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Review

Gastrointestinal Epithelial Autophagy: A Critical Regulator of Intestinal Mucosal Homeostasis and Pathogenesis in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal disorder driven by intestinal barrier dysfunction and mucosal immune dysregulation.Multiple pathological pathways disrupt intestinal mucosal immunity to initiate IBD progression, including aberrant innate immune receptor activation, imbalance between pro- and anti-inflammatory lymphocyte subsets, defective mucosal antimicrobial secretion, and dysregulated interaction between epithelium and gut commensals. Gastrointestinal epithelial cells (IECs) form the critical frontline barrier, and their functional impairment is central to IBD pathogenesis. Autophagy, a conserved lysosomal catabolic process essential for cellular homeostasis, is a key regulator of IEC function. Mounting evidence links impaired autophagic flux in IECs to disrupted barrier integrity, exacerbated inflammation, and gut microbial dysbiosis, thereby promoting IBD onset and progression.This review systematically summarizes the molecular mechanisms governing autophagy in IECs, focusing on core ATG genes and key signaling pathways (PI3K/Akt/mTOR, AMPK, NF-κB). It further dissects autophagy's multifaceted roles in maintaining mucosal homeostasis, including barrier preservation, modulation of cell fate, and crosstalk with the microbiota and immune system. Additionally, the review highlights the clinical relevance of autophagy-related genetic polymorphisms (e.g., ATG16L1, IRGM) in IBD susceptibility and the pathological evidence of defective autophagy in patient tissues. Finally, it discusses the therapeutic potential of autophagy modulators and outlines key unanswered questions and future research directions for developing precision IBD therapies.

Key Words

Gastrointestinal epithelial cells, Autophagy, Inflammatory bowel disease, Intestinal barrier; Mucosal immunity, Signaling pathways

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1. Introduction

Inflammatory bowel disease (IBD) is a complex multifactorial chronic inflammatory disorder of the gastrointestinal tract, primarily including Crohn's disease (CD) and ulcerative colitis (UC), with a growing global prevalence that poses a severe burden on public health [1]. Epidemiological data show that the incidence of IBD has increased by more than twofold in the past three decades, with the highest prevalence in North America and Europe, and a rapid upward trend in Asia, Latin America, and other emerging economies. The pathogenesis of IBD has not been fully elucidated, but it is widely recognized that it involves an intricate interplay between genetic susceptibility [2], environmental triggers, intestinal microbial dysbiosis, and dysregulated mucosal immune responses. Among these, the intestinal epithelial barrier, composed of a single layer of polarized gastrointestinal epithelial cells (IECs) including enterocytes, goblet cells, Paneth cells, and enteroendocrine cells, is the first line of defense against luminal antigens and pathogens.

The intestinal epithelial barrier exerts dual functions: a physical barrier formed by tight junctions (TJs), adherens junctions, and desmosomes between IECs, and a functional barrier involved in immune surveillance, nutrient absorption, and microbial interaction. Impaired intestinal barrier integrity, characterized by increased paracellular permeability and reduced expression of TJ-associated proteins, is an early pathological feature of IBD, which leads to the translocation of luminal microbial antigens into the mucosal tissue, triggering excessive activation of innate and adaptive immune responses and driving the development of chronic inflammation. Studies have confirmed that IEC dysfunction is both a cause and a consequence of IBD pathogenesis, and restoring intestinal epithelial barrier function has become a key target for IBD treatment [3].

Autophagy, a highly conserved cellular process from yeast to humans, is a lysosome-dependent catabolic pathway that mediates the degradation and recycling of cytoplasmic components, including damaged organelles, misfolded protein aggregates, and intracellular pathogens. The autophagic process is tightly regulated by a set of evolutionarily conserved autophagy-related genes (ATGs), which orchestrate the sequential steps of autophagosome formation, maturation, and fusion with lysosomes. Beyond its basal housekeeping function in maintaining cellular homeostasis, autophagy is involved in a variety of physiological and pathological processes, including cell survival, differentiation, immune response, and disease progression. In the gastrointestinal tract, autophagy is constitutively active in IECs, and its physiological activity is essential for maintaining intestinal mucosal homeostasis [4].

Emerging evidence has highlighted the critical role of IEC autophagy in IBD pathogenesis. Genome-wide association studies (GWAS) have identified multiple ATGs as susceptibility loci for IBD, with *ATG16L1* and *IRGM* being the most well-characterized. Functional studies have shown that genetic polymorphisms in these genes lead to impaired autophagic function in IECs, resulting in Paneth cell dysfunction, reduced antimicrobial peptide secretion, and defective clearance of intracellular pathogens. Furthermore, mouse models with IEC-specific deletion of *Atg* genes (e.g., *Atg5*, *Atg7*, *Atg16L1*) exhibit spontaneous intestinal inflammation or increased susceptibility to chemically induced colitis, accompanied by intestinal barrier dysfunction and microbial dysbiosis. These findings confirm that IEC autophagy is a key regulatory node in intestinal mucosal homeostasis and IBD pathogenesis [5].

Despite significant progress in understanding the association between autophagy and IBD, the precise molecular mechanisms by which IEC autophagy modulates intestinal barrier function, mucosal immunity, and microbial interaction remain incompletely understood. Additionally, the translational potential of targeting autophagy for IBD treatment is still in the preclinical stage, with limited clinical evidence for the efficacy and safety of autophagy modulators. This review aims to provide a comprehensive and up-to-date overview of the current research on IEC autophagy in IBD, focusing on the molecular regulation of IEC autophagy, its physiological roles in intestinal mucosal homeostasis, the pathological mechanisms of autophagy dysfunction in IBD, and the therapeutic potential of autophagy-targeted strategies. We also address unresolved questions and future research directions, aiming to advance the understanding of this field and provide a theoretical basis for the development of novel IBD therapies [6].Most previously published reviews separately describe single ATGs or isolated signaling pathways relevant to IBD, while few literatures systematically construct an integrated framework linking epithelial autophagy, genetic susceptibility, intestinal barrier breakdown, microbiota dysbiosis and aberrant mucosal immunity. The present review fills this research gap via hierarchical mechanistic integration and detailed translational therapeutic prospect analysis to highlight its novelty compared with existing summaries.

