ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 March 21; 30(11): 1470-1643

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 11 March 21, 2024

EDITORIAL

1470 MicroRNAs in hepatocellular carcinoma treatment: Charting the path forward

Lin HT, Castaneda AFA, Krishna SG, Mumtaz K

1475 Innovative pathways allow safe discharge of mild acute pancreatitis from the emergency room

Kothari DJ, Sheth SG

1480 Current remarks and future directions on the interactions between metabolic dysfunction-associated fatty liver disease and COVID-19

Brilakis L, Theofilogiannakou E, Lykoudis PM

1488 Routine utilization of machine perfusion in liver transplantation: Ready for prime time?

Parente A, Sun K, Dutkowski P, Shapiro AJ, Schlegel A

1494 Advancements in Barrett's esophagus detection: The role of artificial intelligence and its implications

Massironi S

REVIEW

1497 MicroRNAs: A novel signature in the metastasis of esophageal squamous cell carcinoma

Wei QY, Jin F, Wang ZY, Li BJ, Cao WB, Sun ZY, Mo SJ

MINIREVIEWS

1524 Morphological and biochemical characteristics associated with autophagy in gastrointestinal diseases

Chang YF, Li JJ, Liu T, Wei CQ, Ma LW, Nikolenko VN, Chang WL

ORIGINAL ARTICLE

Retrospective Study

1533 Efficacy of radiofrequency ablation combined with sorafenib for treating liver cancer complicated with portal hypertension and prognostic factors

Yang LM, Wang HJ, Li SL, Gan GH, Deng WW, Chang YS, Zhang LF

Clinical Trials Study

1545 Effect of *Aspergillus niger* prolyl endopeptidase in patients with celiac disease on a long-term gluten-free diet

Stefanolo JP, Segura V, Grizzuti M, Heredia A, Comino I, Costa AF, Puebla R, Temprano MP, Niveloni SI, de Diego G, Oregui ME, Smecuol EG, de Marzi MC, Verdú EF, Sousa C, Bai JC

1556 Effects of *Lactobacillus paracasei* N1115 on gut microbial imbalance and liver function in patients with hepatitis B-related cirrhosis

Hu YC, Ding XC, Liu HJ, Ma WL, Feng XY, Ma LN

World Journal of Gastroenterology

Weekly Volume 30 Number 11 March 21, 2024

Contents

Prospective Study

1572 Washed microbiota transplantation for Crohn's disease: A metagenomic, metatranscriptomic, and metabolomic-based study

Chen SJ, Zhang DY, Wu X, Zhang FM, Cui BT, Huang YH, Zhang ZL, Wang R, Bai FH

Basic Study

1588 Silent information regulator sirtuin 1 ameliorates acute liver failure *via* the p53/glutathione peroxidase 4/gasdermin D axis

Zhou XN, Zhang Q, Peng H, Qin YJ, Liu YH, Wang L, Cheng ML, Luo XH, Li H

1609 Identification of an immune-related gene signature for predicting prognosis and immunotherapy efficacy in liver cancer *via* cell-cell communication

Li JT, Zhang HM, Wang W, Wei DQ

META-ANALYSIS

1621 Effects of neoadjuvant chemotherapy *vs* chemoradiotherapy in the treatment of esophageal adenocarcinoma: A systematic review and meta-analysis

Csontos A, Fazekas A, Szakó L, Farkas N, Papp C, Ferenczi S, Bellyei S, Hegyi P, Papp A

CASE REPORT

1636 Myocardial metastasis from ZEB1- and TWIST-positive spindle cell carcinoma of the esophagus: A case report

Shibata Y, Ohmura H, Komatsu K, Sagara K, Matsuyama A, Nakano R, Baba E

World Journal of Gastroenterology

Weekly Volume 30 Number 11 March 21, 2024

Contents

ABOUT COVER

Editorial Board of *World Journal of Gastroenterology*, David L Morris, MD, FRCS (Ed), Professor, Department of Surgery, University of New South Wales, Sydney 2217, New South Wales, Australia. david.morris@unsw.edu.au

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu (Biliary Tract Disease)

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
March 21, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 March 21; 30(11): 1524-1532

DOI: 10.3748/wjg.v30.i11.1524

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Morphological and biochemical characteristics associated with autophagy in gastrointestinal diseases

Yi-Fan Chang, Jia-Jing Li, Tao Liu, Chong-Qing Wei, Li-Wei Ma, Vladimir N Nikolenko, Wei-Long Chang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Machado NC, Brazil

Received: November 9, 2023
Peer-review started: November 9, 2023
First decision: December 15, 2023
Revised: January 5, 2024
Accepted: February 20, 2024
Article in press: March 21, 2024
Published online: March 21, 2024

Yi-Fan Chang, Tao Liu, Chong-Qing Wei, Wei-Long Chang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Jia-Jing Li, Department of Pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Li-Wei Ma, Department of Clinical Laboratory, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Vladimir N Nikolenko, Department of Human Anatomy and Histology, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow 119991, Russia

Corresponding author: Wei-Long Chang, PhD, Doctor, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe East Road, Erqi District, Zhengzhou 450052, Henan Province, China. changwl365@foxmail.com

Abstract

Autophagy is a cellular catabolic process characterized by the formation of double-membrane autophagosomes. Transmission electron microscopy is the most rigorous method to clearly visualize autophagic engulfment and degradation. A large number of studies have shown that autophagy is closely related to the digestion, secretion, and regeneration of gastrointestinal (GI) cells. However, the role of autophagy in GI diseases remains controversial. This article focuses on the morphological and biochemical characteristics of autophagy in GI diseases, in order to provide new ideas for their diagnosis and treatment.

Key Words: Autophagy; Morphological study; Biochemical characteristics; Subcellular structure; Transmission electron microscopy; Gastrointestinal diseases

Core Tip: Autophagy, from a morphological standpoint, shares similarities with other biological processes such as phagocytosis and apoptosis. As an intracellular catabolic mechanism, autophagy, along with the ubiquitin-proteasome system, contributes to maintaining cellular homeostasis. Moreover, autophagy also assumes a role in programmed cell death when apoptosis is absent. Numerous studies have established the close association between autophagy and the physiological functions of different gastrointestinal (GI) cells. Morphological investigations have furnished substantial evidence highlighting autophagy's pro-survival role in benign conditions like intestinal ischemia-reperfusion injury, inflammatory bowel disease, and GI motility disorders. Further research into the involvement of autophagy in GI tumors is necessary to unravel these unresolved mysteries in the future.

Citation: Chang YF, Li JJ, Liu T, Wei CQ, Ma LW, Nikolenko VN, Chang WL. Morphological and biochemical characteristics associated with autophagy in gastrointestinal diseases. *World J Gastroenterol* 2024; 30(11): 1524-1532
URL: https://www.wjgnet.com/1007-9327/full/v30/i11/1524.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i11.1524

INTRODUCTION

Autophagy, as a cellular catabolic process, is closely related to the digestion, secretion, and regeneration of gastrointestinal (GI) cells. Morphological studies have shown that autophagy is similar to other biological phenomena such as phagocytosis and apoptosis, and it is involved in maintaining cellular homeostasis and programmed cell death, as well as cell growth, development, and differentiation. Autophagy has been found to play a pro-survival role in benign GI diseases like intestinal ischemia-reperfusion (I/R) injury, inflammatory bowel disease (IBD), and GI motility disorders. However, under pathological conditions, the role of autophagy in GI diseases varies, possibly due to the different degrees of autophagy or the presence of other factors. Therefore, more studies on the role of autophagy in GI tumors are required to address these unresolved questions in the future.

