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EDITORIAL

From macroautophagy to mitophagy: Unveiling the hidden role of mitophagy in gastrointestinal disorders

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Abstract

In this editorial, we comment on an article titled "Morphological and biochemical characteristics associated with autophagy in gastrointestinal diseases", which was published in a recent issue of the *World Journal of Gastroenterology*. We focused on the statement that "autophagy is closely related to the digestion, secretion, and regeneration of gastrointestinal cells". With advancing research, autophagy, and particularly the pivotal role of the macroautophagy in maintaining cellular equilibrium and stress response in the gastrointestinal system, has garnered extensive study. However, the significance of mitophagy, a unique selective autophagy pathway with ubiquitin-dependent and independent variants, should not be overlooked. In recent decades, mitophagy has been shown to be closely related to the occurrence and development of gastrointestinal diseases, especially inflammatory bowel disease, gastric cancer, and colorectal cancer. The interplay between mitophagy and mitochondrial quality control is crucial for elucidating disease mechanisms, as well as for the development of novel treatment strategies. Exploring the pathogenesis behind gastrointestinal diseases and providing individualized and efficient treatment for patients are subjects we have been exploring. This article reviews the potential mechanism of mitophagy in gastrointestinal diseases with the hope of providing new ideas for diagnosis and treatment.

Key Words: Mitophagy; Gastrointestinal diseases; Parkin; Autophagic receptor; Colorectal cancer; Gastric cancer; Inflammatory bowel disease

Core Tip: Mitochondria are not only the energy factories of eukaryotic cells but are also closely related to apoptosis, and their dysfunction plays an important role in various gastrointestinal diseases. Mitophagy, an important mechanism to remove damaged mitochondria *in vivo*, has been found to alleviate the severity of inflammatory bowel diseases and plays a dual role in promoting and inhibiting the occurrence and development of gastrointestinal cancer. A complete understanding of the mitophagy pathway in gastrointestinal diseases will be helpful for developing new treatment strategies. Therefore, we investigated the mechanisms underlying mitophagy and its contribution to gastrointestinal diseases.

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INTRODUCTION

Cells are continually exposed to various threats, including pathogens[1,2], genetic mutations[3], and oxidative stress[4,5]. These challenges can lead to organelle dysfunction, subsequently inducing autophagy. There are three different types of autophagy in cells: Macroautophagy, micro-autophagy, and chaperone-mediated autophagy. Macroautophagy is usually called autophagy. Autophagy, as the second type of programmed cell death mechanism, helps cells to remove damaged organelles, pathogens or aggregates and then participates in cell growth, development and differentiation[6]. In the last 10 years, the research on the mechanism of autophagy in infection[7], cancer[8], neurodegenerative diseases[9] and other diseases has made breakthrough progress.

Mitophagy is a selective autophagy pathway, an important branch of autophagy, and has a unique mechanism. Mitophagy was named when Lemasters *et al*[10] discovered that damaged mitochondria are engulfed by autophagic vesicles and enveloped in microtubule-associated proteins light chain 3 (LC3) in serum. Mitochondria play an important role in aerobic respiration and adenosine triphosphate (ATP) production *via* oxidative phosphorylation in all eukaryotic cells, and their abnormal functions are closely related to the occurrence and progression of many diseases. Importantly, the mitochondrial quality control system can eliminate damaged mitochondrial proteins or parts of the mitochondrial network and update their components through mitophagy, maintaining a steady state of the mitochondria[11]. In the last 10 years, significant progress has been made in understanding the molecular mechanism and pathophysiological role of mitophagy in human diseases. Several key mitophagy signaling pathways have been identified, including the ubiquitin-dependent pathway mediated by the PINK1-Parkin pathway or other E3 ubiquitin ligases in the mitochondria and the receptor-mediated ubiquitin-independent pathway. With the gradual clarification of the mitophagy pathway, the pathophysiological role of mitophagy in cardiovascular, lung, liver, gastrointestinal, and other organ-related diseases has been explained, providing a new direction for the treatment of diseases[12].

Gastrointestinal diseases include gastrointestinal peristalsis, infectious inflammation (such as *Helicobacter pylori* infection, cholera, and intestinal parasites), noninfectious inflammation (such as chronic gastroenteritis and Crohn's disease), and gastrointestinal cancer[13]. Chang *et al*[14] summarized the morphological and biochemical characteristics of autophagy in gastrointestinal diseases. However, the integration of the unique mechanism of mitophagy and its role in gastrointestinal diseases is still lacking. Recent studies have indicated that mitophagy is closely related to gastrointestinal diseases (Table 1)[15-24]. In this review, we elaborate on the molecular mechanism of mitophagy, summarize its role in the occurrence and progression of inflammatory bowel diseases (IBD), gastric cancer, and colorectal cancer (CRC), and suggest that mitophagy-related pathways may be important targets for clinical treatment.

MITOPHAGY MECHANISMS

According to a known mechanism, mitophagy can be divided into ubiquitin-dependent and-independent mitophagy. Ubiquitin-dependent mitophagy is mainly coordinated by the PINK1 protein kinase and Parkin Ubiquitin E3 ligase[25]. Moreover, research has demonstrated other E3 ubiquitin ligases in the mitochondria, such as Ariadne RBR E3 Ub protein ligase 1 (ARIH1)[26], mitochondrial E3 ubiquitin ligase 1 (MUL1)[27], and Gp78[28], that can mediate ubiquitin-dependent mitophagy without relying on Parkin. Notably, ubiquitin-independent mitophagy is mainly mediated by a direct interaction between LC3 and autophagy receptor proteins (Figure 1).