2. Molecular Mechanisms of Autophagy in Gastrointestinal Epithelial Cells

2.1 Core ATGs Regulating IEC Autophagy

The autophagic process is governed by a complex network of over 40 evolutionarily conserved ATGs, which are classified into functional groups based on their roles in autophagosome initiation, nucleation, elongation, closure, and fusion with lysosomes. In IECs, a subset of core ATGs is constitutively expressed and plays non-redundant roles in regulating basal and inducible autophagic flux, with *ATG16L1*, *IRGM*, and LC3 (encoded by *MAP1LC3*) being the most critical for IBD pathogenesis.Table 1 summarizes the core ATGs critical for IEC function, their associated IBD susceptibility variants, and the functional consequences of their deficiency [7]. To intuitively demonstrate the core signaling network governing IEC autophagy and its abnormal status in IBD, Figure 1 systematically illustrates the

regulatory mechanisms of the PI3K/Akt/mTOR, AMPK, and NF-κB pathways and their dysregulation during disease progression.

Table 1. Core ATGs and their pathological roles in IBD.

Core ATG Gene	Key Function in IEC Autophagy	IBD Susceptibility Variant	Functional Consequence of Dysfunction in IBD
ATG16L1	Forms the ATG5-ATG12-ATG16L1 complex; mediates LC3 lipidation and autophagosome elongation	T300A (rs2241880)	Reduced protein stability; impaired Paneth cell granule exocytosis; defective clearance of *Salmonella enterica*; altered antimicrobial peptide secretion
IRGM	Promotes autophagosome maturation and fusion with lysosomes; interacts with NOD2	rs13361189 (promoter deletion)	Decreased gene expression; blocked autophagosome-lysosome fusion; impaired bacterial clearance; synergistic inflammation with NOD2 deficiency
LC3 (*MAP1LC3*)	Autophagosome marker; mediates cargo sequestration; interacts with ZO-1 to stabilize TJs	No common coding variants	Reduced expression of ZO-1 and occludin; increased intestinal paracellular permeability; enhanced susceptibility to chemically induced colitis
ULK1	Initiates autophagy via the ULK1-ATG13-FIP200 complex; regulated by AMPK/mTOR	Multiple minor variants	Impaired autophagy initiation; excessive IEC apoptosis; defective mucosal regeneration; severe UC-like pathology
NOD2[*]	PRR that recruits ATG16L1 to trigger xenophagy; not a core ATG but critical regulator	R702W, G908R, 1007fs	Failure to activate autophagy in response to MDP; defective bacterial clearance; Paneth cell dysfunction

Note: Although not a core ATG, NOD2 is included due to its critical role in linking innate immunity to autophagy in IECs.

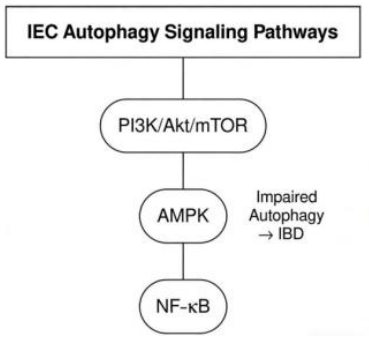

Figure 1. Regulatory network of core ATG genes and three key signaling pathways governing IEC autophagy under physiological and IBD pathological conditions.

ATG16L1 is a core component of the autophagosome elongation machinery, forming a stable complex with ATG5 and ATG12 (ATG5-ATG12-ATG16L1 complex) that localizes to the isolation membrane and mediates the lipidation of LC3-I to LC3-II, a key step in autophagosome biogenesis. The *ATG16L1* T300A variant (rs2241880) is the most well-characterized genetic polymorphism associated with CD susceptibility, with a significantly increased risk of CD in carriers of this variant across different ethnic population. Functional studies have shown that the T300A variant leads to reduced ATG16L1 protein stability and impaired autophagosome formation in IECs, resulting in defective clearance of intracellular pathogens (e.g., *Salmonella enterica*) and abnormal Paneth cell granule exocytosis. Paneth cells, specialized IECs in the small intestinal crypts, secrete antimicrobial peptides (e.g., α-defensins) that regulate intestinal microbial composition, and ATG16L1 deficiency-induced Paneth cell dysfunction is a key link between autophagy impairment and microbial dysbiosis in CD [8].

IRGM (immunity-related GTPase family M) is a unique ATG that lacks orthologs in yeast and is specifically involved in the maturation of autophagosomes and their fusion with lysosomes in mammalian cells. *IRGM* interacts with key autophagic proteins including ATG5, ATG16L1, and LC3, and promotes the clearance of intracellular bacteria by regulating the trafficking of autophagosomes to lysosomes. GWAS have identified multiple *IRGM* genetic variants (e.g., rs13361189) associated with increased susceptibility to CD and UC, with the risk allele leading to reduced *IRGM* expression and impaired autophagic flux in IECs. *IRGM*-deficient mice exhibit defective clearance of intestinal bacteria and increased susceptibility to dextran sulfate sodium (DSS)-induced colitis, accompanied by enhanced mucosal inflammation and intestinal barrier dysfunction. Notably, *IRGM* also interacts with NOD2, a key pattern recognition receptor associated with CD susceptibility, and the combined deficiency of *IRGM* and NOD2 exerts a synergistic effect on aggravating intestinal inflammation [9].

