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EDITORIAL

Autophagy and its role in gastrointestinal diseases

Bo-Zong Shao, Wen-Gang Zhang, Zhen-Yu Liu, En-Qiang Linghu

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Abstract

Gastrointestinal disorders encompass a spectrum of conditions affecting various organs within the digestive system, such as the esophagus, stomach, colon, rectum, pancreas, liver, small intestine, and bile ducts. The role of autophagy in the etiology and progression of gastrointestinal diseases has garnered significant attention. This paper seeks to evaluate the impact and mechanisms of autophagy in gastrointestinal disorders by synthesizing recent research findings. Specifically, we delve into inflammation-related gastrointestinal conditions, including ulcerative colitis, Crohn's disease, and pancreatitis, as well as gastrointestinal cancers such as esophageal, gastric, and colorectal cancers. Additionally, we provide commentary on a recent publication by Chang *et al* in the *World Journal of Gastroenterology*. Our objective is to offer fresh perspectives on the mechanisms and therapeutic approaches for these gastrointestinal ailments. This review aims to offer new perspectives on the mechanisms and therapeutic strategies for gastrointestinal disorders by critically analyzing relevant publications. As discussed, the role of autophagy in gastrointestinal diseases is complex and, at times, contentious. To harness the full therapeutic potential of autophagy in treating these conditions, more in-depth research is imperative.

Key Words: Autophagy; Inflammation; Cancer; Inflammatory bowel disease; Pancreatitis

Core Tip: Extensive research has implicated autophagy in the pathogenesis and advancement of diverse gastrointestinal disorders. Nevertheless, the precise role of autophagy in these ailments remains incompletely understood, and the specific underlying mechanisms remain elusive. Consequently, further investigation is warranted to address these gaps in knowledge.

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INTRODUCTION

The term "autophagy" was coined in the 1960s[1]. Derived from the Greek roots "auto" (self) and "phagy" (eat), autophagy describes cellular metabolic processes in which cytoplasmic proteins and specific organelles are self-degraded [2]. Since its inception, the mechanisms of autophagy have been extensively explored by the scientific community. Research on autophagy won the Nobel prize in physiology or medicine in 2016[3]. Classic autophagy is classified into three types: Micro-autophagy, chaperone-mediated autophagy, and macro-autophagy[3]. Micro-autophagy represents a nonselective lysosomal process. Chaperone-mediated autophagy operates as a discerning form of autophagy that hinges on the recognition of chaperones through specific motifs within the targeted proteins, as well as lysosomal chaperones. Macro-autophagy, on the other hand, is the most extensively investigated variant of autophagy. It is a metabolic process characterized by the formation of double-membraned autophagosomes, which serve as functional units that subsequently merge with lysosomes to facilitate further degradation and recycling. In addition to traditional autophagy, specialized selective autophagy, such as pexophagy and reticulophagy, has been identified. These distinct varieties of selective autophagy embody unique roles and functions within specific organelles and under specific environmental conditions.

The autophagy-lysosomal system represents one of the classical pathways for protein degradation, alongside the ubiquitin–proteasome system. This intricate process is orchestrated by over 30 autophagy-related genes (Atgs), the majority of which are conserved in mammalian cells. Autophagy induction is a two-step process[4] (illustrated in Figure 1). Initially, under conditions of stress, such as hypoxia, phagophores form to envelop substrates. Phagophore formation necessitates the assembly of the Atg1 complex and the class III phosphatidylinositol 3-kinase (PI3K) complex. The Atg1 complex includes Unc-51-like kinase, focal adhesion kinase family interacting protein of 200 kD, *ATG13*, and *ATG101*. Following initiation, the bilayer membrane undergoes a series of processes, including expansion, elongation, and nucleation, leading to the formation of double-membrane, sphere-shaped autophagosomes. This process relies on the assembly of the *ATG16L1* complex, which is composed of *ATG5*, *ATG12*, and *ATG16L1*, as well as the participation of two ubiquitin-like proteins, *ATG12* and Atg8 (light chain 3). In the second step, autophagosomes subsequently shed their "coat proteins" [light chain 3-II (LC3-II)] and merge with lysosomes to form functional autolysosomes. This process is facilitated by *ATG3* and *ATG7*. The class I PI3K-mammalian target of rapamycin (mTOR) pathway acts as an inhibitory regulator of autophagy, whereas the class III PI3K pathway serves as an autophagy inducer. Various autophagy inducers and inhibitors have been utilized in experimental studies and clinical practice to modulate autophagy levels[5]. For example, rapamycin is commonly employed to increase autophagy levels by inhibiting mTORC1 activation. Conversely, the inhibition of autophagy is achieved through mechanisms such as 3-methyladenine. Additionally, chloroquine disrupts autophagy through its influence on the acidic environment of lysosomes, whereas bafilomycin A1 disturbs the formation of autolysosomes.