PINK1-Parkin-mediated ubiquitin-dependent pathway plays an important role in mitophagy

The activation of PINK1 is one of the most upstream events in mitophagy[29]. Under normal physiological conditions, PINK1 is maintained at an extremely low level of PINK1 in the mitochondria and is almost undetectable through a series of input and degradation cycle mechanisms[30]. When affected by pathological factors, such as mitochondrial damage[31] and increased mitochondrial reactive oxygen species[32], it leads to abnormal mitochondrial membrane potential and depolarization. When mitochondria are depolarized, PINK1 is stabilized on the outer membrane of mitochondria (OMM), where it catalyzes the phosphorylation of S65 in the Ub and Ub-like domains of Parkin, thus activating the E3 ubiquitin

Table 1 Research progress of mitophagy in gastrointestinal diseases

Year of publication	Diseases of concern	Problem solved	Ref.
2017	SRMD	SRMD leads to intestinal mucosal injury: Defective mitochondria with excess O_2^- production inhibit mitophagy, ultimately triggering Bax-dependent apoptosis and NF-κB-intervened proinflammatory mucosal injury	[15]
2020	*H. pylori* associated gastritis	There was a link between *H. pylori* infection-promoted mitophagy and inflammation	[16]
2022-2024	Functional dyspepsia	Traditional Chinese medicine can improve gastrointestinal motility disorders, and the mechanism may be related to the inhibition of mitophagy and mitochondria fission	[17-19]
2023	I/R injury	Increased NET formation induces inhibition of mitophagy and lipid peroxidation in IECs, leading to ferroptosis of endothelial cells and microvascular dysfunction	[20]
2023	Malnutrition enteropathy	Dysregulation of SIRT1 and mTORC1 pathways leads to disruption of autophagy, mitochondrial homeostasis, which triggers intestinal barrier dysfunction and nutrient malabsorption	[21]
2023	IBD	Bergapten treatment alleviated NLRP3 inflammasome activation and pyroptosis by promoting mitophagy, suggesting BeG as a potential anti-inflammatory drug for the treatment of inflammatory diseases	[93]
2021-2023	IBD	Polystyrene nanoplastic induced Crohn's ileitis-like features are related to mitophagy, while Biogenic selenium nanoparticles can alleviate intestinal epithelial barrier damage by regulating mitophagy, which provides new insights for further evaluating the safety of nanoparticles	[22-24]
2023	IBD	NSAIDs induce mitochondrial stress and mitophagy in IECs, which are related to the pathophysiology of Crohn's disease	[89]
2021	CRC	Mitophagy suppresses CRC growth: PINK1 inhibits CRC growth by reducing acetyl-CoA production and activating P53	[70]
2023	CRC	Mitophagy promotes CRC growth: GPR176 activates cAMP/PKA signaling pathway and regulate mitophagy to promote the tumorigenesis and progression of CRC	[74]
2018	Gastric cancer	Mitophagy promotes gastric cancer growth: Hippo-Yap promotes tumor progression by activating SIRT1/Mfn2/ mitophagy	[63]
2023	Gastric cancer	Mitophagy suppresses gastric cancer growth: 8-paradol promoted PINK1/Parkin-associated mitophagy, mediating cell apoptosis	[67]

SRMD: Stress-related mucosal disease; *H. pylori*: *Helicobacter pylori*; I/R injury: Ischemia-reperfusion injury; NET: Neutrophil extracellular traps; IECs: Intestinal epithelial cells; SIRT1: Sirtuin 1; mTORC1: Mechanistic target of rapamycin complex 1; IBD: Inflammatory bowel diseases; NLRP3 inflammasome: NOD-like receptor thermal protein domain associated protein 3 inflammasome; CRC: Colorectal cancer; GPR176: G protein-coupled receptors 176; Mfn2: Mitofusin 2.

ligase activity of Parkin[33]. PS65-Ub can further recruit Parkin from the cytoplasm to the OMM, such that the abundance of pS65-Ub gradually increases, eventually leading to the assembly of Ub chains of about 4400 times, establishing a feed-forward loop and finally wrapping the damaged mitochondria with pS65-Ub chains[33]. Additionally, the pS65-Ub chain further recruits autophagy receptors to the damaged OMM[34], and common autophagic receptors that aggregate in the OMM include OPTN[35], NDP52[36], and P62[37]. The activation of the PINK1-Parkin system immediately activates a fraction of TANK-binding kinase 1 (TBK1), which then binds to and phosphorylates the autophagy receptor upon its binding to the Ub chain. This, in turn, enhances the affinity of the autophagy receptor for the Ub chain, extends the duration of autophagy receptors on the OMM, and facilitates mitophagy[38]. These autophagy receptors aggregated on the OMM bind to ATG8 family proteins through the LC3 interaction region (LIR) motif, and with the help of ATG8 family proteins, ubiquitinated OMM attaches to the autophagy membrane[35,37,39]. The autophagy receptors mentioned above are concentrated in the OMM. Notably, a recent study found that the autophagy receptor PHB2, located on the inner membrane of mitochondria, promotes mitophagy mediated by PINK1-Parkin by stabilizing PINK 1 and increasing mitochondrial recruitment of Parkin[40]. PHB2 is ubiquitinated by Parkin, facilitating its interaction with LC3 and accelerating autophagy clearance in damaged mitochondria (Figure 1)[41].