LC3, the mammalian homolog of yeast Atg8, is a specific marker of autophagosomes and is essential for autophagosome formation and cargo sequestration. LC3 exists in two forms: the cytosolic LC3-I and the lipidated LC3-II, which is conjugated to phosphatidylethanolamine and localized to the autophagosome membrane. The conversion of LC3-I to LC3-II and the ratio of LC3-II/LC3-I are widely used to evaluate autophagic activity, while the accumulation of p62 (a selective autophagy substrate) indicates impaired autophagic flux. In IECs, LC3-dependent autophagy is essential for maintaining intestinal barrier function by modulating the expression and localization of TJ proteins. Studies have shown that LC3 interacts with ZO-1, a core TJ-associated protein, and promotes its translocation to the apical junctional complex of IECs, thereby enhancing tight junction integrity. LC3 deficiency in IECs leads to reduced expression of ZO-1 and occludin, increased intestinal permeability, and enhanced susceptibility to colitis [10].

2.2 Key Signaling Pathways Modulating IEC Autophagy

IEC autophagy is tightly regulated by multiple intracellular signaling pathways that integrate extracellular cues (e.g., nutrients, cytokines, microbial signals) to modulate autophagic flux, with the PI3K/Akt/mTOR, AMPK, and NF-κB pathways being the most important in the context of IBD. These pathways form a complex regulatory network that fine-tunes basal and inducible autophagy in IECs, and their dysregulation is a major cause of autophagy impairment in IBD [11].

The PI3K/Akt/mTOR pathway is the primary negative regulator of autophagy in eukaryotic cells, and its hyperactivation is a key feature of autophagy dysfunction in IBD. Under nutrient-rich conditions, PI3K activates Akt, which in turn phosphorylates and activates mTOR (mammalian target of rapamycin), a serine/threonine kinase that inhibits autophagy initiation by phosphorylating the ULK1-ATG13-FIP200 complex. In IECs, pro-inflammatory cytokines highly expressed in IBD (e.g., TNF-α, IL-1β) activate the PI3K/Akt/mTOR pathway, leading to mTOR hyperactivation and subsequent inhibition of autophagic flux. Studies have shown that TNF-α-induced PI3K/Akt/mTOR activation in colonic epithelial cells reduces LC3 lipidation and increases p62 accumulation, resulting in impaired autophagy and reduced expression of TJ proteins. Inhibition of mTOR by rapamycin or its analogs restores autophagic flux in IECs, improves intestinal barrier integrity, and attenuates chemically induced colitis in mice, confirming the critical role of the PI3K/Akt/mTOR pathway in regulating IEC autophagy in IBD [12].

The AMPK (AMP-activated protein kinase) pathway is the major positive regulator of autophagy in IECs, and its inactivation contributes to autophagy impairment in IBD. AMPK is a cellular energy sensor that is activated when the intracellular AMP/ATP ratio increases (e.g., under nutrient deprivation, hypoxia, or cellular stress). Activated AMPK promotes autophagy initiation through two complementary mechanisms: direct phosphorylation and activation of the ULK1-ATG13-FIP200 complex, and phosphorylation and inhibition of mTOR, thereby relieving mTOR-mediated autophagy suppression [13]. In IECs, AMPK is constitutively active and essential for maintaining basal autophagic flux and intestinal barrier function. AMPK deficiency in IECs leads to impaired autophagy, increased intestinal permeability, and enhanced susceptibility to DSS-induced colitis, while activation of AMPK by metformin (a first-line antidiabetic drug) enhances autophagic flux in IECs, upregulates the expression of TJ proteins, and attenuates intestinal inflammation in colitis models. Notably, AMPK also regulates the interaction between IECs and the intestinal microbiota by modulating the secretion of antimicrobial peptides, further highlighting its multifaceted role in intestinal mucosal homeostasis [14].

The NF-κB pathway, a master regulator of mucosal inflammation, exerts a dual context-dependent effect on IEC autophagy. NF-κB is activated by pro-inflammatory cytokines and microbial-associated molecular patterns (MAMPs) in IBD, and its nuclear translocation regulates the expression of hundreds of pro-inflammatory genes. In acute inflammatory responses, moderate NF-κB activation upregulates the expression of core ATGs (e.g., *ATG5*, *ATG7*, *LC3*) in IECs, thereby promoting autophagic flux and enhancing the clearance of intracellular pathogens. However, prolonged and excessive NF-κB activation in chronic IBD inhibits autophagy by activating the PI3K/Akt/mTOR pathway and inducing oxidative stress, which impairs lysosomal function and autophagosome-lysosome fusion.This dual role of NF-κB in regulating IEC autophagy reflects the complex crosstalk between inflammation and autophagy in IBD pathogenesis. Functionally, activated NF-κB translocates into nucleus to transcriptionally upregulate abundant pro-inflammatory mediators such as TNF-α, IL-1β, IL-6 and chemokines, which recruit and activate lamina propria macrophages and adaptive immune cells to amplify mucosal inflammatory cascade; sustained inflammatory accumulation further disturbs epithelial autophagic homeostasis in a feedback loop. Accordingly, targeting the NF-κB pathway to restore the balance between inflammation and autophagy may be a novel therapeutic strategy for IBD [15].

Collectively, PI3K/Akt/mTOR, AMPK and NF-κB constitute an interconnected regulatory loop governing epithelial autophagy during IBD progression: AMPK counteracts mTOR to trigger protective homeostatic autophagy under physiological stress; transient moderate NF-κB activation collaborates with ATG proteins to initiate defensive autophagy against invasive pathogens, whereas chronic excessive NF-κB overexpression suppresses autophagy indirectly via hyperactivating PI3K/Akt/mTOR cascade, finally disrupting epithelial homeostasis.