On the basis of previous research both within our laboratory and from other sources[4], autophagy has been demonstrated to actively participate in and regulate numerous diseases across various domains. In the context of gastrointestinal diseases, the role of autophagy in influencing the pathogenesis and progression of these conditions has been extensively investigated. The influence of autophagy is exerted through the regulation of inflammation and immune responses, as well as the modulation of cellular functions and biological status, including gastrointestinal epithelial cells, inflammatory cells, and even cancer cells. A recent publication by Chang *et al*[6] in the *World Journal of Gastroenterology* comprehensively reviewed the impact of autophagy on the functions of gastrointestinal cells, including digestive cells, secretory cells, regenerative cells, and physical barriers. The authors illustrate how autophagy plays a pivotal role in influencing several gastrointestinal diseases by modulating inflammatory reactions. As a result, autophagy is a crucial determinant in maintaining homeostasis within the digestive system. In the following sections, we comprehensively examine the role of autophagy in various well-characterized gastrointestinal diseases, including inflammation-associated conditions such as ulcerative colitis (UC), Crohn's disease (CD), and pancreatitis, as well as gastrointestinal malignancies such as esophageal, gastric, and colorectal cancers.

AUTOPHAGY IN INFLAMMATION-RELATED GASTROINTESTINAL DISEASES

UC is a type of inflammatory bowel disease (IBD) characterized by chronic inflammation affecting the entire length of the colon and rectum. The pathogenesis of UC involves a complex interplay of factors, including abnormalities in the immune system, environmental influences, disturbances in the gut microbiota, exogenous infections, and specific genetic mutations. However, the precise mechanisms underlying its pathogenesis remain incompletely understood. UC typically manifests as a pattern of inflammation spreading from the rectum to the distal colon, eventually encompassing the entire large intestine. In recent years, considerable attention has been given to exploring the role of autophagy in UC. Studies have revealed a potential association between decreased autophagic activity and the onset of UC[7]. Recent findings have highlighted the potential of activating the intestinal nuclear receptor vitamin D receptor (VDR) *via* autophagy. This has