An in-depth study found that many factors, such as TBK1, Phosphatase and Tensin Homolog (PTEN-L), and DJ-1, regulate ubiquitin-dependent mitophagy. In addition to the function of the phosphorylated autophagy receptors mentioned above, TBK1 can promote the downstream steps of mitophagy by phosphorylating S72 in RAB7A through the Ub chain on the OMM[38]. RAB7AS72 is located in the "switch II" domain, which participates in the exchange of guanosine diphosphate/guanosine triphosphate and its interaction with other proteins, thus regulating mitophagy[38]. PTEN-L, a negative regulatory factor of mitophagy located in the OMM, effectively prevents Parkin mitochondrial translocation, reduces Parkin phosphorylation, inhibits its E3 Ligase activity, decreases the level of pSer65-Ub, blocks the feed-forward mechanism of mitophagy, and ultimately inhibits mitophagy[42]. DJ-1 is a 19.9 kda protein encoded by the PARK7 gene. Its deletion does not interfere with the activation of PINK1 or Parkin after mitochondrial depolarization but blocks downstream mitophagy by inhibiting the recruitment of the selective autophagy receptor OPTN to mitochondrial

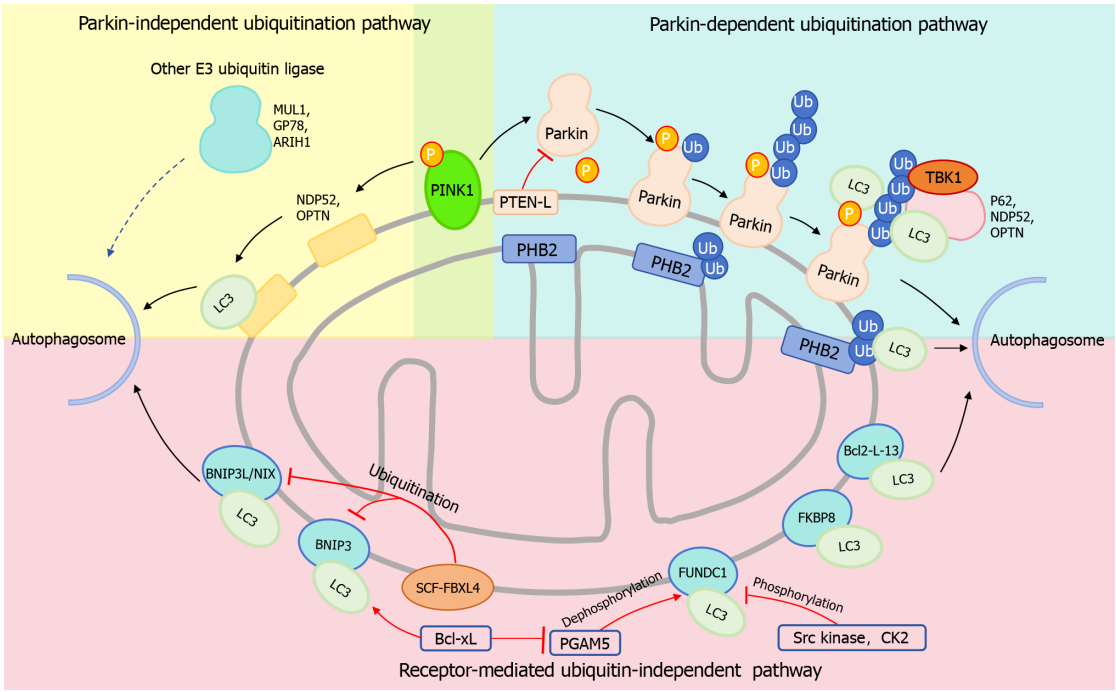

Figure 1 Major Signaling pathways of mitophagy. Parkin-dependent Ubiquitinated Mitophagy Pathway: Following the depolarization of the mitochondrial membrane, PINK1 recruits and activates the E3 ubiquitin ligase activity of Parkin, leading to the formation of ubiquitin chains. These chains then attract a series of autophagy receptors including P62, NDP52, and OPTN. Subsequently, these receptors bind to light chain 3 (LC3), facilitating the connection of the polyubiquitinated mitochondrial outer membrane to the autophagosome membrane, thereby mediating mitophagy. In this process, TANK-binding kinase 1 kinase enhances the affinity of the autophagy receptor for the Ub chain by phosphorylating the receptor. PTEN-L can reduce Parkin phosphorylation and inhibit its E3 ligase activity, thereby inhibiting mitophagy. Parkin-Independent Ubiquitinated Mitophagy Pathway: E3 ubiquitin ligases such as ARIH1, MUL1, and Gp78 may serve as compensatory pathways for Parkin-mediated mitophagy, although the precise mechanisms are yet to be elucidated. Furthermore, PINK1 has the ability to recruit NDP52 and OPTN to mitochondria, thereby directly initiating mitophagy in a Parkin-independent manner. Receptor-Mediated Ubiquitination-Independent Mitophagy Pathway: Proteins including FK506 binding protein 8, BCL2-interacting protein 3 like/NIP3-like protein X (BNIP3L/NIX), BNIP3, FUN14 domain containing 1 (FUNDC1), and Bcl2-L-13 directly bind to LC3, enabling the mitochondrial membrane to connect to the autophagosome membrane and mediate mitophagy. SCF-FBXL4 mediates the ubiquitination and degradation of BNIP3L/NIX and BNIP3, thereby inhibiting mitophagy. Under hypoxia conditions, phosphoglycerate mutase 5 (PGAM5) promotes the dephosphorylation of FUNDC1, enhancing FUNDC1-mediated mitophagy. Conversely, Src kinase and Casein kinase 2 phosphorylate FUNDC1, inhibiting its mitophagy-promoting activity. Although Bcl-xL positively regulates the binding of BNIP3 to LC3, it inhibits FUNDC1-mediated mitophagy by suppressing PGAM5. LC3: Light chain 3; BNIP3L/NIX: BCL2-interacting protein 3 like/NIP3-like protein X; FUNDC1: FUN14 domain containing 1; TBK1: TANK-binding kinase 1.

depolarization[43].