Autophagy occurs in all eukaryotic cells, including plant and animal cells, and is an evolutionarily conserved cellular catabolic process. The occurrence of autophagy cannot be separated from the existence of lysosomes. However, autophagy is rare in cells in a state of normal proliferation. Taking gastric tissue as an example, autolysosomes are difficult to observe by transmission electron microscopy (TEM) under normal circumstances[1]. Autophagy is elevated only when cells lack energy sources (starvation), face external stimuli (invasion by pathogens), and be in disease states (degenerative lesions, cancer, *etc*.). Thus, autophagy is also thought to often play a pro-survival role. However, in some cases, inhibiting autophagy can actually help to cure diseases. For example, studies have found that autophagy enhances the drug resistance of tumor cells to chemotherapy in kidney cancer, prostate cancer, and other cancers. The combination of autophagy inhibitor drugs and chemotherapy drugs can achieve good therapeutic effects. In addition, autophagy is also considered as a programmed death process. Excessive autophagy is thought to cause cell death. Thus, the effects of autophagy on cells in different states are complex (Figure 1).

AUTOPHAGY

Before the advent of electron microscopy, a variety of particle-containing vesicles could only be observed by ordinary light microscopy. Since 1933, the advent of TEM has accelerated the study of morphology to the subcellular level[2]. Compared with ordinary microscopes, electron microscopes can magnify tens of thousands of times, so submicroscopic structures within cells can be observed. Thus, electron microscopy is the "gold standard" for studying autophagic morphology. TEM images can provide information such as autophagosome integrity, changes in the number and volume of autophagic vesicles, and autophagosome-lysosomal interactions. In addition, this technique allows visualization of organelles inside autophagic chamber to distinguish whether autophagy is selective autophagy. Observing by TEM, we can clearly capture the moment of fusion of autophagosomes and lysosomes and the morphological changes of organelles during degradation.

The process of autophagy can be divided into five stages: Initiation, elongation, closure, fusion, and decomposition. Morphological studies of autophagy have found that a bilayer membrane structure derived from the endoplasmic reticulum without ribosomes is first formed in the cell, and the degenerate organelles form distinct aggregates, which are gradually surrounded by this bilayer membrane structure. The membrane of the autophagosome is continuously elongated and gradually envelops the aggregates. Eventually, autophagosomes fuse with lysosomes to release acid-lysozymes to break down the contents. Generally, typical features of different stages of autophagy can be observed simultaneously by TEM. According to the type of autophagic body contents, autophagy can be divided into selective autophagy and non-selective autophagy. Non-selective autophagy occurs when various organelles such as the endoplasmic reticulum and mitochondria accumulate in autophagosomes. When selective autophagy occurs, aggregation of only one type of content can be observed in autophagosomes. Common inclusions include mitochondria, lipids, and foreign pathogens (such as bacteria and viruses). Autophagy is also divided into macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. The autophagy mentioned in this article mainly refers to macroscopic autophagy.

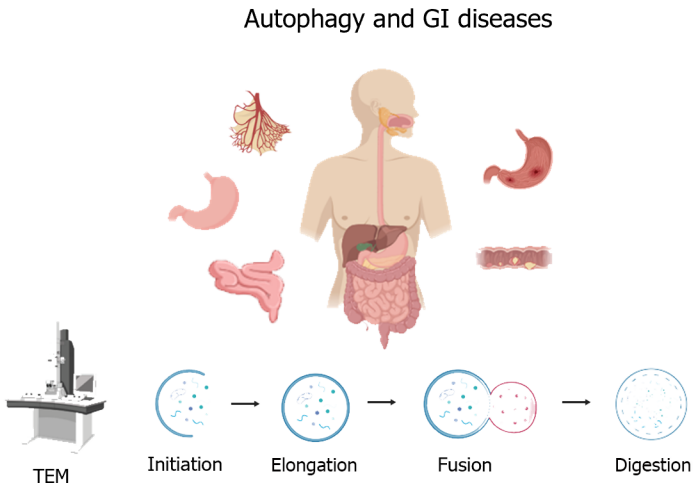

Figure 1 Overview of autophagy in gastrointestinal diseases. Created with MedPeer (www.medpeer.cn). TEM: Transmission electron microscopy; GI: Gastrointestinal.

AUTOPHAGY AND GI CELLS

The GI tract is the largest contact area with the external environment of the cavity organs. Many biochemical reactions occur in the GI tract every day. GI epithelial cells together with a variety of microorganisms constitute the first barrier of the human digestive system. GI cells are made up of three types of cells: Digestive cells (master cells and absorptive cells), secretory cells (goblet cells and Paneth cells), and regenerative cells (stem cells). Goblet cells are mucus-secreting cells that form a physical barrier between intestinal epithelial cells (IECs) and the external environment. One study found that autophagy produced a thicker, less penetrating mucus layer in mice, which enhanced intestinal anti-inflammatory function[3]. Mucus production protects gastric mucosal epithelial cells from chemicals (*e.g.*, alcohol and nonsteroidal anti-inflammatory drugs) and microorganisms. In that study, Naama *et al*[3] also found that autophagy relieves endoplasmic reticulum stress through autophagy-related protein Beclin1, thereby promoting goblet cell mucus secretion. Similarly, Paneth cells secrete antimicrobial proteins that are highly dependent on endoplasmic reticulum stress and autophagy levels[4]. Gorbunov *et al*[5] found that autophagy plays a role not only in secretory cells, but also in intestinal stem cells. Yang *et al*[6] demonstrated that autophagy is required for ileal stem cell maintenance and mammalian survival. In addition, recent studies have shown that autophagy is required to maintain increased enterocyte proliferation in honeybees[7].

According to reports, amino acid deficiency can regulate autophagy activity in IECs[8]. The researchers found that autophagic vacuoles increased by TEM and confocal microscopy[9]. In addition, exposure of IECs to hypoxia and lipopolysaccharide for 24 h not only increased the number of autophagic vesicles, but also significantly increased their diameter[10]. Interestingly, in the midgut epithelial cells of shrimp, approximately 40% of cells show signs of autophagy. The endoplasmic reticulum pool, electron transparent content, vacuoles, poly-vesicles, lamellar bodies, vesicles of autophagosome in lipids, and electron dense particles were observed. In addition, the researchers observed that degenerated mitochondria were mainly concentrated in autophagosomes (mitochondrial autophagy). A study has found that the reduction of intestinal cell volume in shrimp involves a programmed process that requires autophagy. In addition, UBA1 knockout significantly reduced the size of midgut cells, and double membrane autophagosomes containing mitochondria or ribosomes were observed in the cytoplasm[11].

AUTOPHAGY AND GI PHYSICAL BARRIER FUNCTION

GI epithelial cells constitute the first barrier to protect the alimentary tract from injury. The intestinal epithelial tight junction (TJ), which is the second line of defense in the intestinal mucosa, protects against permeation of luminal antigens, endotoxins, and bacteria into the blood stream. Recent research found that autophagy promotes membrane localization of occluding protein, a principal TJ component involved in TJ barrier enhancement, which could protect against inflammation-induced barrier loss[12]. Furthermore, Kim *et al*[13] discovered that protease-activated receptor 2 regulates autophagy and intestinal epithelial TJs, thus reducing intestinal epithelial permeability. Additionally, another study discovered that rapamycin (autophagy inducer) dramatically improved intestinal damage in benzo[a]pyrene induced intestinal epithelial TJ disruption[14]. In conclusion, the activation of autophagy plays an important role in maintaining intestinal barrier function against toxic chemicals, intestinal inflammation, and intestinal permeability.

