role for IL-17F and perhaps an alternative role for IL-17A[131-133]. Furthermore, supporting a protective role for IL-17A, it has been shown that IL-17A directly inhibits Th1 cells and suppresses development of inflammation[134]. Additionally, anti-IL-17A monoclonal antibody treatment was shown to exacerbate DSS induced colitis[135]. These studies suggest that IL-17A may protect against the development of mucosal inflammation whereas IL-17F may drive it.

As demonstrated by the data above, the biology of IL-17 deficiency has been complicated, with some studies showing a pathogenic role, while others suggesting a protective role. However, there has been a significant amount of data suggesting that IL-17A has played a pathogenic role in IBD. Therefore, a double-blind, randomized, placebo-controlled study tested whether the anti-IL-17A monoclonal antibody, secukinumab, would be beneficial in CD patients[136]. Surprisingly, the study found that blockade of IL-17A was ineffective and caused a higher rate of adverse advents as compared to placebo, suggesting a protective role of IL-17A[136]. Although the study was halted prematurely, exploratory analysis of CD candidate genetic polymorphisms found that a subset of patients with a minor allele of TL1A actually had an improved clinical score over the course of the treatment[136]. These data suggest that in the right genetic context, secukinumab therapy may be beneficial to some patients, which further supports the concept of treating each individual with IBD based upon their own genetic composition.

## TL1A: CONNECTING THE INNATE AND ADAPTIVE IMMUNE SYSTEM

Tumor necrosis factor super family 15 (*TNSF15*) encodes the protein TL1A, a member of the TNF superfamily, is expressed either membrane bound or secreted by monocytes, macrophages, DCs, fibroblasts, and endothelial cells in response to stimulation by cytokines and microorganisms[137-140]. It binds to death domain receptor 3 (DR3), mainly expressed on T-cells, to initiate a number of immune responses, such as activation of T-cells resulting in the secretion of proinflammatory mediators[141]. TL1A has been implicated in the pathogenesis of many autoimmune diseases, including asthma, rheumatoid arthritis, and IBD[96,140,142-144]. Numerous studies have supported the concept that TL1A is a major regulator of mucosal inflammation at the interface between the innate and adaptive immune system[145-147].

In 2005, in a study of Japanese CD patients, polymorphisms in the *TNFSF15* gene was identified as having a strong association with CD[148]. This association has been reproduced in other studies, including European and Jewish CD and UC patients, and has been demonstrated to be the dominant gene in East-Asians with IBD[12,149-153]. Haplotypes within the gene confer either risk or protection, which is dependent upon the ethnicity of the individual. In non-Jewish CD patients, haplotype A is a risk allele, while haplotype B is protective[148-150,153]. However, in Jewish CD patients, haplotype B has a trend towards risk, as these patients had worsened disease as manifested by higher incidents of surgery and increased responses to *E. coli* outer membrane porin C (OMPC)[154,155]. Furthermore, monocytes isolated from Jewish patients that were haplotype B secreted increased amounts of TL1A than haplotype A carriers after stimulation[156].

Given the information generated from the human GWAS studies, transgenic mice have been created that overexpress TL1A. In 2011, Meylan *et al*[146] and Taraban *et al*[147] found that murine colitis driven by TL1A overexpression in T-cells and DCs was found to be dominated by a Th2 response over Th1, with elevation in IL-13 and unchanged levels of IFN-γ. Also, in both models, spontaneous intestinal inflammation developed, with disease severity being greatest in the terminal ileum and correlating to transgene expression level. This observation was abolished with anti-IL-13 treatment. Shih *et al*[143] reported similar observations in another model of TL1A overexpression. However, they also found that these mice had increased levels of IFN-γ and intestinal fibrosis. The differences in these mouse models may be secondary to differences in the generation of the mice and/or different gut microflora between animal facilities. Regardless, all models demonstrated intestinal inflammation and this supports evidence of TL1A polymorphisms being associated with IBD. Given this information, studies utilizing anti-TL1A antibodies were undertaken. In models of TNBS and DSS colitis anti-TL1A neutralizing antibody treatment was shown to ameliorate weight loss and intestinal inflammation[146,157]. These studies suggest a role for using blocking antibodies to TL1A to ameliorate pathological T-cell responses in IBD.

## CONCLUSION

In current immunology there are new Th cell subsets, such as IL-9 producing Th9 cells, IL-22 producing Th22 cells, follicular helper T-cells, and emerging types of Treg cells that are now also all being implicated in the pathogenesis of IBD[158-161]. Furthermore, historically it was thought that terminally differentiated Th cells seldom re-differentiate to other Th subsets, however now the plasticity between Th cells is now extensively under investigation[162].

It has been well documented that the adaptive im-

mune system plays an important role in the development and perpetuation of the inflammatory cascade in IBD. In particular, T-cells have been shown to be key players in driving intestinal inflammation. However, a number of unresolved issues exist that need to be addressed in order to develop successful and appropriate therapeutic strategies. Recent advances have clarified the importance of the innate immune system in IBD pathobiology. Furthermore, besides anti-TNF agents, molecules targeting specific T-cell derived molecules have largely failed. This is likely due to the complexities and redundancies of cytokine networks and highlights how different each individual's immune system is in the context of their own genetics. The studies of the interactions between the different components of the innate and adaptive immune system, as well as the interactions with the intestinal microbiota, and how these interactions relate in the overwhelming context of an individual's genetics are areas that will open new horizons in the knowledge of mechanisms of gut inflammation.

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