Parkin-independent ubiquitin-dependent mitophagy

ARIH1 and Parkin belong to the same RING-in-between-RING family and are widely expressed in cancer cells. Villa *et al* [26] found that they can ubiquitinate damaged mitochondria in a PINK1-dependent manner, leading to their elimination *via* autophagy. In addition, Yun *et al*[27] found that increasing the protein level of MUL1 in *Drosophila* can counteract the harmful effects caused by the deletion of PINK1 or Parkin, whereas removing MUL1 from PINK1 or Parkin mutants aggravates symptoms, suggesting that MUL1 may participate in the compensatory pathway of the PINK1/Parkin pathway. Furthermore, GP78 is a key E3 ubiquitin ligase involved in endoplasmic reticulum-mediated degradation. In HEK293 cells subjected to Parkin knockdown *via* siRNA, mitophagy triggered by GP78 remained unaffected, indicating that it operates in Parkin-induced mitophagy independently[28]. In addition, the ubiquitin-binding protein Vps13D has been found in *D. melanogaster*. Studies have shown that this protein plays a role downstream of PINK1, which is parallel to Parkin in mitophagy, and regulates the localization of ubiquitin and ATG8 around the mitochondria[44]. However, the specific working mechanisms of these proteins are not clear, and further research is needed. Another study showed that PINK1 could recruit the autophagy receptors NDP52 and OPTN into the mitochondria and directly activate mitophagy without relying on Parkin[45].

Receptor-mediated ubiquitin-independent pathway mediates mitophagy

The non-ubiquitin-dependent mitophagy pathway is mediated by the direct interactions between LC3 and mitophagy receptor proteins. These mitophagy receptor proteins include NIP3-like protein X/BCL2-interacting protein 3 like (NIX/BNIP3L), BCL2-interacting protein 3 (BNIP3), FUN14 domain containing 1 (FUNDC1), Bcl2-like protein 13 (Bcl2-L-13), and FK506 binding protein 8 (FKBP8)[46]. They directly bind to LC3 *via* the LIR region, skip ubiquitination, and directly initiate mitophagy. BNIP3 and BNIP3L/NIX were similar to some extent, indicating that they all contained an atypical BH3 domain. Under the condition of moderate hypoxia (apparent 1%-3% oxygen), hypoxia-inducible factor-1a activates the up-regulation of both transcription factors[47]. Posttranslational modifications regulate mitophagy mediated by

BNIP3L/NIX and BNIP3. SCF-FBXL 4 (SkP1/Cul1/F-box protein ubiquitin ligase complex), located in the OMM, mediates the ubiquitination and degradation of BNIP3L/NIX and BNIP3, thus inhibiting mitophagy[48]. However, phosphorylation of serine residues in BNIP3 LIR and BNIP3L LIR promoted mitophagy[49,50]. In addition, the homodimeric form of BNIP3L recruits autophagosomes more robustly than the monomeric form does[51]. Endogenous FUNDC1 is located only in mitochondria. Under hypoxia, phosphoglycerate mutase 5 (PGAM5) promotes FUNDC1 dephosphorylation and FUNDC1-mediated mitophagy, while Src kinase and Casein kinase 2 phosphorylate FUNDC1 and inhibit FUNDC1-mediated mitophagy[52,53]. Notably, Bcl-xL plays different roles in the regulation of mitophagy mediated by BNIP3 and FUNDC1; moreover, it positively regulates the binding between BNIP3 and LC3[49] but inhibits FUNDC1-mediated mitophagy by inhibiting PGAM5[54]. Moreover, iron deficiency can trigger mitophagy mediated by FUNDC1, which is, in turn, mediated by the activation of PGAM5[55]. Bcl2-L-13, a mammalian functional homolog of ATG32, mediates mitophagy by binding to LC3B through the WXXI motif of LIR[56], and the Unc-51-like Kinase (ULK1) complex is necessary for this process[57]. FKBP8 is a significant anti-apoptotic protein featuring a characteristic LIR motif at its N-terminus, which promotes non-ubiquitination of mitophagy *via* interaction with LC3A. During this process, FKBP8 can exit the mitochondria to evade degradation[46]. In addition to the LIR sequence, FKBP8 contains an LIR motif-like sequence that binds to optical atrophy1 to mediate mitochondrial fragmentation, thus inducing mitophagy[58].

THE ROLE OF MITOPHAGY IN GASTROINTESTINAL DISORDERS

Mitophagy plays an important role in gastric cancer, CRC and IBD. Numerous studies have supported the double-edged sword effect of autophagy in cancer. Specifically, mitophagy plays an inhibitory role in the initial stage of tumorigenesis or cancerous transformation; in contrast, mitophagy provides survival advantages for established and metastatic tumors and can prevent cell death induced by chemotherapy drugs[40,59]. In addition, the anti-inflammatory role of mitophagy in IBD has been extensively studied. The subsequent section will focus on the role of mitophagy in gastric cancer, CRC, and IBD and its potential as a therapeutic target (Tables 2 and 3).

Gastric cancer and mitophagy

Gastric cancer is the fifth most common cancer worldwide, with a high mortality rate[60]. The use of traditional endoscopy and ultrasonic endoscopy (EUS) facilitates the diagnosis of gastric cancer in the early stages and the evaluation of invasion depth, which is beneficial for improving, to some extent, its outcomes[61]. The inclusion of therapeutic EUS in the treatment of complex hepatobiliary, pancreatic, and gastrointestinal diseases has significantly enhanced the quality of life for tumor patients[62]. Defining the survival, migration, treatment, and drug resistance mechanisms of gastric cancer has always been a topic of great concern (Figure 2). In view of the survival and migration of gastric cancer cells, experiments have demonstrated that Sirtuin 1 (SIRT1), a Yes-associated protein (Yap) signal, activates mitophagy and promotes mitochondrial homeostasis[63]. The Yap-STRT1 mitophagy pathway blocks the caspase-9-related apoptosis axis, enhances cell migration based on F-actin, and participates in the migration and survival of gastric cancer cells[63]. Furthermore, an additional study demonstrated that gamma-glutamyltransferase 7 (GGT7) was significantly downregulated in gastric cancer cells, markedly inhibiting their growth, G1-S transition, and migration ability. This inhibition may be associated with the occurrence of GGT7-induced mitophagy[64].