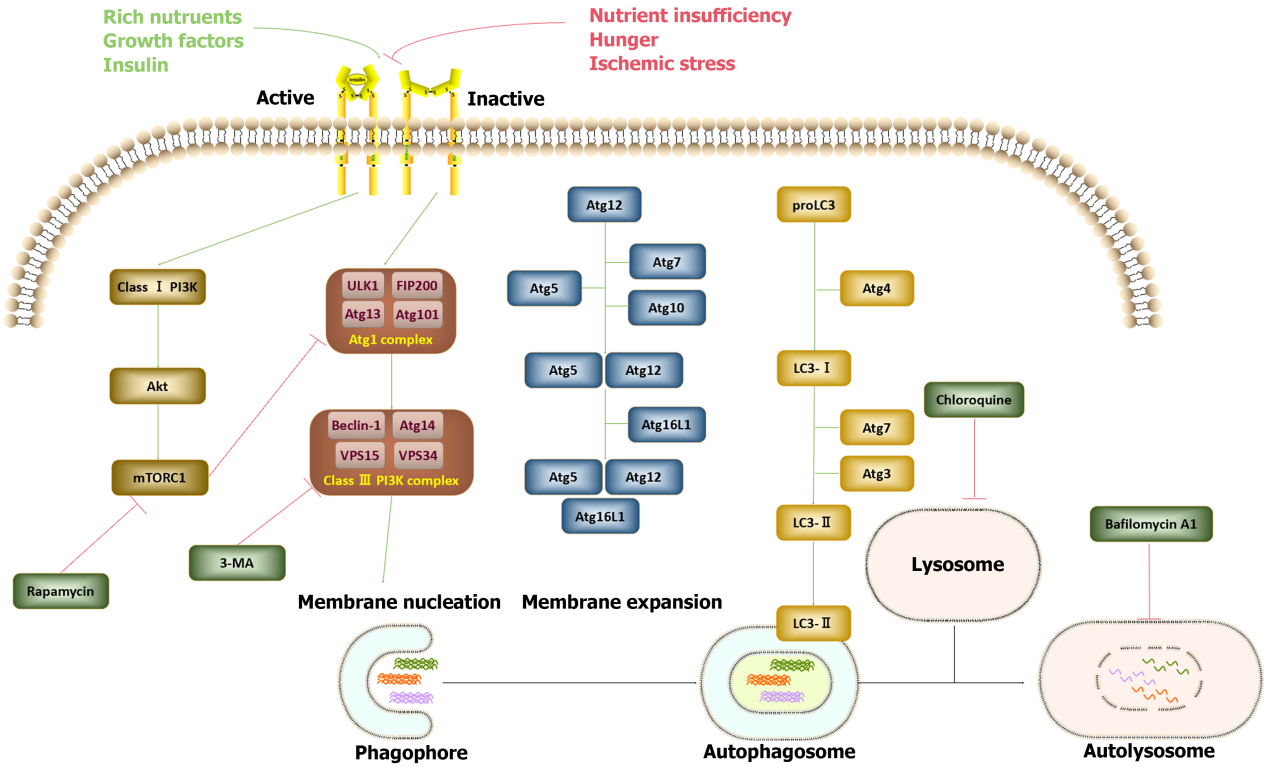

Figure 1 Illustrative diagram elucidating the signaling pathways governing the initiation and regulation of autophagy. Autophagy, a cellular process, is stimulated under conditions such as nutrient deficiency, starvation, or ischemic stress. The initiation of autophagy involves distinct groups of autophagy-related gene (Atg) proteins. The formation of the Atg1 complex, comprising *ULK1*, focal adhesion kinase family kinase-interacting protein of 200 kDa, *ATG13*, and *ATG101*, triggers the assembly of the class III phosphatidylinositol 3-kinase (PI3K) complex, encompassing beclin-1, *ATG14*, *VSP15*, and *VSP34*, thereby initiating membrane nucleation and phagophore formation. Subsequent membrane expansion and fusion, facilitated by *ATG5-ATG12-ATG16L1* and light chain 3-II, give rise to the autophagosome, which subsequently fuses with a lysosome, resulting in the establishment of a functional autophagy unit. Conversely, under conditions characterized by ample nutrients, growth factors, and insulin, activation of the class I PI3K-Akt- mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway inhibits the formation of the Atg1 complex. While rapamycin serves as an autophagy inducer by inhibiting mTORC1, 3-MA, bafilomycin A1, and chloroquine obstruct the autophagy process through varied mechanisms. PI3K: Phosphatidylinositol 3-kinase.

been demonstrated in several studies[8-10]. Notably, decreased expression of VDR and dysregulated vitamin D/VDR signaling pathways have been observed in patients with UC. Moreover, Zhou *et al*[11] reported mTOR-dependent deficiency in autophagy flux in human intestinal epithelial cells derived from active UC patients. In dextran sulfate sodium (DSS)-induced UC models, Wu *et al*[12] reported the contribution of autophagy to gut microbiota homeostasis in UC models. In line with these findings, recent investigations conducted by our research team have demonstrated that inducing autophagy *via* the adenosine 5'-monophosphate-activated protein kinase-mTOR-p70S6K pathway through the activation of specific receptors alleviates UC symptoms and suppresses intestinal inflammation in DSS-induced mouse models[13]. Collectively, these studies underscore the therapeutic potential of autophagy in ameliorating the onset and progression of UC. Notably, polymorphisms in specific Atgs, including *CASP1*, *SERPINA1*, and *CCL2*, have been linked to an increased risk of UC. These findings identify novel molecular targets for the development of autophagy-modulating therapies for the management of active UC[14].