The intestinal epithelium is frequently exposed to the invasion of many foreign pathogens, leading to increased permeability and intestinal barrier loss. When bacteria infect host cells, selective autophagy initially engulfs the pathogens to limit the access to nutrients. Although autophagy initially triggers an innate immune response that induces intestinal immune cells to produce interferon and clear harmful pathogens, some bacteria (such as *Escherichia coli*,

Salmonella, and *Listeria*) have evolved strategies to inhibit or escape it. For example, *Escherichia coli* hinders the autophagosome-lysosome fusion to inhibit autophagic flux, thus preventing the clearance of acidic hydrolase[15]. Besides that, Yang *et al*[16] suggested that *Salmonella* escapes host immune responses by inhibiting autophagy degradation. Previously, a large number of bacteria have been shown to evade NOD pathway-mediated intestinal immune surveillance by inhibiting autophagy[17,18]. Molecule evidence has been found that autophagy is involved in the secretion of membrane vesicles from *Listeria monocytogenes in vitro*[19]. In addition, one similar study discovered that *Fusobacterium* modulates autophagy to survive, thus aggravating experimental colitis *via* the miR-574-5p/CARD3 axis[20]. The latest findings show that bacterial extracellular vesicles induced mitophagy through mTOR pathways relieve oxidative stress in colonic epithelial cells[21]. Libertellenone T, a compound isolated from *Endolichenic fungus*, also induces autophagy to strengthen the epithelial barrier function of the colon[22].

In contrast, some viruses exploit autophagy for replication to survive inside intestinal cells. Recently, the effect of autophagy on SARS-CoV-2 infection has drawn much attention. Some studies showed that SARS-CoV-2 exploits host autophagy machinery for intestinal dissemination[23,24]. Furthermore, Cloherty *et al*[25] proofed that Berbamine, a selection of autophagy-blocking drugs, can suppress intestinal SARS-CoV-2 infection as well as prevent SARS-CoV-2-mediated disruption of the intestinal barrier *via* an autophagy-mediated BNIP3 mechanism. However, not all viruses have evolved such an escape mechanism. One study discovered that autophagy induced by urolithin A, an intestinal metabolite of ellagic acid, inhibits enterovirus 71 replication in infected cells[26]. In addition, another study discovered that the autophagy gene (ATG) *Epg5* plays an important role in intestinal antiviral signaling by modulating interferon-γ responses[27].

ATG MUTATIONS AND INTESTINAL INFLAMMATION

Autophagy dysfunction can lead to disruption of intestinal barrier function, triggering an immune response and leading to chronic intestinal inflammation. Genome-wide association studies have found that mutations in ATGs are associated with IBD. At present, many autophagy-related genes (such as *ATG16L1, ULK1, NOD2, LRRK2,* and *IRGM*) have been shown to be susceptibility genes for IBD[28,29]. One study found that ATG5 expression in intestinal myeloid cells modulates IL-12, thereby preventing uncontrolled IFN-γ-driven intestinal inflammation[30]. Furthermore, mice with specific deletion of ATG16L1 in IECs have aggravated intestinal injury[31]. ATG16L1^{T300A} is a single nucleotide polymorphism of the susceptibility gene for Crohn's disease (CD)[32]. Further studies have shown that autophagy disorder caused by the ATG16L1^{T300A} polymorphism contributes to the increased risk of CD through NF-κB-mediated inflammation[33]. In addition, researchers have found that ATG16L1 interferes with Paneth cell secretion of antimicrobial agents and dendritic cell antigen presentation, which leads to intestinal mucosal barrier dysfunction and the development of CD.

In recent years, more and more animal experiments have revealed the presence of a large number of autophagic vesicles accompanied by mitochondrial vacuolization in DSS-induced colitis. In Wistar rats, vitamin D has been shown to alleviate stress colitis through mTOR-STAT3 signaling and regulation of autophagy[34]. Similarly, we found that activation of estrogen receptor β, which is highly expressed in intestinal tissues, can inhibit colitis by promoting NLRP6-mediated autophagy[35]. In addition, Ma and collaborators demonstrated that Parkin loss may lead to high drug resistance in DSS-induced colitis[36].

AUTOPHAGY AND GI DISEASES

Intestinal I/R injury

Intestinal I/R injury is a common GI barrier dysfunction. The ultrastructural changes of the intestinal epithelium under the transmission electron microscope can provide information about the early changes of intestinal I/R, including the ischemia phase and reperfusion phase. One study showed that a large number of autophagosomes were found in the cytoplasm of colonic epithelial cells after 1 h of ischemia, with organelle damage, cytolysis, and lysosome formation[37]. However, in another study, a significant reduction in autophagic vacuoles was observed in intestinal tissues 4 h after reperfusion by TEM[38]. Another study found that the number of autophagosomes and autolysosomes increased at 4 h and decreased at 20 h after I/R upon electron microscopy analysis of intestinal epithelial tissues taken at 0, 4, and 20 h after I/R[39]. Thus, based on morphological evidence, autophagy has a conflicting role in the pathology of I/R-induced intestinal injury. In addition to TEM results, several studies have found that the autophagy-related marker LC3BII/I ratio and the mitophagy-related PINK1/Parkin pathway are significantly up-regulated during intestinal I/R injury[40-42]. Consistent with this, Liu *et al*[43] demonstrated in rat experiments that inhibition of autophagy alleviated intestinal I/R injury through the miR-146a/TXNIP axis. Similarly, upregulation of miR-182 in I/R mice leading to a significant reduction in autophagosomes has also found morphological evidence observed by TEM[44]. Studies have found that selenium nanoparticles can effectively alleviate intestinal epithelial barrier damage by inhibiting autophagy mediated by the TBC1D15/Rab7 signaling pathway[45]. In contrast to the above studies, activation of the AMPK/ SIRT1-autophagy pathway alleviated intestinal I/R injury[46,47]. These studies seem to suggest that autophagic changes during the ischemic phase play a more decisive role in the course of the disease. Therefore, studying the role of autophagy in intestinal I/R injury may require a more unified modeling approach and further analysis of the morphological changes of autophagy in different periods. Another common intestinal barrier dysfunction is necrotizing enterocolitis. The

ultrastructure of rapamycin-treated IEC-6 and Caco2 cells was observed by TEM, and the formation of autophagic vacuoles was significantly accumulated, which could be reduced by human β-defensin-3 (hBD3) treatment[48].

GI motility disorders

Functional dyspepsia (FD) is a common GI motility disorder, affecting 11.5%-29.2% of people worldwide. Interstitial cells of Cajal (ICC), especially muscle ICC (ICC-MY), are the key cells to GI motility. Early studies found that the impaired autophagy of ICC was closely related to gastric hypomotility in rats with gastroparesis[49], especially with the reduction and structural abnormalities of ICC-MY cells. Zhang *et al*[50] observed a large number of autophagosomes in the ultrastructure of ICC-MY in the FD model group by electron microscopy, and even degeneration or reduction of organelles. This suggests that increased autophagy and decreased differentiation of ICC-MY play an important role in FD. In addition, Drp-1 mediated mitophagy in ICC significantly promoted gastric motility in FD rats. Lee *et al*[51] also found that the traditional Chinese medicine compound Chaihu Shugan powder inhibits ICC autophagy through the PI3K/PDK1 pathway, thus playing a role in promoting GI motility. In addition, many studies have found that electroacupuncture can improve GI motility disorders by activating autophagy[52-54]. In addition, Fu *et al*[55] demonstrated that exosomes derived from patients with irritable bowel syndrome have an inhibitory effect on autophagy in human colonic epithelial cells by promoting ATG14. Although there are still many mysteries about how autophagy is impaired in GI motility disorders, with the further accumulation and analysis of morphological evidence, it is believed that more new regulatory mechanisms will be discovered in the future.

GI cancers

GI cancers have attracted much attention due to their high recurrence and metastasis rates, difficult diagnosis, and poor prognosis. More and more evidence has shown that although chemotherapy drugs are clinically effective, it has become a common phenomenon that many patients develop chemotherapy resistance in GI cancers during treatment.