Drug resistance in gastric cancer cells is primarily manifested through tumor necrosis factor α (TNFα) and chemotherapy drugs. As a pro-inflammatory and pro-apoptotic cytokine, TNFα is an important host defense system against the progress of gastric cancer; however, its therapeutic effect is limited by drug resistance[65]. Experiments indicate that TNFα treatment initiates Parkin-dependent mitophagy, and excessive mitophagy prevents mitochondrial apoptosis, mitigating the toxic effect of TNFα on cancer cells[65]. Furthermore, the suppression of mitophagy to enhance the responsiveness of gastric cancer cells to TNFα might present a novel approach to treating gastric cancer. Cisplatin remains the principal medication for managing gastric cancer; however, it demonstrates significant drug resistance, posing a crucial challenge that necessitates immediate attention in clinical settings. Moreover, research has indicated that metformin, an antidiabetic medication, may reduce the sensitivity of cancer cells to cisplatin[66]. Metformin stimulates the phosphorylation of AMPK (Thr172) and increases the expression of mitophagy markers, including Parkin and PINK1, in an AMPK signal-dependent manner, significantly increasing the mitophagy of cancer cells, reducing ATP production, and protecting gastric cancer cells from the therapeutic toxicity of cisplatin[66]. To explore the mechanism behind metformin reducing the sensitivity of gastric cancer cells to cisplatin and provide new possibilities for solving the cisplatin resistance of gastric cancer patients.

Some studies have suggested potential drugs and strategies for treating gastric cancer associated with mitophagy: 8-paradol, a phenolic compound derived from ginger, can induce cell apoptosis by enhancing mitophagy *via* the PINK1-Parkin pathway. Furthermore, the suppression of mitophagy using chloroquine ameliorates mitochondrial dysfunction and apoptosis triggered by 8-paradol. This observation underscores the pivotal role of mitophagy in the anticancer activity elicited by 8-paradol[67]. The Newcastle disease virus, a paramyxovirus, is utilized in cancer treatment. It can induce mitochondrial damage, elevate mitochondrial reactive oxygen species, and disrupt electron transport chain function. Consequently, this leads to the activation of the PINK1-Parkin pathway and the formation of a ubiquitin chain with Mitofusin 2. Furthermore, the molecular receptor p62 recognizes damaged mitochondria, mediates mitophagy, and regulates cancer cells[68].

CRC and mitophagy

According to the 2020 global cancer data, CRC is now the second leading cause of cancer-related mortality globally[60].

Table 2 Pathways regulating mitophagy in gastric cancer, colorectal cancer, and inflammatory bowel diseases

Diseases	Molecules	Effects/mechanisms	Significance	Ref.
Gastric cancer	Yap	Activates the SIRT1/Mfn2/mitophagy axis. Knockdown of Yap impairs the expression of adhesive proteins, reduces F-actin expression, and inhibits lamellipodium formation	Tumor-promoting effects: It contributes to the migration and survival of gastric cancer cells	[63]
	GGT7	Binds with the mitophagy regulator RAB7 to induce mitophagy. GGT7 inhibits ROS production and MAPK cascades	Tumor-suppressing effect: It inhibits the growth, G1-S phase transition and migration of gastric cancer cells	[64]
CRC	piR823	Promotes ubiquitination and proteasome-dependent degradation of PINK1, thereby inhibiting mitophagy	Tumor-promoting effects: It is involved in CRC tumorigenesis	[71]
	MST1	Inhibits mitophagy through the JNK/p53/BNIP3 pathway, leading to oxidative stress and initiating mitochondria-mediated apoptosis	Tumor-suppressing effect: It inhibits tumor proliferation	[73]
	GPR176	Inhibits mitophagy through the cAMP/PKA/BNIP3L axis	Tumor-promoting effects: It promotes the development of CRC	[74]
IBD	NR1D1	Acts as a positive regulator of BNIP3 expression, promoting mitophagy and maintaining the immune homeostasis of IECs	Inhibitory effect on colitis: It reduces the severity and progression of colitis	[88]

CRC: Colorectal cancer; IBD: Inflammatory bowel diseases; Yap: Yes-associatide protein; GGT7: Gamma-glutamyltransferase 7; SIRT1: Sirtuin 1; Mfn2: Mitofusin 2; JNK: c-Jun N-terminal kinase; BNIP3: BCL2-interacting protein 3; BNIP3L: BCL2-interacting protein 3 like; IECs: Intestinal epithelial cells; MST1: Mammalian sterile 20-like kinase 1; GPR176: G protein-coupled receptors 176; PKA: Protein kinase A; NR1D1: Nuclear receptor subfamily 1 group D member 1.

