

Role of autophagy in the pathogenesis 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.

Recently, some studies provided strong evidence that the process of autophagy affects several aspects of mucosal immune responses. Autophagy is a cellular stress response that plays key roles in physiological processes, such as innate and adaptive immunity, adaptation to starvation, degradation of aberrant proteins or organelles, antimicrobial defense, and protein secretion. Dysfunctional autophagy is recognized as a contributing factor in many chronic inflammatory diseases, including IBD. Autophagy plays multiple roles in IBD pathogenesis by altering processes that include intracellular bacterial killing, antimicrobial peptide secretion by Paneth cells, goblet cell function, proinflammatory cytokine production by macrophages, antigen presentation by dendritic cells, and the endoplasmic reticulum stress response in enterocytes. Recent studies have identified susceptibility genes involved in autophagy, such as *NOD2*, *ATG16L1*, and *IRGM*, and active research is ongoing all over the world. The aim of this review is a systematic appraisal of the current literature to provide a better understanding of the role of autophagy in the pathogenesis of IBD. Understanding these mechanisms will bring about new strategies for the treatment and prevention of IBD.

Key words: Autophagy; Inflammatory bowel disease; Genome-wide association study; Ulcerative colitis; Crohn's disease

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Core tip: Recent studies provide strong evidence that the process of autophagy affects several aspects of mucosal immune responses. Autophagy is a cellular stress response that plays key roles in physiological processes. Dysfunctional autophagy is recognized as a contributing factor in many chronic inflammatory diseases, including inflammatory bowel disease (IBD). Autophagy plays multiple roles in IBD pathogenesis. Recent studies have identified susceptibility genes involved in autophagy, such as *NOD2*, *ATG16L1*, and

IRGM, and active research is ongoing around the world. The aim of this review is a systematic appraisal of current literature to provide a better understanding of the role of autophagy in IBD pathogenesis.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease involving idiopathic inflammation, mainly in the gastrointestinal tract; defined more specifically, it comprises ulcerative colitis (UC) and Crohn's disease (CD). Both are characterized by onset at a young age, and the number of affected patients has risen sharply in recent years in Europe and the United States, as well as in Japan^[1]. Thus, there is a pressing need to understand their pathologies and create effective treatments. Researchers, mainly in Europe and the United States, have been trying to identify disease-susceptibility genes for IBD. Nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) was the first susceptibility gene identified for CD^[2,3], and in recent years genome-wide association studies (GWAS) have made it possible to perform comprehensive searches for susceptibility genes. In 2007, autophagy-related 16-like 1 (*ATG16L1*) was identified as an autophagy-related gene^[4]. This was the first study to show a relationship between autophagy and a specific disease. Since then, the role of autophagy in the pathogenesis of IBD has been investigated all over the world.

This review will evaluate the current literature to provide a better understanding of the role of autophagy in the pathophysiology of IBD.

PATHOLOGY AND PATHOGENESIS OF IBD

The gastrointestinal tract not only absorbs fluid and nutrients, but is constantly involved in regulating and maintaining the gut flora, immune responses to food antigens and other substances, and homeostasis. IBD occurs when this homeostasis is impaired. Recent research has shown that IBD is caused by chronic intestinal inflammation, which occurs because of gene variations that can lead to disease susceptibility, changes in the structure of the intestinal flora needed to maintain intestinal homeostasis, and abnormal intestinal mucosal immune responses^[5-7].

The role of genetic factors in IBD has been previously reported^[8], and several researchers are seeking

disease-susceptibility genes and trying to find customized treatments for individual patients^[9]. To date, approximately 200 loci have been identified as being associated with both forms of IBD. Within these 200 loci, based upon single nucleotide polymorphism frequencies in IBD subjects versus controls, are approximately 1500 potential associated genes^[10,11]. Representative autophagy-related genes are *NOD2*, *ATG16L1*, and immunity related guanosine triphosphatase M (*IRGM*)^[1-3,12]. Autophagy has been linked to a variety of diseases, but its link to IBD is currently the subject of much debate.