CD is a distinct entity within the spectrum of IBD. CD manifests as localized or regional enteritis of uncertain etiology and is influenced by a multitude of pathogenetic factors, including compromised immunity, environmental stressors, familial predisposition, and specific genetic mutations. In contrast to UC, CD is more susceptible to genetic influences. Extensive genome-wide association studies conducted in 2007 highlighted the significant association between mutations in certain Atgs, notably *ATG16L1* and immunity-related GTPase M (IRGM), and the pathogenesis of CD[15,16]. Moreover, investigations by Rioux *et al*[17] revealed that polymorphisms in Atgs are related to CD-associated adherent-invasive Escherichia coli replication. Nucleotide binding oligomerization domain-containing protein 2 (*NOD2*) has emerged as a pivotal inducer of autophagy, orchestrating the recruitment of *ATG16L1* to the cell membrane[18]. Notably, mutations in *NOD2* observed in CD patients have been linked to disruptions in intestinal microbiota homeostasis and heightened gut inflammatory responses[19,20]. In addition to *NOD2*, *IRGM*, *ULK-1*, and *XBP-1*, mutations or deletions in other Atgs are highly related to the pathogenesis of IBD, particularly CD, according to recent reviews[21]. Studies utilizing 2,4,6-trinitrobenzenesulfonic acid-induced models have reported that inhibiting autophagy exacerbates CD symptoms and intestinal inflammation, highlighting the protective role of autophagy in CD[22]. Collectively, these findings underscore the specific involvement of autophagy in the onset and progression of CD. On the basis of our insights into the role of autophagy in the pathogenesis and progression of CD, targeting impaired autophagy, particularly that caused by polymorphisms in Atgs, may represent a promising therapeutic approach for CD[23].

In addition to UC and CD, pancreatitis has emerged as another prevalent inflammation-related gastrointestinal disorder. Pancreatitis, characterized by pancreatic self-digestion primarily mediated by trypsin, manifests as damage to and necrosis of pancreatic tissue due to the overactivation of self-protective inflammatory and immune responses. Extensive evidence underscores the close association between autophagy and pancreatitis. As previously documented, the onset of acute pancreatitis triggers a significant increase in autophagosome formation within pancreatic acinar cells [24]. However, recent findings have revealed elevated levels of both LC3-II and sequestosome 1 in mouse models of pancreatitis[25], suggesting impaired autophagy. Furthermore, multiple investigations have demonstrated a decrease in lysosome formation in cerulein-treated mouse pancreatic acinar cells, as evidenced by the downregulation of lysosome-associated membrane proteins (*LAMP1* and *LAMP2*), which play crucial roles in stabilizing lysosomal membranes and safeguarding the cytoplasm from acid hydrolases[26,27]. These studies underscore the importance of restoring autophagic function in the management of pancreatitis.

AUTOPHAGY IN GASTROINTESTINAL CANCERS

Gastrointestinal cancers encompass a spectrum of malignancies affecting tissues within the gastrointestinal tract, such as the esophagus, stomach, colon, and rectum[28]. Esophageal cancer has been extensively linked with autophagy. A recent study revealed that 22 autophagic long-chain noncoding ribonucleic acids are strongly associated with the survival rate of patients with esophageal adenocarcinoma[29]. Research by Fang *et al*[30] revealed that the induction of autophagy protected esophageal cancer cells exposed to diketopyrrolopyrrole treatment. Moreover, autophagy is related to microRNA-193b-related chemoresistance to 5-fluorouracil[31]. Furthermore, microRNA-498 has been identified as a suppressor of esophageal cancer through the inhibition of autophagy[32]. These findings underscore the intricate interplay between autophagy and esophageal cancer progression, suggesting potential avenues for therapeutic intervention in this malignancy. In contrast, several studies have presented conflicting findings. A recent investigation demonstrated that silencing autophagy exacerbates radiotherapy resistance in esophageal squamous cell carcinoma[33]. Moreover, inducing autophagy can elicit autophagy-mediated cell cycle arrest[34,35]. We hypothesize that the conflicting outcomes of autophagy in esophageal cancer may stem from variations in the induction methods used and the extent of autophagy activation. Therefore, further research is urgently needed to clarify the exact function of autophagy in esophageal cancer.