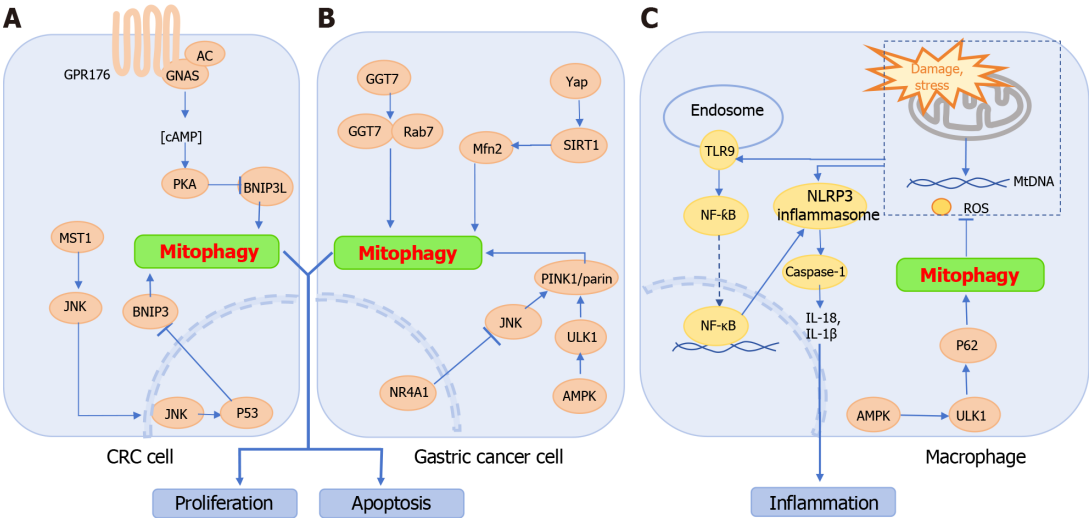

Figure 2 Pathways regulating mitophagy in colorectal cancer, gastric cancer, and inflammatory bowel disease. A: Colorectal cancer cells: GPR176 recruits GNAS to inhibit BCL2-interacting protein 3 like through the AC/cAMP/PKA pathway, thereby suppressing mitophagy. Additionally, MST1 activates the c-Jun N-terminal kinase (JNK) pathway, up-regulating P53 expression, which in turn inhibits BNIP3 transcription and activity, leading to mitophagy arrest; B: Gastric cancer cells: Interactions between GGT7 and Rab7 promote mitophagy. Yap activates sirtuin 1, enhancing Mfn2 expression and sustaining mitophagy. JNK upregulates Parkin to activate mitophagy; however, overexpression of NR4A1 inhibits mitophagy by suppressing JNK. Furthermore, the AMPK/ULK1/Parkin axis also supports mitophagy; C: Macrophages in inflammatory bowel disease: Damaged or stressed mitochondria in macrophages release mtDNA and reactive oxygen species, which directly contribute to NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome formation and activate NF-κB *via* the TLR9 pathway, triggering NLRP3 inflammasome activation and subsequent Caspase-1 activity. This results in the production of IL-1β and IL-18. Enhancing the AMPK-ULK1-P62 axis-driven mitophagy efficiently removes damaged mitochondria, inhibiting NLRP3 inflammasome activation and exerting anti-inflammatory effects. CRC: Colorectal cancer cell; NLRP3: NOD-like receptor thermal protein domain associated protein 3; SIRT1: Sirtuin 1; JNK: c-Jun N-terminal kinase.

While surgical intervention and adjuvant chemotherapy can effectively treat early-stage CRC, a significant proportion (25%-50%) of patients progress to metastasis, resulting in a dismal 5-year survival rate of approximately 14%[69]. Hence, delving deeper into the molecular mechanisms underlying CRC tumorigenesis and progression is imperative to develop new therapeutic strategies. Several studies have underscored the critical role of mitophagy in these processes (Figure 2). Thus, this subsection aims to comprehensively review how the mitophagy pathway contributes to CRC development, drug resistance, and treatment.

Table 3 Drugs affecting mitophagy in gastric cancer, colorectal cancer, and inflammatory bowel diseases

Diseases	Drugs	Effects/mechanisms	Significance	Ref.
Gastric cancer	TNFα	Activates Parkin-dependent mitophagy, and excessive mitophagy blocks mitochondrial apoptosis	Relates to the resistance of gastric cancer cells to TNFα	[65]
	Metformin	Activates AMPK signaling pathway and up-regulates the expression of mitophagy-related proteins PINK1, Parkin, and LC3B	Promotes the resistance of gastric cancer cells to cisplatin	[66]
CRC	Mito-CP, mito-metformin	Induces the release of ULK1, which promotes mitophagy	Tumor-suppressing effect: It inhibits tumor proliferation	[78]
	Aloe gel glucomannan	Activates PINK1/Parkin pathway to promote mitophagy; it activates the transcription factor EB to induce mitochondrial damage and ROS generation	Tumor-suppressing effect: It Inhibits tumor proliferation	[79]
	δ-valbetaine	Activates mitophagy through the PINK1/Parkin pathway	Tumor-suppressing effect: Inducing apoptosis of CRC cells	[80]
	Oxymatrine	Induces mitophagy and reduces NLRP3 inflammasome activation in CRC cells	Tumor-suppressing effect: Inhibit the growth and migration of CRC cells	[81]
	Small molecule andrographolide	Inactivates the NLRP3 inflammasome induced by mitophagy in macrophages	Alleviates colitis progression and reduces the risk of colitis-related cancers	[82]
IBD	Sodium butyrate	Activates Pink1/Parkin expression to promote mitophagy; it inhibits phosphorylation of NF-κB and activation of the NLRP3 inflammasome	Has an inhibitory effect on ulcerative colitis	[92]
	NSAIDs	Induces mitochondrial stress which leads to impaired mitophagy	Proinflammatory effects	[89]
	Bergapten	Promotes mitophagy and maintains mitochondrial homeostasis to inhibit NLRP3 inflammasome activation and pyroptosis	Anti-inflammatory activity	[93]
	Ginsenoside Rd	Activates AMPK/ULK1/p62 signaling pathway to trigger mitophagy, thereby inhibiting NLRP3 inflammasome	Anti-inflammatory activity	[94]

CRC: Colorectal cancer; IBD: Inflammatory bowel disease; LC3B: Microtubule-associated proteins light chain 3B; ULK1: UNC-51-like Kinase 1; ROS: Reactive oxygen species; NLRP3: NOD-like receptor thermal protein domain associated protein 3; NSAIDs: Non-steroidal anti-inflammatory drugs.