3. Role of Gastrointestinal Epithelial Autophagy in Intestinal Mucosal Homeostasis

3.1 Maintenance of Intestinal Barrier Integrity

The intestinal epithelial barrier is the critical physical barrier separating the luminal microenvironment (containing trillions of microorganisms) from the mucosal immune system, and its integrity is essential for preventing excessive immune activation and maintaining intestinal homeostasis. IEC autophagy is a non-redundant regulator of intestinal barrier integrity, and its impairment directly leads to barrier dysfunction by modulating the expression, localization, and stability of TJ-associated proteins [16].

TJs, the most apical intercellular junctions between IECs, are composed of transmembrane proteins (e.g., occludin, claudins, JAM-A) and cytoplasmic scaffolding proteins (e.g., ZO-1, ZO-2, ZO-3) that form a selective paracellular barrier. The expression and localization of these TJ proteins are tightly regulated, and their downregulation or mislocalization is the main cause of increased intestinal permeability in IBD. IEC autophagy maintains TJ protein homeostasis by two main mechanisms: first, clearing misfolded and aggregated TJ proteins via selective autophagy, thereby preventing their cytoplasmic accumulation and maintaining normal TJ assembly; second, directly interacting with TJ scaffolding proteins to promote their translocation to the apical junctional complex, thereby enhancing tight junction stability. For example, LC3 interacts with ZO-1 and promotes its binding to occludin and claudin-1, forming a stable TJ complex. *Atg5* or *Atg7* deficiency in IECs leads to reduced expression of ZO-1, occludin, and claudin-1, abnormal TJ assembly, and increased paracellular permeability, while restoration of autophagic flux by mTOR inhibitors upregulates TJ protein expression and restores intestinal barrier function [17]. Figure 2 shows the mechanism by which IEC autophagy maintains intestinal mucosal barrier integrity.

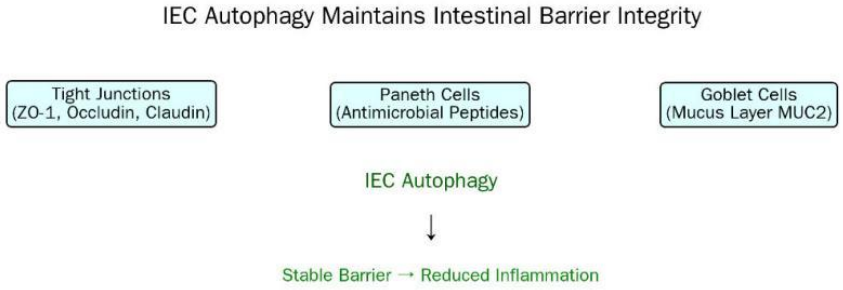

Figure 2. Mechanism of intestinal mucosal barrier integrity maintained by IEC autophagy.

In addition to regulating TJs, IEC autophagy also maintains the function of specialized IEC subsets that are essential for intestinal barrier integrity, including Paneth cells and goblet cells. Paneth cells secrete antimicrobial peptides (e.g., α-defensins, lysozyme) that shape the intestinal microbial community and prevent the overgrowth of pathogenic bacteria. ATG16L1 deficiency in Paneth cells leads to abnormal granule exocytosis and reduced secretion of antimicrobial peptides, resulting in microbial dysbiosis and increased bacterial translocation. Goblet cells secrete mucins (e.g., MUC2) that form a thick mucus layer covering the intestinal epithelium, acting as a physical barrier against microbial adhesion. Autophagy deficiency in goblet cells impairs mucin synthesis and secretion, leading to a thin mucus layer and increased microbial contact with the intestinal epithelium. These findings confirm that IEC autophagy maintains intestinal barrier integrity through both direct regulation of TJs and indirect modulation of specialized IEC function [18].

Nevertheless, most functional evidence supporting barrier-protective effects of autophagy originates from gene-knockout murine experiments; high-quality prospective human clinical trials are still lacking to verify whether pharmacological restoration of autophagy could reliably repair damaged epithelial barrier in clinical IBD patients, leaving translational evidence insufficient at present.

3.2 Modulation of IEC Proliferation and Apoptosis Balance

The intestinal epithelium is one of the most rapidly renewing tissues in the human body, with a turnover rate of 3–5 days, and the balance between IEC proliferation (in the crypts) and apoptosis (at the villus tips) is essential for maintaining intestinal mucosal integrity. Dysregulation of this balance—characterized by increased IEC apoptosis and/or abnormal proliferation—is a key pathological feature of IBD, leading to mucosal damage, ulcer formation, and impaired barrier function. IEC autophagy fine-tunes the proliferation-apoptosis balance by acting as a cellular "stress sensor" that responds to environmental insults (e.g., inflammation, oxidative stress, microbial toxins).

IEC autophagy exerts a cytoprotective effect by inhibiting excessive apoptosis under stress conditions. Inflammatory cytokines and oxidative stress in IBD induce mitochondrial damage and reactive oxygen species (ROS) accumulation in IECs, triggering the intrinsic apoptotic pathway [19]. Autophagy clears damaged mitochondria via mitophagy (a subset of selective autophagy), thereby reducing ROS production and inhibiting caspase activation. *Atg5* or *Atg7* deficiency in IECs leads to increased mitochondrial damage, ROS accumulation, and caspase-3 activation, resulting in excessive IEC apoptosis and mucosal damage. Conversely, activation of autophagy by AMPK agonists or mTOR inhibitors reduces mitochondrial ROS production and inhibits IEC apoptosis in colitis models. Notably, autophagy also inhibits the

extrinsic apoptotic pathway by downregulating the expression of death receptors (e.g., TNFR1) on the IEC surface, further highlighting its cytoprotective role [20].