AUTOPHAGY

Autophagy (from the Greek "auto" oneself and "phagy" to eat) refers to any cellular degradative pathway that involves the delivery of cytoplasmic cargo to the lysosome. During this process, the endoplasmic reticulum or other membranous cellular structures respond to stimuli by generating a double-membrane structure called a phagophore. On this phagophore, *ATG16L1* forms a complex with an *ATG5-ATG12* conjugate, which multimerizes and then lipidates *LC3 (LC3-II)*. Simultaneously, the phagophore elongates to envelop the cytoplasm or organelle to be degraded, forming an autophagosome, a unique double-membrane organelle. The outer membrane of the autophagosome then fuses with a lysosome to form an autolysosome, and the inner membrane degrades and absorbs its contents (Figure 1)^[13-15]. This process, along with the ubiquitin proteasome pathway (UPP) system, triggers the intracellular protein degradation mechanism. The process is also responsible for mechanisms such as adaptation to starvation, defense against infections, carcinogenesis, antigen presentation, and quality control of intracellular proteins. It maintains appropriate cellular homeostasis and provides the structural processes necessary for organ renewal^[16]. Yet, unlike the UPP system, autophagy is also able to degrade mitochondria and other organelles.

A remarkable analysis of autophagy-related factor groups showed that, in addition to its role in metabolism, autophagy plays an important role in the innate immune response^[13]. Innate immunity is a mechanism by which nearly all multicellular organisms protect themselves from pathogens. Innate immunity signaling pathways are activated when the structural patterns of a pathogen's components are recognized (*i.e.*, the cell wall components of a bacterium or the genome of a virus). As noted above, autophagy was initially considered to be a nonspecific mechanism for degrading substances by incorporating them into a membrane structure, but recent research has shown that autophagosomes selectively isolate a variety of substrates^[17]. However, besides autophagy of pathogens (xenophagy)^[18,19] and autophagy of damaged mitochondria (mitophagy)^[20,21], very little

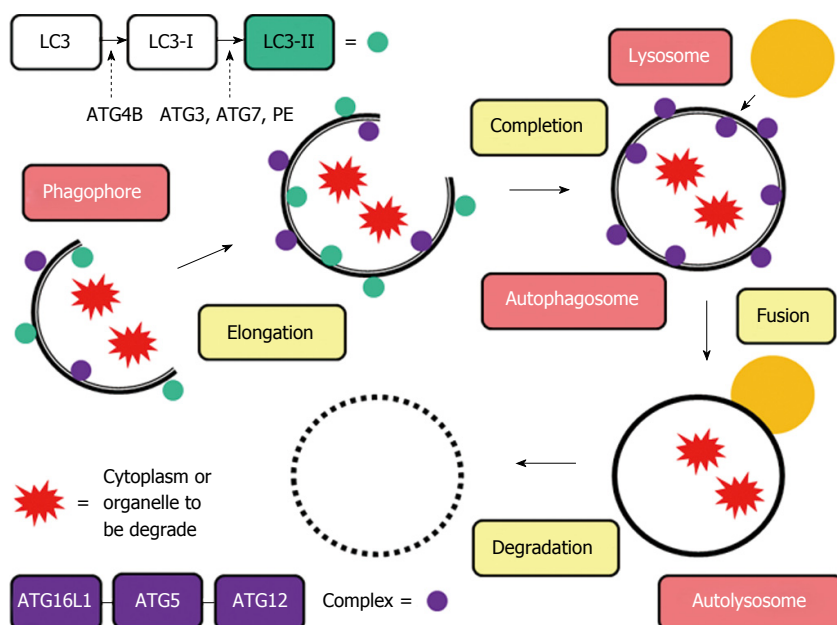


Figure 1 Autophagy mechanism. The autophagy pathway. During this process, the endoplasmic reticulum or other membranous cellular structures respond to stimuli by generating a double-membrane structure called a phagophore. On this phagophore, *ATG16L1* forms a complex with an *ATG5-ATG12* conjugate, which multimerizes and then lipidates LC3 (LC3-II). Simultaneously, the phagophore elongates to envelop the cytoplasm or organelle to be degraded, forming an autophagosome, a unique double-membrane organelle. The outer membrane of the autophagosome then fuses with a lysosome to form an autolysosome, and the inner membrane degrades and absorbs its contents.