The role of PINK1 in inhibiting tumor growth within CRC has been elucidated. Yin *et al*[70] explored mouse colon cancer cells and found that PINK1 overexpression not only promoted mitophagy and decreased glycolysis through the activation of the p53 signaling pathway but also inhibited acetyl-CoA production within tumor cells, thus impeding tumor growth. The non-coding RNA piR823 interacts with PINK1, promoting its ubiquitination and proteasome-dependent degradation, thereby hindering mitophagy[71]. However, evidence suggests that PINK1 promotes survival in CRC. Chen *et al*[72] demonstrated that disruption of the mitophagy pathway due to PINK1 KD leads to a cytosolic iron imbalance, which can be rescued by ferritophagy activation through nuclear receptor coactivator 4 overexpression. These findings suggest that PINK1 regulates intracellular iron availability in conjunction with mitophagy and ferroautophagy, maintaining intracellular iron homeostasis, which is vital for supporting CRC cell survival and growth.

The receptor-mediated mitophagy pathway assumes a dual role in CRC development. Mammalian Ste20-like kinase 1, found to be down-regulated in CRC, inhibits mitophagy *via* the c-Jun N-terminal kinase (JNK)/p53/BNIP3 pathway, thereby inducing oxidative stress and initiating mitochondrial-mediated apoptosis, which contributes to the inhibition of tumor growth[73]. In contrast, the GPR176/GNAS complex inhibits mitophagy *via* the cAMP/PKA/BNIP3L axis, thereby promoting CRC development[74]. In addition to promoting or inhibiting tumor cells, Ziegler *et al*[75] found that elevated levels of mitophagy in intestinal epithelial cells induced adaptive immune responses in CD8+ T cells, providing a therapeutic target for tumor immunity.

Further, mitophagy has been implicated in drug resistance and radioresistance of CRC. Yan *et al*[76] observed that the level of mitophagy and the expression of BNIP3L were significantly increased in cancer stem cells (CSCs) after treatment with doxorubicin (DXR); however, silencing BNIP3L significantly inhibited mitophagy and enhanced the sensitivity of CSCs to DXR, suggesting that mitophagy is involved in DXR resistance in CSCs. Wei *et al*[77] proposed a mechanism by which mitophagy contributes to CRC radioresistance. Notably, excessive activation of mitophagy leads to decreased RING1b expression, which culminates in the deubiquitination of histone H2A at K119, thereby facilitating enhanced repair of radiation-induced DNA damage.

Given the significant role of mitophagy in both tumorigenesis and the progression of CRC, researchers have identified mitophagy as a promising therapeutic target for CRC. Specifically, in KRAS-mutant CRC, Mito-CP and Mito-metformin induce the release of ULK1, which promotes mitophagy and serves an anti-proliferative function[78]. Aloe gel glucomannan was found to induce mitochondrial damage and reactive oxygen species (ROS) generation, thereby inducing cytotoxic mitophagy in colon cancer cells through the PINK1/Parkin pathway and activation of the transcription factor EB[79]. Similarly, δ-valbetaine induces apoptosis in colon cancer cells by activating mitophagy through the PINK1/Parkin pathway[80]. Additionally, traditional Chinese medicine extracts have been shown to play an important role in the treatment of CRC. Oxymatrine treatment induces mitophagy in CRC cells and reduces NOD-like receptor

thermal protein domain associated protein 3 (NLRP3) inflammasome activation, inhibiting the growth and migration of CRC cells *in vitro* and *in vivo*[81]. However, the small molecule andrographolide (Andro) was shown to inactivate the NLRP3 inflammasome induced by mitophagy in macrophages, helping to mitigate colitis progression and tumor burden, thereby reducing the risk of colitis-associated cancer[82].

IBD and mitophagy

IBD is a group of autoimmune diseases characterized by gastrointestinal inflammation, primarily ulcerative colitis (UC) and Crohn's disease. In recent years, the incidence and prevalence of IBD in Asian populations have gradually increased [83]. Several studies have reported that mitochondria are related to the inflammatory response (Figure 2). When mitochondria are damaged, mtDNA and mtROS are released. mtDNA can not only activate NLRP3 inflammasome[84] but also trigger the toll-like receptor 9 pathway to induce an NF-κB and MAPK inflammatory cascade[85]. Moreover, ROS affect the secretion of inflammatory cytokines[86]. Finally, mitophagy removes damaged mitochondria, suggesting that it may be a protective factor for IBD.

NIX is an important receptor protein that mediates mitophagy. Vincent *et al*[87] found that NIX expression was upregulated in the intestinal epithelial cells (IECs) of patients with UC, and compared to wild-type mice, NIX-/- mice exhibited stronger inflammatory characteristics and loss of mucosal integrity when experimental colitis occurred. Moreover, research has demonstrated that the expression level of the circadian clock gene NR1D1 is reduced in patients with UC, and NR1D1 knockout results in a disruption of IECs immune homeostasis and a diminished mitophagy. Subsequent studies have identified that NR1D1 positively influences the expression of the autophagy receptor BNIP3, thereby enhancing mitophagy[88]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been identified as a risk factor for IBD. This condition induces mitochondrial stress in IECs, resulting in impaired mitophagy. Such impairment leads to the release of mitochondrial damage-associated molecular patterns with pro-inflammatory potential. These mitochondrial components then act as pro-inflammatory molecules[89].