Gastric cancer, also known as stomach cancer, is one of the most formidable human malignancies globally and poses a significant health burden [36,37]. Recent investigations have extensively probed the role of autophagy in gastric cancer. Numerous studies suggest that modulating autophagy levels could be a promising therapeutic strategy for gastric cancer treatment. Notably, the interplay between autophagy and programmed cell death (PD)-1 has garnered considerable attention. Wang *et al*[38] demonstrated that inhibiting autophagy could augment PD-L1 expression, thereby increasing sensitivity to PD-L1-targeted immunotherapy. Moreover, studies have revealed the involvement of unfolded protein response-induced autophagy activation mediated by *SEC62*, an endoplasmic reticulum membrane protein implicated in protein transport, in promoting gastric cancer metastasis[39]. However, the role of autophagy in the context of *Helicobacter pylori* (*H. pylori*) infection is complex. Autophagy has been shown to confer protection against *H. pylori* infection [40], thereby influencing the incidence of gastric cancer[40,41]. Prolonged exposure to *H. pylori* has been demonstrated to suppress autophagy in gastric epithelial cells[42]. Furthermore, the degradative functions of autophagy induced by vitamin D3 are effective in protecting gastric epithelial cells against *H. pylori* infection[43]. These findings underscore the need to carefully consider the multifaceted and occasionally contradictory effects of autophagy in the treatment of gastric cancer, particularly its influence on *H. pylori* infection.

Colorectal cancer is a prevalent malignant tumor affecting the digestive tract[21]. It is the fourth most prevalent malignancy globally and accounts for approximately 11% of all diagnosed malignant tumors worldwide[44]. Extensive research, including investigations conducted by our team and other researchers, has highlighted the role of autophagy in regulating inflammation in diseases[45-47]. Similarly, in colorectal cancer, autophagy has emerged as a significant player in modulating inflammatory and immune processes. Notably, autophagy has metabolic homeostatic roles centered on preserving regulatory Treg cells[48]. Additionally, induction of mitophagy has been shown to stimulate antitumor adaptive immunity[49]. Conversely, a deficiency in autophagy has been associated with tumor progression in colorectal cancer[50,51]. Intriguingly, however, a separate study revealed that the Thr300Ala variation of *ATG16L1*, a pivotal Atg, was correlated with improved overall survival in human patients with colorectal cancer[52]. These data suggest that the inflammatory and immunoregulatory functions of autophagy may play crucial roles in mitigating tumorigenesis. Additionally, specific mutations in Atgs could offer therapeutic advantages in colorectal cancer.

CONCLUSION

This paper provides an in-depth exploration of the role of autophagy in several prominent gastrointestinal disorders, including inflammation-related conditions such as UC, CD, and pancreatitis, as well as gastrointestinal cancers, including esophageal, gastric, and colorectal cancers. Our discussion underscores the intricate and occasionally competitive effects of autophagy on gastrointestinal ailments. The complex and sometimes contradictory roles of autophagy in gastrointestinal diseases may be attributed to its varying effects at different stages of disease development, the differential induction of autophagy, or the intricate nature of gastrointestinal pathogenesis and progression. Despite extensive research in this area, the precise mechanisms through which autophagy operates in gastrointestinal diseases remain

elusive. The complexity of the role of autophagy in gastrointestinal diseases has hindered the successful clinical application of autophagy-modulating therapies. Consequently, further studies are essential to fully elucidate the role of autophagy in these diseases and to develop appropriate modulation strategies tailored to different stages of disease progression.

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