Table 1 Genetic variants related to inflammatory bowel disease and autophagy

Gene	Chromosomal site	Relation to autophagy
<i>NOD2</i>	16q12.1	Intracellular bacterial sensing Autophagosome formation
<i>ATG16L1</i>	2p37.1	Autophagosome formation Suppressing Paneth cells
<i>IRGM</i>	5q33.1	Phagosome maturation Virus-induced autophagy
<i>IL-23R</i>	1p31.3	Through effects on IL-1 secretion
<i>XIAP</i>	Xq25	Physiological inhibitor of autophagy
<i>LRRK2</i>	12q12	Autophagosomal-lysosomal degradation
<i>ULK1</i>	12q24.33	Regulated by TORC1 and AMPK
<i>VDR</i>	12q13.11	Regulate the expression of <i>NOD2</i>
<i>MTMR3</i>	22q12.2	Autophagosome formation

is understood about which substrates autophagy degrades when it functions as part of innate immunity.

IBD- AND AUTOPHAGY-RELATED GENETIC VARIANTS

Autophagic dysfunction causes several diseases^[22-24], among which CD is being most extensively researched. The above mentioned GWAS found several genetic variants linked to CD onset, such as *NOD2* and *ATG16L1*. A summary of these variants is given below (Table 1).

NOD2, ATG16L1

NOD2, located on chromosome 16q12.1, was the

first disease-susceptibility gene discovered for CD. Its genetic variants are common in European and American patients, but have not been found in Asian patients. *NOD2* is a pattern-recognition receptor that is involved in the homeostasis of intestinal immunity. It acts through mechanisms like autophagy, intracellular bacterial sensing, controlling the expression of the antibacterial peptide α -defensin in the Paneth cells of the small intestine, and improving immune tolerance by suppressing toll-like receptor (TLR) signals^[25]. *NOD2* recruits the autophagy protein *ATG16L1* to the plasma membrane at the bacterial entry site; mutant *NOD2* failed to recruit *ATG16L1* to the plasma membrane and wrapping of invading bacteria by autophagosomes was impaired. Therefore, patients with CD with *NOD2* variants are considered to exhibit disorders of autophagy^[26-28]. When the mechanism of autophagy is impaired, lipopolysaccharides and damage-associated molecular patterns trigger signaling by stimulating TLR and NOD-like receptors, tumor necrosis factor (TNF), and other inflammatory cytokines. They also stimulate caspase-1 causing interleukin (IL)-1 β and IL-18 cleavage from precursors, which promotes extracellular secretion (inflammasomes). In an experiment using mice knocked out for *ATG16L*, which encodes *ATG16L1*, the protein necessary for the autophagic recruitment, TLR and TNF stimulation led to abnormal inflammasome activity in macrophages and other innate immunity cells^[29].

ATG16L1 is a homolog of *ATG16* that was first reported by Mizushima *et al*^[30,31]. Along with *AT5* and *ATG12*, this molecule is required to form autophagosomes. Prescott *et al*^[32] reported that the incidence of

CD was likely to be two times higher in people with the T300A variant, an *ATG16L1* variant with a threonine-to-alanine substitution at amino-acid position 300. Later, a meta-analysis of 25 studies showed that T300A caused disease susceptibility to CD^[33]. However, no significant difference was observed in an analysis of patients from Japan, South Korea, and China from 25 studies. This suggests that European and American patients exhibit different genetic factors compared to Asian patients, as is seen with *NOD2*. Moreover, a meta-analysis of 14 studies on UC reported an odds ratio of 1.06, or almost no difference^[33].

The report that *ATG16L1* is a CD-susceptibility gene was a groundbreaking discovery suggesting a role for autophagy in the onset of IBD. Since then, several researchers have published studies on the link between *ATG16L1* and IBD.