Gastric cancer: Gastric cancer has attracted much attention due to its high recurrence and metastasis rates, difficult diagnosis, and poor prognosis. Common treatments include surgical resection, radiotherapy[56], and chemotherapy. *Helicobacter pylori* infection is a common cause in patients with gastric cancer. A study of *H. pylori*-positive human biopsy specimens revealed onion-like (autophagosome-like) structures containing intact bacteria as well as autolysosomes enclosing degraded material[57]. A number of studies have confirmed that autophagy is related to the chemoresistance in gastric cancer, including resistance to oxaliplatin, cisplatin, and paclitaxel[58-62]. It was found that in paclitaxel-pretreated BGC gastric cancer cells, typical double-membrane autophagic vacuoles and residual organelles around the nucleus could be clearly captured by TEM[62]. Further morphological studies revealed that overexpression of *SIRT5, Sec62,* and *TOB1* genes can induce autophagy in gastric cancer cells[63-65]. Of course, autophagy activation is not present in all drug-resistant gastric cancer cell lines. He *et al*[66] observed multiple autophagosomes (double-membrane structure) and autolysosomes (single-membrane structure) in the cytoplasm of BGC gastric cancer cells treated with 5-FU. Moreover, the ratio of autophagosome area to that of the cytoplasm was significantly different from that of the control group. However, in AGS cells treated with 5-FU, few autophagosomes and autolysosomes were observed by TEM. In addition, gastric cancer cell-derived exosomes (GC-Ex) have been found to have the ability to induce neutrophil autophagy[67]. The number of autophagosomes was increased in treated neutrophils. TEM and immunofluorescence staining showed that neutrophils treated with GC-Ex had more autophagosomes than those in the control group. Further study showed that FTO silencing reduced the number of autophagosomes in SGC-7901/DDP cells[68].

Colorectal cancer: Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death in the world. Multiple clinicopathological studies have confirmed that several autophagy-related genes, such as *ATG9B, ATG4B*, and *ULK1*, are CRC prognostic markers[69-72]. Accumulating evidence suggests that cytoprotective autophagy not only increases cancer cell survival, but also enhances tumor drug resistance in CRC[73-75]. One study showed that inhibition of autophagy enhanced doxorubicin hydrochloride-induced apoptosis in human colon cancer cells [76]. Further studies found that MTOR signaling dependent mitochondrial dysfunction promotes colorectal cancer cell death[77]. Regulation of the Beclin1/Beclin2 signaling pathway may be the key to inducing autophagic death of colorectal cancer cells[78-80]. In addition, a study on the mechanism of lipopolysaccharide-induced injury in the colon adenoma cell lines Caco-2 and HT-29 showed that autophagic flow was blocked at the autolysosome stage *in vitro* and *in vivo*[81]. Moreover, Bacillus Calmette-Guerin has been shown to induce autophagic cell death through TLR2 and TLR4 signaling pathways in a radiosensitive colorectal cell line[82]. In addition, Liu *et al*[83] found that induction of autophagy-related ferroptosis through the MEK1/2/ERK/c-FOS axis enhanced the sensitivity of colon cancer cells to chemotherapy. TEM showed mitochondrial destruction and increased number of autophagosomes in the diabetic group compared with the non-diabetic group[40].

Autophagy and GI drugs: Autophagy is closely related to the occurrence and development of GI cancer and drug resistance. A large number of studies have found that a variety of natural compounds can induce autophagy to exert anti-cancer effects. For example, salidroside was found to induce autophagy in AGS cells[84]. Moreover, autolysosome accumulation in gastric cancer cells treated with narcicycline and galangin was observed under the electron microscope. TEM showed that the number of autophagosomes increased in lutein-treated IEC-6 cells[8]. In addition, several Chinese herbs such as ononin, celastrol, licorice, and Jianpi-Qingchang decoction have been shown to protect IECs and treat experimental colitis by activating mitophagy[85-88]. Subsequently, Truzzi and colleagues demonstrated that stimulation of autophagy by a combination of spermidine and eugenol supplements reduced intestinal inflammatory parameters[89].

CONCLUSION

From the perspective of morphology, autophagy is similar to the biological phenomena such as phagocytosis and apoptosis. As an intracellular catabolic mechanism, autophagy and the ubiquitin-proteasome system jointly assume the role of maintaining cellular homeostasis. Not only that, autophagy also plays a role in programmed cell death in cells lacking apoptosis. Autophagy is inextricably linked to cell growth, development, and differentiation. A large number of studies have confirmed that autophagy is closely related to the physiological functions of the GI tract in different types of GI cells. Morphological studies have provided us with a large amount of evidence that autophagy plays a pro-survival role in benign diseases such as intestinal I/R injury, IBD, and GI motility disorders. However, under pathological conditions, the role of autophagy is not the same, which may be due to the different degrees of autophagy or the existence of other factors. Therefore, more studies on the role of autophagy in GI tumors are needed to solve these unsolved mysteries in the future.

FOOTNOTES

Co-first authors: Yi-Fan Chang and Jia-Jing Li.

Co-corresponding authors: Vladimir N Nikolenko and Wei-Long Chang.

Author contributions: Chang YF and Li JJ contributed equally to this work; Chang WL contributed to study conceptualization; Liu T, Wei CQ, Ma LW, and Nikolenko VN contributed to manuscript writing and editing; all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 81900533; Science and Technology Project of Henan Science and Technology Department, No. 232102520032.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Country/Territory of origin: China

ORCID number: Yi-Fan Chang 0009-0001-2080-1644; Vladimir N Nikolenko 0000-0001-9532-9957; Wei-Long Chang 0009-0007-0822-0592.

S-Editor: Yan JP
L-Editor: Wang TQ
P-Editor: Cai YX

REFERENCES

1 **Jia Q**, Li L, Wang X, Wang Y, Jiang K, Yang K, Cong J, Cai G, Ling J. Hesperidin promotes gastric motility in rats with functional dyspepsia by regulating Drp1-mediated ICC mitophagy. *Front Pharmacol* 2022; **13**: 945624 [PMID: 36034863 DOI: 10.3389/fphar.2022.945624]
2 **Ruska E**. Nobel lecture. The development of the electron microscope and of electron microscopy. *Biosci Rep* 1987; **7**: 607-629 [PMID: 3322421 DOI: 10.1007/BF01127674]
3 **Naama M**, Telpaz S, Awad A, Ben-Simon S, Harshuk-Shabso S, Modilevsky S, Rubin E, Sawaed J, Zelik L, Zigdon M, Asulin N, Turjeman S, Werbner M, Wongkuna S, Feeney R, Schroeder BO, Nyska A, Nuriel-Ohayon M, Bel S. Autophagy controls mucus secretion from intestinal goblet cells by alleviating ER stress. *Cell Host Microbe* 2023; **31**: 433-446.e4 [PMID: 36738733 DOI: 10.1016/j.chom.2023.01.006]
4 **Lu R**, Zhang YG, Xia Y, Zhang J, Kaser A, Blumberg R, Sun J. Paneth Cell Alertness to Pathogens Maintained by Vitamin D Receptors. *Gastroenterology* 2021; **160**: 1269-1283 [PMID: 33217447 DOI: 10.1053/j.gastro.2020.11.015]
5 **Gorbunov NV**, Kiang JG. Up-regulation of autophagy in small intestine Paneth cells in response to total-body gamma-irradiation. *J Pathol* 2009; **219**: 242-252 [PMID: 19681094 DOI: 10.1002/path.2591]
6 **Yang Y**, White E. Autophagy in PDGFRA(+) mesenchymal cells is required for intestinal homeostasis and mammalian survival. *Autophagy* 2023; **19**: 726-728 [PMID: 35708538 DOI: 10.1080/15548627.2022.2090694]
7 **Guo Y**, Hu R, Li N, Wu J, Yu H, Tan J, Li Z, Xu S. Autophagy Is Required to Sustain Increased Intestinal Cell Proliferation during Phenotypic Plasticity Changes in Honey Bee (Apis mellifera). *Int J Mol Sci* 2023; **24** [PMID: 36768248 DOI: 10.3390/ijms24031926]
8 **Chang CJ**, Lin JF, Hsiao CY, Chang HH, Li HJ, Lee GA, Hung CF. Lutein Induces Autophagy *via* Beclin-1 Upregulation in IEC-6 Rat Intestinal Epithelial Cells. *Am J Chin Med* 2017; **45**: 1273-1291 [PMID: 28893091 DOI: 10.1142/S0192415X17500707]
9 **Shi H**, Zhao X, Ding Z, Han C, Jiang Y, Qian W, Lin R, Hou X. Na+/H+ Exchanger Regulates Amino Acid-Mediated Autophagy in Intestinal Epithelial Cells. *Cell Physiol Biochem* 2017; **42**: 2418-2429 [PMID: 28848079 DOI: 10.1159/000480184]
10 **Yamoto M**, Lee C, Chusilp S, Yazaki Y, Alganabi M, Li B, Pierro A. The role of autophagy in intestinal epithelial injury. *Pediatr Surg Int* 2019; **35**: 1389-1394 [PMID: 31555857 DOI: 10.1007/s00383-019-04566-2]
11 **Chang TK**, Shravage BV, Hayes SD, Powers CM, Simin RT, Wade Harper J, Baehrecke EH. Uba1 functions in Atg7- and Atg3-independent autophagy. *Nat Cell Biol* 2013; **15**: 1067-1078 [PMID: 23873149 DOI: 10.1038/ncb2804]