In addition to inhibiting apoptosis, IEC autophagy also modulates IEC proliferation to maintain mucosal homeostasis. The Wnt/β-catenin pathway is the master regulator of IEC proliferation, and its hyperactivation leads to excessive crypt hyperplasia and abnormal mucosal regeneration in IBD. Autophagy deficiency in IECs leads to the accumulation of β-catenin and hyperactivation of the Wnt/β-catenin pathway, resulting in increased crypt cell proliferation and mucosal hyperplasia. In contrast, activation of autophagy by rapamycin inhibits β-catenin accumulation and normalizes IEC proliferation, promoting orderly mucosal regeneration. This regulatory effect of autophagy on IEC proliferation is critical for repairing mucosal damage in IBD, as excessive and disordered proliferation leads to the formation of dysplastic crypts and impaired barrier function [21]. Persistent abnormal overactivation of Wnt/β-catenin signaling further drives malignant transformation of dysplastic intestinal crypt epithelial cells: accumulated nuclear β-catenin initiates transcription of oncogenic targets including c-Myc and Cyclin D1, which accelerates uncontrolled epithelial proliferation and facilitates the progression from inflammatory dysplasia to colon adenocarcinoma.

Importantly, IEC autophagy exerts a dose-dependent effect on cell survival: basal autophagy is cytoprotective, while excessive autophagy leads to autophagic cell death (type II programmed cell death). In IBD, the balance between cytoprotective autophagy and autophagic cell death is disrupted, with basal autophagy being impaired in most cases, while localized excessive autophagy may occur in severe ulcerative lesions. This dual effect of autophagy highlights the need for precise modulation of autophagic flux in IBD treatment, rather than simple induction or inhibition [22].

However, existing pharmacological modulators cannot achieve cell-specific precise autophagy tuning in clinic, as systemic autophagy intervention simultaneously affects immune cells and intestinal epithelia, easily leading to off-target side effects and restricting the clinical application of single-agent autophagy regulators.

3.3 Bidirectional Interaction with Intestinal Microbiota and Mucosal Immune Cells

The intestinal mucosal microenvironment is a dynamic ecosystem composed of IECs, intestinal microbiota, and mucosal immune cells, and their bidirectional crosstalk is essential for maintaining intestinal homeostasis. IEC autophagy acts as a central hub mediating this crosstalk, by regulating IEC responses to microbial signals and modulating the secretion of inflammatory mediators that shape immune cell function. Disruption of this crosstalk due to autophagy impairment is a key link between microbial dysbiosis and immune dysregulation in IBD [23].

IEC autophagy mediates the IEC-microbiota interaction by regulating the recognition and clearance of intestinal bacteria. IECs express pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) and NOD-like receptors (NLRs) that recognize MAMPs from commensal and pathogenic bacteria. Activation of these PRRs triggers inducible autophagy in IECs, which promotes the clearance of intracellular pathogenic bacteria and modulates the response to commensal bacteria. For example, NOD2, a NLR that recognizes muramyl dipeptide (MDP) from bacterial cell walls, interacts with ATG16L1 and IRGM to activate autophagy in IECs, enhancing the clearance of intracellular bacteria. NOD2 or *ATG16L1* deficiency in IECs leads to defective bacterial clearance, increased bacterial translocation, and subsequent mucosal immune activation. Additionally, IEC autophagy modulates the composition of the intestinal microbiota by regulating the secretion of antimicrobial peptides from Paneth cells and goblet cells, and autophagy impairment-induced microbial dysbiosis further exacerbates autophagy dysfunction, forming a vicious cycle [24].

IEC autophagy also mediates the crosstalk between IECs and mucosal immune cells by regulating the secretion of cytokines, chemokines, and danger-associated molecular patterns (DAMPs). IECs are not only physical barriers but also non-professional immune cells that secrete a variety of inflammatory mediators that regulate the recruitment and activation of mucosal immune cells (e.g., macrophages, dendritic cells, T cells). Autophagy deficiency in IECs leads to the excessive secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and chemokines (e.g., CXCL1, CXCL8), which recruit pro-inflammatory macrophages and Th1/Th17 cells to the mucosal tissue, driving chronic inflammation. Conversely, intact IEC autophagy promotes the secretion of anti-inflammatory cytokines (e.g., IL-10, TGF-β) and immune regulatory factors, which induce the differentiation of regulatory T cells (Tregs) and M2-type macrophages, maintaining immune tolerance [25]. For example, metformin-induced AMPK activation enhances autophagy in IECs, reduces pro-inflammatory cytokine secretion, and increases Treg infiltration in the colonic mucosa of colitis mice. Additionally, IEC autophagy modulates antigen presentation to dendritic cells, promoting the induction of peripheral immune tolerance to commensal bacteria. Autophagy deficiency in IECs leads to abnormal antigen presentation, triggering the activation of autoreactive T cells and breaking immune tolerance [26] (Figure 3).

Current relevant data are mostly obtained from animal knockout models and in vitro cell experiments; human mucosal specimen research can only reveal correlation instead of definite causal links between epithelial autophagy defect and immune tolerance collapse, which requires further prospective human research to validate.

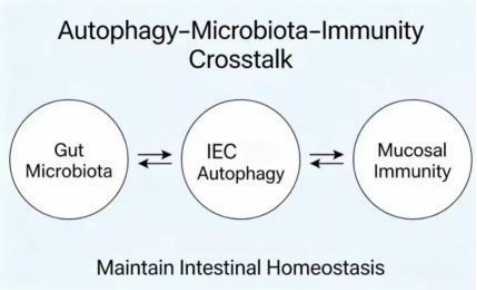

Figure 3. Bidirectional crosstalk among gut microbiota, IEC autophagy and mucosal immunity for sustaining intestinal homeostasis.