Paneth cells are a specialized type of epithelial cell that are involved in innate immunity in the small intestine. When they come into contact with bacteria or other antigens, these cells release secretory granules containing antimicrobial peptides and a variety of proteins. In 2008, Cadwell *et al.*^[34] engineered a mouse with low expression of *ATG16L1* (Atg16L1^{HM} mouse). Tissue analysis did not find lysozymes that are normally seen in the ileal mucosa, but found abnormal Paneth cell granule secretion. Moreover, they analyzed Paneth cells in non-inflamed areas of the ileum in patients with CD homozygous for the *ATG16L1* variant T300A, and found abnormal Paneth cells that strongly resembled those observed in Atg16L1^{HM} mice. This suggests that *ATG16L1* may also play an important role by suppressing Paneth cells in humans. In a relatively recent study, Lassen *et al.*^[35] generated a knock-in mouse model expressing ATG16L1^{T300A}. Such mice do not develop spontaneous inflammation, although they exhibit morphological defects in both Paneth cells and goblet cells. Furthermore, the presence of the T300A mutation in *ATG16L1* leads to aberrant functionality of Paneth cells. These findings indicate the reason there is believed to be a close relationship between *ATG16L1* variants and Paneth cells.

Further, Murthy *et al.*^[36] reported that *ATG16L1* amino-acid positions 296 to 299 form a caspase cleavage motif, which greatly increases *ATG16L1* sensitivity when the cellular stress response activates caspase-3 in the presence of the T300A variant. This may result in impaired autophagy, leading to CD onset, and suggests that *ATG16L1* plays a role at the molecular level in CD onset.

In 2010, Cadwell *et al.*^[37] reported interesting data on role of *ATG16L1* by using Atg16L1^{HM} mice infected with MNV CR6, a species of mouse norovirus. MNV CR6-infected Atg16L1^{HM} mice showed abnormal secretion of Paneth cell granules, similar to that described above. This was not observed in wild-type mice without an *ATG16L1* variant, or in mice infected

with a different MNV strain or with inactivated MNV. Administration of dextran sulfate sodium (DSS) to these infected mice led to pathology similar to that observed in human patients with CD: inflammation extending to the muscle layer and mesentery, and atrophy of the ileal villi, neither of which has been previously reported with DSS colitis. These symptoms were significantly suppressed by administering TNF- α antibodies or antibiotics. A recent report suggested that *ATG16L1* polymorphisms promote disease through defects in "sensing" protective signals from the microbiome, defining a potentially critical gene-environment etiology for IBD^[38].

These data suggest that in addition to *ATG16L1* variants, CD onset is influenced by a complex variety of environmental factors, including viral infections and enterobacteria.

IRGM

In a 2007 GWAS, Parkes *et al.*^[39] reported that the *IRGM* gene on chromosome 5q33.1 was a CD-susceptibility gene. In humans, *IRGM* is a 20 kDa protein formed from 181 amino acids that is expressed in the large intestine, small intestine, and lymphocytes. *IRGM* is related to bacterial killing, vacuolar trafficking and acidification, phagosome maturation, and virus-induced autophagy. Moreover, it is known to be involved in controlling intracellular *Mycobacterium tuberculosis* by autophagy in macrophages^[40]. A small nuclear polymorphism (SNP) with susceptibility is adjacent to *IRGM*, but detailed sequencing of *IRGM* did not reveal any CD-related variants with modified amino acids. This suggests the possibility that changes of *IRGM* expression, transcript splicing, or the ratio of translation of the protein are related to the development of CD.

In 2008, McCarroll *et al.*^[41] discovered a 20 kb deletion polymorphism upstream from *IRGM* that was linked to an SNP correlating with CD. In addition, they reported that the expression of *IRGM* suppressed autophagy of intracellular bacteria, which has been linked to CD, suggesting a role in the pathology of CD.

Recently, Rufini *et al.*^[42] reported that *IRGM* polymorphisms were important for CD susceptibility and phenotype modulation (fibrostricturing behavior, ileal disease, perianal disease, and intestinal resection).