12 **Saha K**, Subramenium Ganapathy A, Wang A, Michael Morris N, Suchanec E, Ding W, Yochum G, Koltun W, Nighot M, Ma T, Nighot P. Autophagy Reduces the Degradation and Promotes Membrane Localization of Occludin to Enhance the Intestinal Epithelial Tight Junction Barrier against Paracellular Macromolecule Flux. *J Crohns Colitis* 2023; **17**: 433-449 [PMID: 36219473 DOI: 10.1093/ecco-jcc/jjac148]

13 **Kim Y**, Lee Y, Heo G, Jeong S, Park S, Yoo JW, Jung Y, Im E. Modulation of Intestinal Epithelial Permeability *via* Protease-Activated Receptor-2-Induced Autophagy. *Cells* 2022; **11** [PMID: 35269499 DOI: 10.3390/cells11050878]

14 **Li J**, Bai J, Si X, Jia H, Wu Z. Benzo[a]pyrene induces epithelial tight junction disruption and apoptosis *via* inhibiting the initiation of autophagy in intestinal porcine epithelial cells. *Chem Biol Interact* 2023; **374**: 110386 [PMID: 36754226 DOI: 10.1016/j.cbi.2023.110386]

15 **David L**, Taieb F, Pénary M, Bordignon PJ, Planès R, Bagayoko S, Duplan-Eche V, Meunier E, Oswald E. Outer membrane vesicles produced by pathogenic strains of Escherichia coli block autophagic flux and exacerbate inflammasome activation. *Autophagy* 2022; **18**: 2913-2925 [PMID: 35311462 DOI: 10.1080/15548627.2022.2054040]

16 **Yang L**, Wang JF, Liu N, Wang X, Wang J, Yang GH, Yang GY, Zhu YH. Lactobacillusjohnsonii L531 Protects against Salmonella Infantis-Induced Intestinal Damage by Regulating the NOD Activation, Endoplasmic Reticulum Stress, and Autophagy. *Int J Mol Sci* 2022; **23** [PMID: 36142312 DOI: 10.3390/ijms231810395]

17 **Liu W**, Zhou Y, Peng T, Zhou P, Ding X, Li Z, Zhong H, Xu Y, Chen S, Hang HC, Shao F. N(ε)-fatty acylation of multiple membrane-associated proteins by Shigella IcsB effector to modulate host function. *Nat Microbiol* 2018; **3**: 996-1009 [PMID: 30061757 DOI: 10.1038/s41564-018-0215-6]

18 **Ge P**, Lei Z, Yu Y, Lu Z, Qiang L, Chai Q, Zhang Y, Zhao D, Li B, Pang Y, Liu CH, Wang J. M. tuberculosis PknG manipulates host autophagy flux to promote pathogen intracellular survival. *Autophagy* 2022; **18**: 576-594 [PMID: 34092182 DOI: 10.1080/15548627.2021.1938912]

19 **Karthikeyan R**, Gayathri P, Ramasamy S, Suvekbala V, Jagannadham MV, Rajendhran J. Transcriptome responses of intestinal epithelial cells induced by membrane vesicles of Listeria monocytogenes. *Curr Res Microb Sci* 2023; **4**: 100185 [PMID: 36942003 DOI: 10.1016/j.crmicr.2023.100185]

20 **Wei S**, Zhang J, Wu X, Chen M, Huang H, Zeng S, Xiang Z, Li X, Dong W. Fusobacterium nucleatum Extracellular Vesicles Promote Experimental Colitis by Modulating Autophagy *via* the miR-574-5p/CARD3 Axis. *Inflamm Bowel Dis* 2023; **29**: 9-26 [PMID: 35998069 DOI: 10.1093/ibd/izac177]

21 **Marzoog TR**, Jabir MS, Ibraheem S, Jawad SF, Hamzah SS, Sulaiman GM, Mohammed HA, Khan RA. Bacterial extracellular vesicles induced oxidative stress and mitophagy through mTOR pathways in colon cancer cells, HT-29: Implications for bioactivity. *Biochim Biophys Acta Mol Cell Res* 2023; **1870**: 119486 [PMID: 37172765 DOI: 10.1016/j.bbamcr.2023.119486]

22 **Gamage CDB**, Kim JH, Yang Y, Taş İ, Park SY, Zhou R, Pulat S, Varlı M, Hur JS, Nam SJ, Kim H. Libertellenone T, a Novel Compound Isolated from Endolichenic Fungus, Induces G2/M Phase Arrest, Apoptosis, and Autophagy by Activating the ROS/JNK Pathway in Colorectal Cancer Cells. *Cancers (Basel)* 2023; **15** [PMID: 36672439 DOI: 10.3390/cancers15020489]

23 **Han L**, Zheng Y, Deng J, Nan ML, Xiao Y, Zhuang MW, Zhang J, Wang W, Gao C, Wang PH. SARS-CoV-2 ORF10 antagonizes STING-dependent interferon activation and autophagy. *J Med Virol* 2022; **94**: 5174-5188 [PMID: 35765167 DOI: 10.1002/jmv.27965]

24 **Gassen NC**, Papies J, Bajaj T, Emanuel J, Dethloff F, Chua RL, Trimpert J, Heinemann N, Niemeyer C, Weege F, Hönzke K, Aschman T, Heinz DE, Weckmann K, Ebert T, Zellner A, Lennarz M, Wyler E, Schroeder S, Richter A, Niemeyer D, Hoffmann K, Meyer TF, Heppner FL, Corman VM, Landthaler M, Hocke AC, Morkel M, Osterrieder N, Conrad C, Eils R, Radbruch H, Giavalisco P, Drosten C, Müller MA. SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals. *Nat Commun* 2021; **12**: 3818 [PMID: 34155207 DOI: 10.1038/s41467-021-24007-w]

25 **Cloherty APM**, Rader AG, Patel KS, Pérez-Vargas J, Thompson CAH, Ennis S, Niikura M, Wildenberg ME, Muncan V, Schreurs RRCE, Jean F, Ribeiro CMS. Berbamine suppresses intestinal SARS-CoV-2 infection *via* a BNIP3-dependent autophagy blockade. *Emerg Microbes Infect* 2023; **12**: 2195020 [PMID: 36951188 DOI: 10.1080/22221751.2023.2195020]

26 **Wang S**, Qiao J, Chen Y, Tian L, Sun X. Urolithin A inhibits enterovirus 71 replication and promotes autophagy and apoptosis of infected cells in vitro. *Arch Virol* 2022; **167**: 1989-1997 [PMID: 35790643 DOI: 10.1007/s00705-022-05471-1]

27 **Lee S**, Kalugotla G, Ingle H, Rodgers R, Wu C, Wang Y, Li Y, Yang X, Zhang J, Borella NR, Deng H, Droit L, Hill R, Peterson ST, Desai C, Lawrence D, Lu Q, Baldridge MT. Intestinal antiviral signaling is controlled by autophagy gene Epg5 independent of the microbiota. *Autophagy* 2022; **18**: 1062-1077 [PMID: 34520306 DOI: 10.1080/15548627.2021.1968607]