The maintenance of mitochondrial homeostasis mediated by mitophagy limits the excessive activation of the NLRP3 inflammasome[90], which plays a key role in colitis[91].

Several substances have been demonstrated to harness this process and improve outcomes in IBD. For example, sodium butyrate is effective in suppressing UC because it inhibits the phosphorylation of NF-κB and activates the NLRP3 inflammasome. Moreover, it also enhances mitophagy through the activation of PINK1/Parkin expression[92]. Similarly, Bergapten, a plant-derived hormone with anti-inflammatory properties, has been shown to inhibit NLRP3 inflammasome activation and pyroptosis in a mouse model of intestinal inflammation, further supporting mitochondrial health by facilitating mitophagy[93]. In addition, Ginsenoside Rd initiates mitophagy by activating the AMPK/ULK1/p62 signaling pathway, which in turn inhibits the NLRP3 inflammasome[94]. Furthermore, probiotics have been demonstrated to ameliorate UC. Specifically, *Lacidophilus acidophilus* enhances the levels of short-chain fatty acids, thereby stimulating the mitophagy/NLRP3 inflammasome pathway. This activation helps to maintain inflammatory homeostasis both *in vivo* and *in vitro* and contributes to the improvement of intestinal barrier function[95]. However, mitophagy-related pathway proteins may also play a role in IBD. Parkin, an E3 ubiquitin ligase, has been identified by Ma *et al*[96] as playing a significant role in the context of IBD, with the vitamin D receptor (VDR) acting as a crucial inhibitory regulator. Specifically, Parkin escalates the incidence of colitis and severe inflammation by facilitating VDR degradation *via* the p62-related autophagy-lysosomal pathway.

CONCLUSION

Mitochondria and mitophagy

Along with acting as the energy factories of cells, mitochondria play crucial roles in cell signal transduction, calcium regulation, reactive oxygen species production, cellular protein homeostasis, anti-inflammatory responses, apoptosis, and intercellular mitochondrial transfer[97-100]. The diverse and important functions of mitochondria are the basis for maintaining cell homeostasis. Under the supervision of quality control system, mitochondria will undergo continuous fission and fusion cycles in cells to maintain their shape, network and inheritance[101]. When mitochondrial function is irreparably damaged or under specific stress conditions such as hypoxia or nutritional deprivation, mitophagy is activated. This process selectively promotes the degradation of mitochondria *via* the autophagy-lysosome pathway[102]. Mitophagy, as a mechanism to maintain the quality and quantity of mitochondria, is involved in the pathophysiological processes such as cell growth, cell differentiation, cell aging and apoptosis.

Advances in mitophagy

Autophagy is an energy-intensive process. Excessive regulation of autophagy can result in cellular homeostasis imbalance, leading to unnecessary degradation and damage of organelles[103]. Therefore, it appears to be a more sensible strategy to develop selective autophagy modulators for the treatment of gastrointestinal diseases. Mitophagy regulators developed over the past decade have shown a certain efficacy in gastrointestinal disease models. In the context of gastric cancer and CRC, mitophagy serves dual functions: It not only maintains mitochondrial homeostasis to prevent cancer but also confers survival advantages and enhances drug resistance in cancer cells, influenced by the complex tumor microenvironment. Regulating mitophagy can be an effective strategy to prevent cancer, halt its progression, and enhance treatment efficacy. In IBD, mitochondrial damage can prompt the release of a series of inflammatory factors, which in turn exacerbate intestinal tissue damage. Moreover, mitophagy plays a crucial role in inhibiting the progression of IBD by removing damaged mitochondria. Thus, developing mitophagy inducers may represent a novel therapeutic approach for

IBD.

Problems to be solved

However, the research to date has demonstrated a correlation between mitophagy and several conditions, such as gastric cancer, intestinal cancer, and IBD, thus offering a new and viable direction for treatment. Nevertheless, numerous challenges remain. The signaling mechanisms of mitophagy are intricate and vary across different tissues, developmental stages, and states of stress or metabolism. Therefore, what are the temporal and spatial regulations of mitophagy under various pathophysiological conditions? Numerous experiments have demonstrated the dual role of mitophagy in cancer; however, the critical question remains: What is the threshold between its inhibitory and promotive effects? Currently, many mitophagy inducers are mitochondrial decoupling agents or mitochondrial toxins developed from *in vitro* experiments. Are these agents clinically effective? Is the pharmacological activity of these known regulators solely attributed to mitophagy regulation? Thus, identifying biomarkers and developing detection methods that can reliably and specifically measure mitophagy flux are essential. This will ensure precise regulation of mitophagy and facilitate the practical evaluation of therapeutic effects. Furthermore, the mechanism of mitophagy in additional gastrointestinal diseases, including gastrointestinal peristalsis, infectious inflammation, and chronic inflammation of the gastrointestinal tract, remains largely unexplored and warrants further investigation.

Future application fields

In summary, further analysis of the molecular mechanisms of mitophagy and its role in regulating the onset and progression of gastrointestinal diseases is warranted. Developing small-molecule drugs that target mitophagy for the treatment of gastrointestinal diseases represents a novel approach. With the appearance of an *in vivo* mitophagy imaging system[12] and a mitophagy modulator characterization system[103], it has gradually become possible to study and verify mitophagy modulators in disease animal models and to characterize drugs. Although there are many problems that need to be solved urgently in mitophagy, it is undeniable that targeted mitophagy is a promising treatment for gastrointestinal diseases.

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FOOTNOTES

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