4. Autophagy Dysfunction in IBD

4.1 Genetic Evidence for Autophagy-Related IBD Susceptibility

GWAS and candidate gene studies have identified over 200 genetic loci associated with IBD susceptibility, among which multiple ATGs are core susceptibility loci, confirming the genetic link between autophagy dysfunction and IBD. These autophagy-related susceptibility genes include *ATG16L1*, *IRGM*, *NOD2*, *ULK1*, *ATG7*, and *BECN1*, with *ATG16L1*, *IRGM*, and *NOD2* being the most well-characterized and having the strongest association with CD. The cumulative effect of these genetic variants leads to impaired autophagic flux in IECs and immune cells, increasing IBD susceptibility [27].

The *ATG16L1* T300A variant is the first identified and most robust autophagy-related CD susceptibility locus, with an odds ratio (OR) of 1.4-1.6 for CD in European and North American populations. This variant is a missense mutation that replaces threonine with alanine at position 300 of the ATG16L1 protein, leading to reduced protein stability and increased proteasomal degradation. Functional studies have shown that the T300A variant impairs autophagosome formation and maturation in IECs, leading to defective Paneth cell function, reduced antimicrobial peptide secretion, and impaired clearance of intracellular pathogens. Notably, the effect of the *ATG16L1* T300A variant is modulated by environmental factors, such as intestinal viral infection, which further exacerbates autophagy dysfunction and intestinal inflammation [28].

IRGM genetic variants are strongly associated with both CD and UC susceptibility, with the most common variant being rs13361189, a deletion polymorphism in the *IRGM* promoter region that leads to reduced gene expression. The *IRGM* rs13361189 variant is associated with an OR of 1.3 for CD and 1.2 for UC in European populations. *IRGM* deficiency leads to impaired autophagosome-lysosome fusion in IECs, defective clearance of intestinal bacteria, and increased bacterial translocation. Additionally, *IRGM* interacts with NOD2 and ATG16L1, and the combined carriage of *IRGM*, *NOD2*, and *ATG16L1* risk variants exerts a synergistic effect on increasing CD risk, with an OR of up to 4.2.

NOD2, although not a core ATG, is a key regulator of autophagy in IECs and immune cells, and its variants are the strongest CD susceptibility loci identified to date. The three most common *NOD2* variants (R702W, G908R, 1007fs) are associated with an OR of 2.0–4.0 for CD. Functional studies have shown that *NOD2* variants fail to interact with ATG16L1 and IRGM, leading to impaired MAMP-induced autophagy in IECs, defective bacterial clearance, and excessive inflammatory responses. *NOD2* deficiency in IECs also leads to Paneth cell dysfunction and microbial dysbiosis, similar to *ATG16L1* deficiency [29].

Other ATGs have also been associated with IBD susceptibility, albeit with weaker effect sizes. For example, *ULK1* (a key gene in autophagy initiation) variants are associated with UC susceptibility, *ATG7* variants are associated with pediatric IBD, and *BECN1* (a core gene in autophagosome nucleation) variants are associated with CD susceptibility in Asian populations. These findings confirm that autophagy dysfunction is a common genetic feature of IBD, and the cumulative effect of multiple autophagy-related genetic variants contributes to the complex genetic architecture of IBD [30].

4.2 Impaired Autophagic Flux in IBD Patient Tissues

Genetic polymorphisms in ATGs lead to functional autophagy impairment in IECs and mucosal immune cells of IBD patients, which is characterized by reduced autophagic activity and impaired autophagic flux in colonic and ileal mucosal tissues. Multiple studies have confirmed the pathological features of autophagy dysfunction in IBD patient tissues using autophagy-specific markers, providing direct clinical evidence for the association between autophagy impairment and IBD [31]. Table 2 compares the distinct patterns of autophagic flux impairment observed in the intestinal epithelial tissues of CD and UC patients.

Table 2. compares the distinct patterns of autophagic flux impairment observed in the intestinal epithelial tissues of CD and UC patients.

Autophagy Marker / Feature	CD	UC	Pathological Interpretation
Primary Affected Site	Ileum (Paneth cells)	Colon (enterocytes/goblet cells)	Reflects the segmental vs. continuous nature of the two diseases.
LC3-II Expression	Increased	Decreased	CD: Blocked fusion (autophagosome accumulation); UC: Reduced autophagy initiation.
p62/SQSTM1 Accumulation	Markedly Increased	Markedly Increased	Common feature indicating impaired overall autophagic flux in both subtypes.
ATG16L1/IRGM Protein Level	Significantly Reduced (especially in risk variant carriers)	Moderately Reduced	Chronic inflammation further downregulates autophagy machinery beyond genetic effects.
Key Defect	Autophagosome-lysosome fusion block; Paneth cell granule dysmorphia.	Defective initiation of autophagy; increased epithelial apoptosis.	Divergent mechanisms leading to impaired barrier function and inflammation.
Signaling Pathway Status	Hyperactivated PI3K/Akt/mTOR; Excessive NF-κB.	Inactivated AMPK; Hyperactivated PI3K/Akt/mTOR	Convergent inhibition of autophagy through distinct upstream signaling defects.