IL-23R

IL-23 is a heterodimeric cytokine produced by activated macrophages and dendritic cells. It consists of two subunits, a p40 subunit, shared with IL-12, and a specific IL-23 subunit called p19^[43,44]. It has been shown that IL-23 is involved in the initiation of the innate and adaptive immune activation that characterizes IBD. It binds a complex of IL-23 receptor (IL-23R) and IL-12R β subunits. *IL-23R* is predominantly expressed on activated/memory T cells, T-cell clones, natural killer cells and, at low levels, in monocytes, macrophages, and dendritic cell populations^[45,46].

Recent studies have shown association of the *IL-23R* gene with chronic inflammatory diseases, especially IBD^[47,48]. It is also reported that autophagy regulates IL-23 secretion and innate T cell responses through effects on IL-1 secretion^[49].

XIAP

XIAP (X-linked inhibitor of apoptosis) is one of several inhibitor of apoptosis proteins (IAPs). IAPs were initially identified in baculoviruses, where they prevent defensive apoptosis of host cells^[50]. Among the mammalian IAPs, *XIAP* is the most extensively studied and best characterized. *XIAP* has the most potent anti-apoptotic ability^[51], which is believed to be primarily related to direct binding and inhibiting of caspases, the apoptotic proteases that are responsible for the initiation and execution of apoptosis^[52]. Huang *et al*^[53] showed that *XIAP* is a physiological inhibitor of autophagy, and has been associated with a variety of diseases that have been linked to autophagy. *XIAP* is related to X-linked lymphoproliferative syndrome type 2 (XLP2), a type of primary immunodeficiency. However, a genetic analysis performed by Zeissig *et al*^[54] found *XIAP* variants in only 4% of male patients with childhood-onset CD. Recently, Schwerd *et al*^[55] showed impaired antibacterial autophagy links granulomatous intestinal inflammation in Niemann-Pick disease type C1 and *XIAP* deficiency with *NOD2* variants in CD.

LRRK2

LRRK2 (leucine-rich repeat kinase 2) is a large multidomain protein belonging to the ROCO family of proteins, which are characterized by the presence of leucine-rich repeats, a Ras of complex (ROC) GTPase domain, a C-terminal ROC linker region, and a kinase domain. *LRRK2* localizes to specific membrane subdomains, including endolysosomal structures in many kinds of cells. Studies showed that *LRRK2* KO mice displayed an increase in the number and size of secondary lysosomes and autolysosome-like structures. Abnormal accumulation of undigested material indicates an impairment in the autophagosomal-lysosomal degradation system (autophagy-lysosomal clearance pathway).

LRRK2 has been identified as a disease-susceptibility gene for Parkinson's disease, leprosy, and CD. The CD-associated SNP is located upstream of the coding sequence of *LRRK2*^[56,57]. It was reported that *LRRK2* expression levels were found to be significantly upregulated in colonic biopsy specimens from inflamed tissues of patients with CD^[58]. *LRRK2* is known to be expressed only in mucosal lymphocytes in the colonic mucosa, but little else is known about it.

ULK1

ULK1 (Unc-51 like autophagy activating kinase 1) is one of the key regulators of autophagy initiation

and progression. Mammals have two homologs of the yeast autophagy-initiating ATG1 kinase, *ULK1* and *ULK2*. *ULK1* is regulated by the nutrient- and energy-sensitive kinases TORC1 and AMPK. The tight regulation of ULK activity by intracellular energy and nutrient levels is in keeping with a central role for autophagy in the protection of cells from starvation.

Henckaerts *et al*^[59] selected human homologs of 12 yeast autophagy genes, known to be found in IBD-related loci from GWAS, and conducted a meta-analysis of these searches. An analysis of correlations with CD identified *ULK1* as a CD-susceptibility gene. *ULK1* activity is regulated by a complex array of multiple phosphorylation and dephosphorylation events that influence the binding of regulatory and effector autophagy proteins^[60,61]. However, little is known about the action of *ULK1* in association with IBD, and further research is necessary.

VDR

VDR (the vitamin D receptor) regulates the expression of *NOD2*, and it has been suggested that it controls the mechanism of autophagy. Unlike other genes, *VDR* has been shown to be a UC-susceptibility gene, not only among Europeans and Americans, but also in Asian and Middle Eastern populations^[62]. Vitamin D deficiency increases the risk of CD onset^[63]; thus, analyzing its signaling pathways could help elucidate the pathology of this disease.