28 **Liu JZ**, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: 26192919 DOI: 10.1038/ng.3359]

29 **Chauhan S**, Mandell MA, Deretic V. IRGM governs the core autophagy machinery to conduct antimicrobial defense. *Mol Cell* 2015; **58**: 507-521 [PMID: 25891078 DOI: 10.1016/j.molcel.2015.03.020]

30 **Merkley SD**, Goodfellow SM, Guo Y, Wilton ZER, Byrum JR, Schwalm KC, Dinwiddie DL, Gullapalli RR, Deretic V, Jimenez Hernandez A, Bradfute SB, In JG, Castillo EF. Non-autophagy Role of Atg5 and NBR1 in Unconventional Secretion of IL-12 Prevents Gut Dysbiosis and Inflammation. *J Crohns Colitis* 2022; **16**: 259-274 [PMID: 34374750 DOI: 10.1093/ecco-jcc/jjab144]

31 **Foerster EG**, Tsang DKL, Goyal S, Robertson SJ, Robert LM, Maughan H, Streutker CJ, Girardin SE, Philpott DJ. ATG16L1 protects from interferon-γ-induced cell death in the small intestinal crypt. *Mucosal Immunol* 2023; **16**: 135-152 [PMID: 36792009 DOI: 10.1016/j.mucimm.2023.02.001]

32 **Baradaran Ghavami S**, Kabiri F, Nourian M, Balaii H, Shahrokh S, Chaleshi V, Sherkat G, Shalileh F, Asadzadeh Aghdaei H. Association between variants of the autophagy related gene ATG16L1 in inflammatory bowel diseases and clinical statues. *Gastroenterol Hepatol Bed Bench* 2019; **12**: S94-S100 [PMID: 32099608]

33 **Gao P**, Liu H, Huang H, Sun Y, Jia B, Hou B, Zhou X, Strober W, Zhang F. The Crohn Disease-associated ATG16L1(T300A) polymorphism regulates inflammatory responses by modulating TLR- and NLR-mediated signaling. *Autophagy* 2022; **18**: 2561-2575 [PMID: 35220902 DOI: 10.1080/15548627.2022.2039991]

34 **Abdelmalak MFL**, Abdelrahim DS, George Michael TMA, Abdel-Maksoud OM, Labib JMW. Vitamin D and lactoferrin attenuate stress-induced colitis in Wistar rats *via* enhancing AMPK expression with inhibiting mTOR-STAT3 signaling and modulating autophagy. *Cell Biochem Funct* 2023; **41**: 211-222 [PMID: 36588325 DOI: 10.1002/cbf.3774]

35 **Zilleruelo I**, Espinoza E, Ruiz I. Influence of the assessment of the severity on the frequency of adverse drug reactions (ADRs). *Int J Clin Pharmacol Ther Toxicol* 1987; **25**: 328-333 [PMID: 3623738]

36 **Ma Z**, Wu J, Wu Y, Sun X, Rao Z, Sun N, Fu Y, Zhang Z, Li J, Xiao M, Zeng Q, Han C, Ding D, Zhang H, Yuan H, Zhang J, Yang S, Chen Y. Parkin increases the risk of colitis by downregulation of VDR *via* autophagy-lysosome degradation. *Int J Biol Sci* 2023; **19**: 1633-1644 [PMID: 37056928 DOI: 10.7150/ijbs.77153]

37 **Grosche A**, Morton AJ, Graham AS, Sanchez LC, Blikslager AT, Polyak MM, Freeman DE. Ultrastructural changes in the equine colonic mucosa after ischaemia and reperfusion. *Equine Vet J Suppl* 2011; 8-15 [PMID: 21790749 DOI: 10.1111/j.2042-3306.2011.00402.x]

38 **Li Z**, Wang G, Feng D, Zu G, Li Y, Shi X, Zhao Y, Jing H, Ning S, Le W, Yao J, Tian X. Targeting the miR-665-3p-ATG4B-autophagy axis relieves inflammation and apoptosis in intestinal ischemia/reperfusion. *Cell Death Dis* 2018; **9**: 483 [PMID: 29706629 DOI: 10.1038/s41419-018-0518-9]

39 **Jiang M**, Wan S, Dai X, Ye Y, Hua W, Ma G, Pang X, Wang H, Shi B. Protective effect of ghrelin on intestinal I/R injury in rats. *Open Med (Wars)* 2022; **17**: 1308-1317 [PMID: 35937002 DOI: 10.1515/med-2022-0520]

40 **Zeng Z**, Liu HM, Zhang YY, Chen R, Sun T, Li W, Sun Q, Xia ZY, Meng QT. Aggravated intestinal ischemiareperfusion injury is associated with activated mitochondrial autophagy in a mouse model of diabetes. *Mol Med Rep* 2020; **22**: 1892-1900 [PMID: 32582983 DOI: 10.3892/mmr.2020.11270]

41 **Li S**, Zhou Y, Gu X, Zhang X, Jia Z. NLRX1/FUNDC1/NIPSNAP1-2 axis regulates mitophagy and alleviates intestinal ischaemia/reperfusion injury. *Cell Prolif* 2021; **54**: e12986 [PMID: 33432610 DOI: 10.1111/cpr.12986]

42 **Zhang Q**, Liu XM, Hu Q, Liu ZR, Liu ZY, Zhang HG, Huang YL, Chen QH, Wang WX, Zhang XK. Dexmedetomidine inhibits mitochondria damage and apoptosis of enteric glial cells in experimental intestinal ischemia/reperfusion injury *via* SIRT3-dependent PINK1/HDAC3/p53 pathway. *J Transl Med* 2021; **19**: 463 [PMID: 34772407 DOI: 10.1186/s12967-021-03027-6]

43 **Zhenzhen L**, Wenting L, Jianmin Z, Guangru Z, Disheng L, Zhiyu Z, Feng C, Yajing S, Yingxiang H, Jipeng L, Zhanhai W, Yan Z, Xin L, Yongqiang L, Yufang L. miR-146a-5p/TXNIP axis attenuates intestinal ischemia-reperfusion injury by inhibiting autophagy *via* the PRKAA/mTOR signaling pathway. *Biochem Pharmacol* 2022; **197**: 114839 [PMID: 34774846 DOI: 10.1016/j.bcp.2021.114839]

44 **Li Y**, Luo Y, Li B, Niu L, Liu J, Duan X. miRNA-182/Deptor/mTOR axis regulates autophagy to reduce intestinal ischaemia/reperfusion injury. *J Cell Mol Med* 2020; **24**: 7873-7883 [PMID: 32510855 DOI: 10.1111/jcmm.15420]

45 **Dou X**, Qiao L, Song X, Chang J, Pi S, Zhang X, Zeng X, Zhu L, Xu C. Biogenic selenium nanoparticles alleviate intestinal epithelial barrier injury by regulating mitochondria-lysosome crosstalk. *Food Funct* 2023; **14**: 4891-4904 [PMID: 37144827 DOI: 10.1039/d2fo03992c]

46 **Li B**, Li W, Zheng M, Wang Y, Diao Y, Mou X, Liu J. Corilagin alleviates intestinal ischemia/reperfusion injury by relieving oxidative stress and apoptosis *via* AMPK/Sirt1-autophagy pathway. *Exp Biol Med (Maywood)* 2023; **248**: 317-326 [PMID: 36680375 DOI: 10.1177/15353702221147560]

47 **Liu X**, Yang B, Tan YF, Feng JG, Jia J, Yang CJ, Chen Y, Wang MH, Zhou J. The role of AMPK-Sirt1-autophagy pathway in the intestinal protection process by propofol against regional ischemia/reperfusion injury in rats. *Int Immunopharmacol* 2022; **111**: 109114 [PMID: 35933747 DOI: 10.1016/j.intimp.2022.109114]