The most common method to evaluate autophagic flux in clinical tissues is detecting the expression of LC3-II and p62. Increased LC3-II levels combined with increased p62 accumulation indicate impaired autophagic flux (i.e., blocked autophagosome-lysosome fusion or lysosomal dysfunction), while decreased LC3-II levels indicate reduced autophagy initiation. Studies have shown that colonic mucosal tissues from CD and UC patients exhibit significantly increased p62 accumulation and altered LC3-II expression, indicating impaired autophagic flux. For example, UC patients have reduced LC3-II levels and increased p62 accumulation in colonic epithelial cells, indicating reduced autophagy initiation and impaired flux, while CD patients have increased LC3-II levels and increased p62 accumulation in ileal epithelial cells, indicating blocked autophagosome-lysosome fusion [32]. These differences may be related to the distinct pathological features of CD (transmural inflammation, ileal involvement) and UC (mucosal inflammation, colonic involvement).

In addition to LC3 and p62, the expression of core autophagy-related proteins is also altered in IBD patient tissues. ATG16L1 and IRGM protein levels are significantly reduced in colonic and ileal epithelial cells of CD patients carrying the risk variants, and their expression is also reduced in non-carriers, indicating that chronic inflammation further downregulates the expression of autophagy-related proteins. NOD2 protein expression is reduced in Paneth cells of CD patients with *NOD2* variants, leading to impaired autophagy activation. Additionally, the expression of signaling molecules regulating autophagy is altered in IBD patient tissues: the PI3K/Akt/mTOR pathway is hyperactivated, the AMPK pathway is inactivated, and the NF-κB pathway is excessively activated, all of which contribute to autophagy dysfunction [33].

Autophagy dysfunction is not limited to IECs in IBD patients; it also occurs in mucosal immune cells including macrophages, dendritic cells, and T cells. For example, macrophages from CD patients exhibit impaired autophagic flux, leading to excessive secretion of pro-inflammatory cytokines and enhanced inflammatory responses. Dendritic cells from IBD patients have reduced autophagy activity, leading to abnormal antigen presentation and impaired Treg induction. These findings confirm that autophagy dysfunction is a systemic feature of IBD, affecting both epithelial and immune cells, and contributing to the dysregulation of the entire mucosal microenvironment [34].

4.3 Animal Models of IEC Autophagy Dysfunction and IBD-like Phenotypes

Animal models have provided invaluable insights into the causal relationship between IEC autophagy dysfunction and IBD pathogenesis, and multiple mouse models with IEC-specific autophagy deficiency exhibit spontaneous or chemically induced colitis with IBD-like pathological features. These models confirm that IEC autophagy deficiency is sufficient to induce intestinal inflammation, and restore the key pathological links between autophagy impairment, intestinal barrier dysfunction, microbial dysbiosis, and immune dysregulation [35].

The most widely used IEC-specific autophagy-deficient mouse models are *Atg5ΔIEC* (IEC-specific *Atg5* deletion) and *Atg7ΔIEC* (IEC-specific *Atg7* deletion) mice. *Atg5ΔIEC* mice develop spontaneous mild colitis under specific pathogen-free (SPF) conditions, characterized by increased intestinal permeability, microbial dysbiosis, and mild mucosal inflammation in the colon . Under conventional conditions or with chemical induction (e.g., DSS), *Atg5ΔIEC* mice develop severe colitis with increased mortality, transmural inflammation, and ulcer formation. *Atg7ΔIEC* mice do not develop spontaneous colitis under SPF conditions but exhibit significantly increased susceptibility to DSS-induced colitis, with severe intestinal barrier dysfunction, excessive IEC apoptosis, and enhanced pro-inflammatory cytokine secretion. These models confirm that IEC autophagy is essential for maintaining intestinal homeostasis under basal conditions and for resisting inflammatory insults under stress conditions [36]. Figure 4 compares the IBD-like phenotypes of IEC-specific autophagy-deficient mouse models.

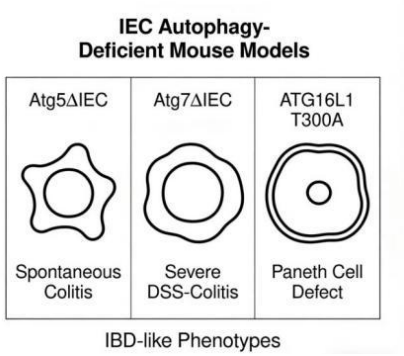

Figure 4. Comparison of IBD-like pathological phenotypes in IEC-specific autophagy-knockout mouse models.

Mouse models carrying human autophagy-related IBD susceptibility variants have also been developed, including *Atg16L1HM* (humanized *ATG16L1* T300A variant) mice and *Irgm-/-* mice. *Atg16L1HM* mice exhibit impaired Paneth cell function and reduced antimicrobial peptide secretion, and develop severe ileitis after infection with murine norovirus, a common intestinal virus. This model confirms the interaction between genetic susceptibility (ATG16L1 T300A) and environmental triggers (viral infection) in driving CD pathogenesis. *Irgm-/-* mice exhibit defective clearance of intestinal bacteria and increased susceptibility to DSS-induced colitis, accompanied by enhanced mucosal inflammation and microbial dysbiosis. Notably, the colitis phenotype of *Irgm-/-* mice can be reversed by antibiotic treatment, confirming that microbial dysbiosis is a key mediator of intestinal inflammation induced by IRGM deficiency [37].