Recently, Wu *et al*^[64] showed a fundamental relationship between the *VDR*, autophagy, and gut microbial assemblage that is essential for maintaining intestinal homeostasis, but also contributes to the pathophysiology of IBD. Furthermore, Abreu-Delgado *et al*^[65] reported that levels of serum vitamin D correlate positively with colonic *VDR* expression in visually normal mucosa; whereas inflammation correlates negatively with colonic *VDR* expression in visually diseased mucosa. The *VDR* needs further research.

MTMR3

MTMR3 (myotubularin-related protein 3) plays a role in autophagosome formation^[66]. The myotubularin family is a class of PI3-phosphatases that regulate several physiological and pathophysiological phenomena, including endosomal trafficking, apoptosis, autophagy, and muscle development. As a member of this family, *MTMR3* has been considered to play a negative role in the initiation stage of autophagy. Recent reports indicate that *MTMR3* has at least two opposite functions in the autophagy pathway, inhibition of mechanistic target of rapamycin complex 1 (mTORC1) and reduction of local PI3P levels^[67,68]. In this regard, the function of *MTMR3* in autophagy remains unclear.

ROLE OF AUTOPHAGY IN IBD THERAPY AND FUTURE PROSPECTS

Widely used therapeutic agents for IBD include

Table 2 Therapeutic agents for inflammatory bowel disease related to autophagy

Drug	Influence on autophagy	Mechanism related to autophagy
5-ASA	Promotion	Through NF- κ B signaling pathway
Corticosteroid	Promotion	Through NF- κ B signaling pathway Through mTORC1 signaling pathway Through overexpression of Bcl-2 in immature T-lymphocytes Osteocyte viability
Thiopurine (AZA, 6-MP)	Promotion	Clearance of TPMT*3A aggregates and/or aggregate precursors Protective role in hepatocytes
Immunomodulatory drugs (CsA, FK506)	Promotion	Response to toxicity Through mTORC1 signaling pathway
Biological drugs (IFX, ADA, <i>etc.</i>)	Inhibition	Anti-TNF agents inhibit autophagy (not yet clear)

5-ASA: 5-aminosalicylic acid; mTORC1: Mechanistic target of rapamycin complex 1; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; TPMT: Thiopurine S-methyltransferase; CsA: Cyclosporine A; IFX: Infliximab; ADA: Adalimumab; TNF: Tumor necrosis factor.

steroids and 5-aminosalicylic acid (5-ASA), as well as immunoregulatory drugs such as azathioprine, and biologicals such as anti-TNF- α formulations. The process of autophagy is closely related to each of these existing therapeutic agents. The following sections summarize these relationships (Table 2).

5-ASA

The mechanism of action of 5-ASA has been described in several studies. The suppression of peroxisome proliferator-activated receptor gamma (PPAR γ) due to the production of inflammatory cytokines is said to contribute to the intestinal inflammation seen in patients with IBD^[69]. 5-ASA is considered to exert its anti-inflammatory action by acting on PPAR γ in epithelial cells, and by regulating signal transmission from NF- κ B and TLR^[70]. Considering that NF- κ B signaling is associated with autophagy^[71], it might be that 5-ASA indirectly regulates autophagy.

Corticosteroids

The first-line treatment to induce remission for CD and UC is often corticosteroids. Corticosteroids downregulate proinflammatory cytokines, including IL-1, IL-6, and TNF α . Furthermore, inflammatory signaling induced by NF- κ B is decreased by interaction with corticosteroid receptors^[72], and, as noted above, NF- κ B signaling regulates autophagy^[71]. It has also been shown that corticosterone treatment affects mTORC1 signaling pathways^[73]. It was reported that mTORC1 pathways and autophagy play an important role in the response to treatment with corticosteroids^[74]. Corticosteroids are able to induce apoptosis in immature T lymphocytes,

as these cells lack the inhibitor of apoptosis protein Bcl-2. It has been shown that overexpression of Bcl-2 in immature T lymphocytes can increase autophagy levels, presumably due to inhibition of apoptosis^[75].