48 **Chen L**, Lv Z, Gao Z, Ge G, Wang X, Zhou J, Sheng Q. Human β-defensin-3 reduces excessive autophagy in intestinal epithelial cells and in experimental necrotizing enterocolitis. *Sci Rep* 2019; **9**: 19890 [PMID: 31882811 DOI: 10.1038/s41598-019-56535-3]

49 **Wei X**, Lin Y, Zhao D, Xiao X, Chen Q, Chen S, Peng Y. Electroacupuncture Relieves Suppression of Autophagy in Interstitial Cells of Cajal of Diabetic Gastroparesis Rats. *Can J Gastroenterol Hepatol* 2020; **2020**: 7920715 [PMID: 32211350 DOI: 10.1155/2020/7920715]

50 **Zhang LM**, Zeng LJ, Deng J, Zhang YQ, Wang YJ, Xie TY, Ling JH. Investigation of autophagy and differentiation of myenteric interstitial cells of Cajal in the pathogenesis of gastric motility disorders in rats with functional dyspepsia. *Biotechnol Appl Biochem* 2018; **65**: 533-539 [PMID: 29274173 DOI: 10.1002/bab.1635]

51 **Li L**, Jia Q, Wang X, Wang Y, Wu C, Cong J, Ling J. Chaihu Shugan San promotes gastric motility in rats with functional dyspepsia by regulating Drp-1-mediated ICC mitophagy. *Pharm Biol* 2023; **61**: 249-258 [PMID: 36655341 DOI: 10.1080/13880209.2023.2166966]

52 **Wang L**, Chen Y, Xu MM, Cao W, Zheng QH, Zhou SY, Yao JP, Xi MH, Qin HY, Li Y, Zhang W. Electroacupuncture Alleviates Functional Constipation in Mice by Activating Enteric Glial Cell Autophagy *via* PI3K/AKT/mTOR Signaling. *Chin J Integr Med* 2023; **29**: 459-469 [PMID: 36973529 DOI: 10.1007/s11655-023-3594-3]

53 **Song LZ**, Xu N, Yu Z, Yang H, Xu CC, Qiu Z, Dai JW, Xu B, Hu XM. The effect of electroacupuncture at ST25 on Parkinson's disease constipation through regulation of autophagy in the enteric nervous system. *Anat Rec (Hoboken)* 2023; **306**: 3214-3228 [PMID: 36655864 DOI: 10.1002/ar.25148]

54 **Yang J**, Wang L, Mei M, Guo J, Yang X, Liu S. Electroacupuncture repairs intestinal barrier by upregulating CB1 through gut microbiota in DSS-induced acute colitis. *Chin Med* 2023; **18**: 24 [PMID: 36894930 DOI: 10.1186/s13020-023-00733-9]

55 **Fu R**, Liu S, Zhu M, Zhu J, Chen M. Apigenin reduces the suppressive effect of exosomes derived from irritable bowel syndrome patients on the autophagy of human colon epithelial cells by promoting ATG14. *World J Surg Oncol* 2023; **21**: 95 [PMID: 36915121 DOI: 10.1186/s12957-023-02963-5]

56 **Shi X**, Zou J, Wang Y, Zhao J, Ye B, Qi Q, Liu F, Hu J, Li S, Tian Y. MST4 as a novel therapeutic target for autophagy and radiosensitivity in gastric cancer. *IUBMB Life* 2023; **75**: 117-136 [PMID: 36239138 DOI: 10.1002/iub.2682]

57 **Hu W**, Zhang L, Li MX, Shen J, Liu XD, Xiao ZG, Wu DL, Ho IHT, Wu JCY, Cheung CKY, Zhang YC, Lau AHY, Ashktorab H, Smoot DT, Fang EF, Chan MTV, Gin T, Gong W, Wu WKK, Cho CH. Vitamin D3 activates the autolysosomal degradation function against Helicobacter pylori through the PDIA3 receptor in gastric epithelial cells. *Autophagy* 2019; **15**: 707-725 [PMID: 30612517 DOI: 10.1080/15548627.2018.1557835]

58 **Ren J**, Hu Z, Niu G, Xia J, Wang X, Hong R, Gu J, Wang D, Ke C. Annexin A1 induces oxaliplatin resistance of gastric cancer through autophagy by targeting PI3K/AKT/mTOR. *FASEB J* 2023; **37**: e22790 [PMID: 36786694 DOI: 10.1096/fj.202200400RR]

59 **Wang J**, Sun Y, Zhang X, Cai H, Zhang C, Qu H, Liu L, Zhang M, Fu J, Zhang J, Wang J, Zhang G. Oxidative stress activates NORAD expression by H3K27ac and promotes oxaliplatin resistance in gastric cancer by enhancing autophagy flux *via* targeting the miR-433-3p. *Cell Death Dis* 2021; **12**: 90 [PMID: 33462197 DOI: 10.1038/s41419-020-03368-y]

60 **Dai X**, Chen Y, Chen N, Dou J, Zhuang H, Wang J, Zhao X, Zhang X, Zhao H. KLF5-mediated aquaporin 3 activated autophagy to facilitate cisplatin resistance of gastric cancer. *Immunopharmacol Immunotoxicol* 2023; **45**: 140-152 [PMID: 36083020 DOI: 10.1080/08923973.2022.2122498]

61 **Nong ZL**, Zhao K, Wang Y, Yu Z, Wang CJ, Chen JQ. CLIC1-mediated autophagy confers resistance to DDP in gastric cancer. *Anticancer Drugs* 2024; **35**: 1-11 [PMID: 37104099 DOI: 10.1097/CAD.0000000000001518]

62 **Yu YF**, Hu PC, Wang Y, Xu XL, Rushworth GM, Zhang Z, Wei L, Zhang JW. Paclitaxel induces autophagy in gastric cancer BGC823 cells. *Ultrastruct Pathol* 2017; **41**: 284-290 [PMID: 28691892 DOI: 10.1080/01913123.2017.1334019]

63 **Gu W**, Qian Q, Xu Y, Xu X, Zhang L, He S, Li D. SIRT5 regulates autophagy and apoptosis in gastric cancer cells. *J Int Med Res* 2021; **49**: 300060520986355 [PMID: 33530803 DOI: 10.1177/0300060520986355]

64 **Su S**, Shi YT, Chu Y, Jiang MZ, Wu N, Xu B, Zhou H, Lin JC, Jin YR, Li XF, Liang J. Sec62 promotes gastric cancer metastasis through mediating UPR-induced autophagy activation. *Cell Mol Life Sci* 2022; **79**: 133 [PMID: 35165763 DOI: 10.1007/s00018-022-04143-2]

65 **Zang WJ**, Hu YL, Qian CY, Feng Y, Liu JZ, Yang JL, Huang H, Zhu YZ, Xue WJ. HDAC4 promotes the growth and metastasis of gastric cancer *via* autophagic degradation of MEKK3. *Br J Cancer* 2022; **127**: 237-248 [PMID: 35637410 DOI: 10.1038/s41416-022-01805-7]

66 **He XX**, Huang CK, Xie BS. Autophagy inhibition enhanced 5FUinduced cell death in human gastric carcinoma BGC823 cells. *Mol Med Rep* 2018; **17**: 6768-6776 [PMID: 29512733 DOI: 10.3892/mmr.2018.8661]

67 **Zhang X**, Shi H, Yuan X, Jiang P, Qian H, Xu W. Tumor-derived exosomes induce N2 polarization of neutrophils to promote gastric cancer cell migration. *Mol Cancer* 2018; **17**: 146 [PMID: 30292233 DOI: 10.1186/s12943-018-0898-6]

68 **Zhang Y**, Gao LX, Wang W, Zhang T, Dong FY, Ding WP. M(6) A demethylase fat mass and obesity-associated protein regulates cisplatin resistance of gastric cancer by modulating autophagy activation through ULK1. *Cancer Sci* 2022; **113**: 3085-3096 [PMID: 35730319 DOI: 10.1111/cas.15469]