Other IEC autophagy-deficient mouse models, such as *LC3b-/-* mice and *UlK1ΔIEC* mice, also exhibit increased susceptibility to chemically induced colitis. *LC3b-/-* mice have reduced expression of TJ proteins and increased intestinal permeability, leading to enhanced DSS-induced colitis, while *UlK1ΔIEC* mice have reduced autophagy initiation and excessive IEC apoptosis, leading to severe UC-like colitis. These models further confirm the critical role of different steps of autophagy (initiation, elongation, flux) in IEC function and intestinal homeostasis. Collectively, these animal models provide direct evidence that IEC autophagy dysfunction is a causal factor in IBD pathogenesis, and validate autophagy as a potential therapeutic target for IBD [38].Consistent with these animal-based findings, multiple human cohort and translational clinical researches have verified reduced autophagic activity in intestinal biopsies collected from CD/UC patients carrying ATG16L1/IRGM susceptible variants, and clinical observational data also links impaired epithelial autophagy to aggravated endoscopic mucosal injury and poor clinical response to conventional anti-inflammatory treatment in human IBD subjects. Figure 5 systematically summarizes the full pathological cascade: autophagy-related genetic variation and abnormal core signaling pathways trigger impaired epithelial autophagy, sequentially inducing intestinal epithelial barrier damage, microbial dysbiosis and aberrant mucosal immunity, ultimately facilitating the initiation and progression of IBD.

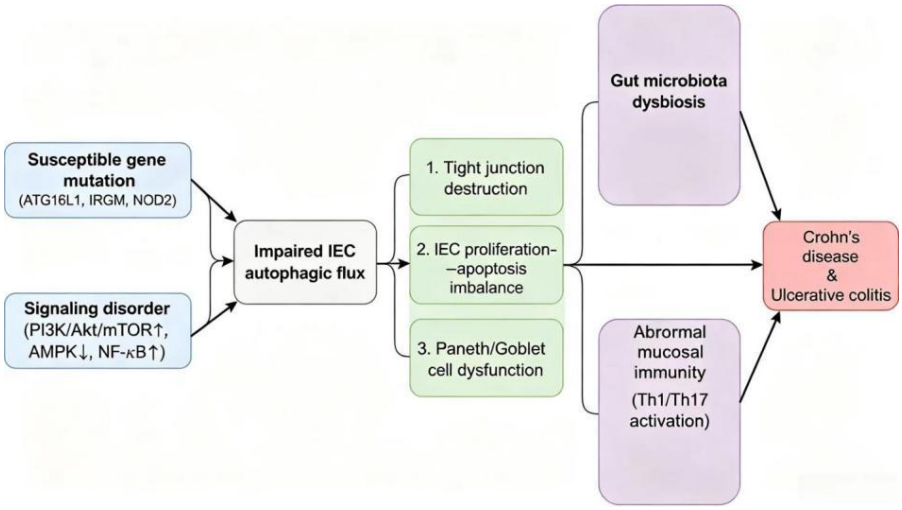

Figure 5. Integrative overview of epithelial autophagy dysfunction linking genetic variants, signaling dysregulation, barrier damage, microbiota dysbiosis, and aberrant mucosal immunity toward IBD pathogenesis.

5. Conclusion

Gastrointestinal epithelial cell autophagy is an evolutionarily conserved and essential process for maintaining intestinal mucosal homeostasis, with multifaceted roles in the maintenance of intestinal barrier integrity, modulation of IEC proliferation and apoptosis balance, and bidirectional crosstalk with the intestinal microbiota and mucosal immune cells.

Genetic polymorphisms in ATGs (e.g., *ATG16L1*, *IRGM*, *NOD2*) and dysregulation of key signaling pathways (e.g., PI3K/Akt/mTOR, AMPK, NF-κB) lead to impaired autophagic flux in IECs of IBD patients, which is a key initiating and driving factor of IBD pathogenesis. Impaired IEC autophagy disrupts intestinal barrier function, triggers microbial dysbiosis, and induces aberrant mucosal immune responses, forming a vicious cycle that promotes the onset and progression of chronic intestinal inflammation.

Synthetic small-molecule pharmacological compounds (e.g., metformin, rapamycin) and natural compounds (e.g., resveratrol, curcumin)–attenuate intestinal inflammation in colitis models by restoring autophagic flux in IECs, improving intestinal barrier function, and modulating mucosal immune and microbial homeostasis. Metformin, a well-tolerated AMPK agonist, has shown promising preliminary clinical results for active UC, making it the most advanced autophagy-targeted drug for IBD. However, there are still multiple challenges to the clinical application of autophagy modulators for IBD, including the heterogeneity of autophagy dysfunction, off-target effects, unclear therapeutic windows, and limited clinical evidence.

Future research should focus on elucidating the precise molecular mechanisms of IEC autophagy in different IBD subtypes and disease stages, developing autophagy-specific biomarkers for patient stratification and therapeutic monitoring, and designing IEC-specific or mucosal-targeted autophagy modulators to improve therapeutic efficacy and reduce side effects. Combination therapy of autophagy modulators with conventional IBD drugs or microbiota-targeted therapies is a promising direction to enhance therapeutic efficacy. With the continuous advancement of research on autophagy and IBD, autophagy-targeted therapy is expected to become a novel precision therapy for IBD, providing new treatment options for patients with this chronic and debilitating disease.

In brief, this review concludes that epithelial autophagy acts as a core homeostatic switch whose functional impairment concurrently triggers epithelial barrier destruction, gut microbial dysbiosis and aberrant mucosal immune activation across CD and UC. Despite promising preclinical results of autophagy-modulating agents, inconsistent autophagy alteration patterns among different IBD subtypes and individual patients hinder uniform clinical medication. Hence, future precision treatment should stratify IBD patients according to their intestinal autophagy status to realize personalized autophagy-targeted intervention.

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Ethics Statement

This study did not carry out human-subject experiments or animal-related trials, so ethical approval is not required.

Data Availability Statement

The datasets generated and analysed in this research are available from the corresponding author upon reasonable request.

Author Contributions

The author took part in research conception, literature sorting-out, manuscript drafting, revision and final-version confirmation. The author approves the submitted manuscript.

Conflict of Interest

The author declares that there are no competing financial or non-financial interests.

Generative AI Statement

No generative artificial intelligence tools were used throughout the writing and preparation of this manuscript.

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