A relationship between corticosteroids and autophagy has been observed, not only for their therapeutic effects, but also for the adverse effects that accompany treatment. It has been shown, both *in vitro* and *in vivo*, that low doses of prednisolone and dexamethasone induce autophagy in osteocytes, and this is associated with osteocyte viability^[76,77]. However, higher doses of corticosteroids induce apoptosis, suggesting that autophagy may act as a protective mechanism against the cytotoxic effects of corticosteroids^[76].

Thiopurines (azathioprine and 6-mercaptopurine)

Thiopurines, including azathioprine and 6-mercaptopurine, are immunosuppressant drugs used to maintain remission in patients with IBD^[78]. Thiopurines and autophagy have also been shown to be correlated by the adverse effects of treatment. The thiopurine S-methyltransferase (TPMT) genetic polymorphism is important for thiopurine metabolism. Individuals with inherited decreases in TPMT activity, mainly as a result of the effects of the TPMT*3A allele (minor allele frequency in Caucasians of approximately 5%)^[79], are at greatly increased risk for severe life-threatening myelosuppression when treated with "standard" doses of thiopurine drugs^[80-83]. It was shown that autophagy might represent an important route for the clearance of TPMT*3A aggregates and/or aggregate precursors^[84]. Due to the severe adverse effects of thiopurines, a potential protective role for autophagy in hepatocytes has been investigated; it has been shown that autophagy has a protective role in hepatocytes during thiopurine therapy^[78].

Immunomodulatory drugs (cyclosporine A, FK506, methotrexate)

Cyclosporine A (CsA), FK506, and methotrexate (MTX) are immunomodulatory drugs used mainly as second-line treatments to induce and maintain remission in severe, steroid-refractory CD^[85], with more recent evidence suggesting a role for FK506 in UC^[86]. Although some evidence suggests that CsA and FK506 are involved in autophagy, no relationship has been identified between MTX and autophagy.

Several studies have shown that treatment with CsA can induce autophagy in response to toxicity (such as CsA-induced nephrotoxicity), either as a survival process or as part of a cell death mechanism^[87-89].

FK506 inhibits calcineurin by forming a complex with the immunophilin FK506 binding protein 12 (FKBP12), which is involved in immunoregulation^[90]. FKBP12 is also the direct target of rapamycin, an inhibitor of mTORC1. The molecular mechanism by which mTORC1 regulates autophagy in mammals is being investigated^[91,92], while future research is expected to help understand the relationship between FK506 and autophagy.

Biological drugs (infliximab, adalimumab, etc.)

The most commonly used biological drug for IBD is the anti-TNF α antibody infliximab. Other anti-TNF α treatments approved for treatment of patients with IBD patients include adalimumab, golimumab for UC only, and certolizumab pegol. Anti-TNF α biosimilars have also recently been developed^[93]. The relationship between TNF α and autophagy has been confirmed in synovial fibroblasts^[94], skeletal muscles^[95], and trophoblastic cells^[96]. These studies suggest that anti-TNF agents would inhibit autophagy, and while the mechanism of action is not yet completely clear, it has been the subject of extensive research lately.

The above data summarizes the relationship between autophagy and various drugs. However, existing medical therapies do not relieve the symptoms in many patients, and surgical intervention is often necessary. There is, therefore, a pressing need to develop new therapeutic agents. As seen in this review, autophagy plays an important role in controlling the immune system; hence drugs that regulate autophagy have received much attention as potential new therapeutic targets for IBD^[97]. Further investigation of the role of autophagy in existing IBD therapies, and development of new therapeutic agents regulating autophagy, are the needs of the hour.

CONCLUSION

GWAS has identified several disease-susceptibility genes, and studies on the pathology and etiology of IBD are being regularly published; however, more aspects of IBD pathogenesis should be clarified. As the number of patients with IBD is still increasing around the world, particularly among the young, it is essential that the mechanism of IBD is elucidated and treatments based on this mechanism are developed. A better understanding of the relationship between autophagy and IBD will result in better IBD therapy in future.

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