69 **Kim IS**, Cho SY, Yang M, Han S, Lee KH, Kim JY, Kim JM, Kang S, Jo EK, Ryu H. ATG9B Is a Poor Prognostic Marker Associated With Immune Evasion in Colon Adenocarcinoma. *Anticancer Res* 2023; **43**: 1943-1957 [PMID: 37097701 DOI: 10.21873/anticanres.16354]

70 **Hu WH**, Liu TT, Liu PF, Morgan P, Lin IL, Tsai WL, Cheng YY, Hsieh AT, Hu TH, Shu CW. ATG4B and pS383/392-ATG4B serve as potential biomarkers and therapeutic targets of colorectal cancer. *Cancer Cell Int* 2023; **23**: 63 [PMID: 37038218 DOI: 10.1186/s12935-023-02909-7]

71 **Lv P**, Wu Z, Lai L, Zhang Y, Pei B. The clinicopathological significance and potential function of ULK1 in colon cancer. *Biotechnol Genet Eng Rev* 2023; 1-14 [PMID: 37191026 DOI: 10.1080/02648725.2023.2210952]

72 **Bednarczyk M**, Muc-Wierzgoń M, Dzięgielewska-Gęsiak S, Fatyga E, Waniczek D. Transcription of Autophagy Associated Gene Expression as Possible Predictors of a Colorectal Cancer Prognosis. *Biomedicines* 2023; **11** [PMID: 36830954 DOI: 10.3390/biomedicines11020418]

73 **Yue Y**, Zhang Q, Wang X, Sun Z. STAT3 regulates 5-Fu resistance in human colorectal cancer cells by promoting Mcl-1-dependent cytoprotective autophagy. *Cancer Sci* 2023; **114**: 2293-2305 [PMID: 36788743 DOI: 10.1111/cas.15761]

74 **Manzoor S**, Saber-Ayad M, Maghazachi AA, Hamid Q, Muhammad JS. MLH1 mediates cytoprotective nucleophagy to resist 5-Fluorouracil-induced cell death in colorectal carcinoma. *Neoplasia* 2022; **24**: 76-85 [PMID: 34952246 DOI: 10.1016/j.neo.2021.12.003]

75 **Saini H**, Dave R, Chatterjee S, Mandloi A, Sharma H, Daiya A, Mukherjee S, Chowdhury R, Chowdhury S. Transcriptomic analysis reveals differential adaptation of colorectal cancer cells to low and acute doses of cisplatin. *Gene* 2023; **864**: 147304 [PMID: 36822527 DOI: 10.1016/j.gene.2023.147304]

76 **Tang H**, Wu D, Yang H, Yang J, Zhang Y, Li M, Liu H, Li Q. [Inhibition of autophagy enhances apoptosis induced by doxorubicin hydrochloride in human colon cancer cells]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2022; **38**: 237-243 [PMID: 35365989]

77 **Zheng Y**, Yang W, Jia Y, Ji J, Wu L, Feng J, Li Y, Cheng Z, Zhang J, Li J, Dai W, Xu X, Wu J, Zhou Y, Guo C. Promotion of colorectal cancer cell death by ezetimibe *via* mTOR signaling-dependent mitochondrial dysfunction. *Front Pharmacol* 2023; **14**: 1081980 [PMID: 36843944 DOI: 10.3389/fphar.2023.1081980]

78 **Kong W**, Zhu H, Zheng S, Yin G, Yu P, Shan Y, Liu X, Ying R, Ma S. Larotrectinib induces autophagic cell death through AMPK/mTOR signalling in colon cancer. *J Cell Mol Med* 2022; **26**: 5539-5550 [PMID: 36251949 DOI: 10.1111/jcmm.17530]

79 **Xu W**, Nie C, Chen X. DUSP4 inhibits autophagic cell death and apoptosis in colorectal cancer by regulating BCL2-Beclin1/Bax signaling. *Mol Biol Rep* 2023; **50**: 3229-3239 [PMID: 36705792 DOI: 10.1007/s11033-023-08270-2]

80 **Qian J**, Cao Y, Zhang J, Li L, Wu J, Yu J, Huo J. Tanshinone IIA Alleviates the Biological Characteristics of Colorectal Cancer *via* Activating the ROS/JNK Signaling Pathway. *Anticancer Agents Med Chem* 2023; **23**: 227-236 [PMID: 35593352 DOI: 10.2174/1871520622666220421093430]

81 **Zhou M**, Xu W, Wang J, Yan J, Shi Y, Zhang C, Ge W, Wu J, Du P, Chen Y. Boosting mTOR-dependent autophagy *via* upstream TLR4-MyD88-MAPK signalling and downstream NF-κB pathway quenches intestinal inflammation and oxidative stress injury. *EBioMedicine* 2018; **35**: 345-360 [PMID: 30170968 DOI: 10.1016/j.ebiom.2018.08.035]

82 **Yuk JM**, Shin DM, Song KS, Lim K, Kim KH, Lee SH, Kim JM, Lee JS, Paik TH, Kim JS, Jo EK. Bacillus calmette-guerin cell wall cytoskeleton enhances colon cancer radiosensitivity through autophagy. *Autophagy* 2010; **6**: 46-60 [PMID: 19901560 DOI: 10.4161/auto.6.1.10325]

83 **Liu Z**, Xu Y, Liu X, Wang B. PCDH7 knockdown potentiates colon cancer cells to chemotherapy *via* inducing ferroptosis and changes in autophagy through restraining MEK1/2/ERK/c-Fos axis. *Biochem Cell Biol* 2022; **100**: 445-457 [PMID: 35926236 DOI: 10.1139/bcb-2021-0513]

84 **Rong L**, Li Z, Leng X, Li H, Ma Y, Chen Y, Song F. Salidroside induces apoptosis and protective autophagy in human gastric cancer AGS cells through the PI3K/Akt/mTOR pathway. *Biomed Pharmacother* 2020; **122**: 109726 [PMID: 31918283 DOI: 10.1016/j.biopha.2019.109726]

85 **Yu T**, Lu X, Liang Y, Yang L, Yin Y, Chen H. Ononin alleviates DSS-induced colitis through inhibiting NLRP3 inflammasome *via* triggering mitophagy. *Immun Inflamm Dis* 2023; **11**: e776 [PMID: 36840499 DOI: 10.1002/iid3.776]

86 **Chen D**, Ye L, Liu Y, Yu J, Ni S, Chen Y, Zhong J. Celastrol activates mitochondrial autophagy through Nur77-TRAF2-p62/SQSTM1 pathway in the treatment of experimental colitis. *Minerva Pediatr (Torino)* 2023; **75**: 760-762 [PMID: 37021620 DOI: 10.23736/S2724-5276.23.07258-0]

87 **Kong J**, Xiang Q, Shi G, Xu Z, Ma X, Wang Y, Xuan Z, Xu F. Licorice protects against ulcerative colitis *via* the Nrf2/PINK1-mediated mitochondrial autophagy. *Immun Inflamm Dis* 2023; **11**: e757 [PMID: 36705402 DOI: 10.1002/iid3.757]

88 **Qiao D**, Liu X, Zhang Y, Zhang Z, Tang Y, Chen Q, Shi Y, Chen Y, Tang Z, Dai Y. Jianpi-Qingchang decoction alleviates ulcerative colitis by modulating endoplasmic reticulum stress-related autophagy in intestinal epithelial cells. *Biomed Pharmacother* 2023; **158**: 114133 [PMID: 36521243 DOI: 10.1016/j.biopha.2022.114133]

89 **Truzzi F**, Whittaker A, D'Amen E, Valerii MC, Abduazizova V, Spisni E, Dinelli G. Spermidine-Eugenol Supplement Preserved Inflammation-Challenged Intestinal Cells by Stimulating Autophagy. *Int J Mol Sci* 2023; **24** [PMID: 36835540 DOI: 10.3390/ijms24044131]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com