Effects of calcium-permeable ion channels on various digestive diseases in the regulation of autophagy (Review)

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Abstract. Autophagy is a process of degradation and catabolism in cells. By removing damaged or dysfunctional organelles, autophagy interacts with the ubiquitin-proteasome degradation system to jointly regulate cell function and energy homeostasis. Since autophagy plays a key role in physiology, disorders of the autophagy mechanism are associated with various diseases. Therefore, thorough understanding of the autophagy regulatory mechanism are crucially important in the diagnosis and treatment of diseases. To date, ion channels may affect the development and treatment of diseases by regulating autophagy, especially calcium-permeable ion channels, in the process of digestive system diseases. However, the mechanism by which calcium ions and their channels regulate autophagy is still poorly understood, thus emphasizing the need for further research in this field. The present review intends to discuss the association, mechanism and application of calcium ions, their channels and autophagy in the occurrence and development of digestive system diseases.

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Abbreviations: ER, endoplasmic reticulum; CMA, chaperone-mediated autophagy; MTORC1, mechanistic target of rapamycin complex 1; AMPK, AMP-activated protein kinase; PI3K, Class III phosphatidylinositol 3-kinase; AMBRA-1, Beclin 1 modulator 1; TRP, transient receptor potential; SOC, store-operated calcium; TPCN, 2-pore segment channel; MPTP, mitochondrial permeability transition pores; MCU, mitochondrial calcium unidirectional transporters; CAMKK2/CaMKKb, calcium/calmodulin dependent kinase 2; MTOR, mechanistic target of rapamycin; InsP3, inositol 1,4,5-trisphosphate; ITPR, inositol 1,4,5-trisphosphate receptor; VDAC1, voltage-dependent anion channel 1; MCUR1, mitochondrial calcium uniporter regulator1; ULK, unc-51 like autophagy activating kinase; SOCE, store-operated calcium entry; ASIC, acid sensing ion channel; KCNH7/HERG3, potassium voltage-gated channel subfamily H member 7; CLIC4, chloride intracellular channel 4; OGT, O-linked β-N-acetylglucosamine (O-GlcNAc) transferase; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; FFA, free fatty acids; LPS, lipopolysaccharide; NAADP, nicotinic acid adenine dinucleotide phosphate; 5-FU, 5-fluorouracil; AP, acute pancreatitis; CCK, cholecystokinin; STIM1, stromal interaction molecule 1; TFEB, transcription factor EB; CaN, calcineurin; IL-1β, interleukin-1β; VacA, vacuolar cytotoxin A

Key words: calcium, autophagy, ion channel, calcium signaling, digestive system diseases

Contents

1. Introduction

Overview of autophagy. Autophagy is a range of biological processes in which the cell degrades parts of itself within the lysosome (or the analogous organelle, such as the vacuole in yeast and plants), followed by the release and reuse of the breakdown products. In a sense, autophagy is a mechanism for cellular recycling. In addition, different autophagy processes are extremely important in cell and body function and homeostasis (1,2). Autophagy usually occurs under basic conditions, and is stimulated under different types of cellular stress, including endoplasmic reticulum (ER) stress, oxidative stress, mitochondrial damage, nutrition and growth factor starvation, hypoxia and some drug treatments (3). At present, according to the intracellular components transported to the lysosome, the autophagy pathway can be divided into the following three categories: Macroautophagy, microautophagy and molecular chaperone-mediated autophagy (CMA) (1,4,5). Macroautophagy is the most common and clinically significant form of autophagy. During the process of macroautophagy, soluble proteins in the cytoplasm and degenerative and necrotic organelles are wrapped by a double-layer membrane structure derived from non-lysosomal cells, namely autophagic bubbles,

and is carried into the lysosome by autophagic vesicles for degradation and processing (1,6). Microautophagy is a pathway directly degraded by lysosomes, in which lysosomal membranes directly invade and encapsulate cytoplasmic components in double-membrane vesicles (4). Chaperone-mediated autophagy (CMA) has a cytoplasmic protein with a specific pentapeptide motif (KFERQ) that recognizes and binds to 70 kDa heat shock homologous protein (Hsc70) and is directly delivered to the lysosome for degradation. The whole process does not require the participation of vesicles, as the substrate of CMA is a soluble protein molecule (5). Hence, the CMA degradation pathway is selective when removing proteins, while macroautophagy and microautophagy have no obvious selectivity. In view of the multi-directional regulation of autophagy, cell autophagy has been confirmed in recent years to be closely associated with metabolic diseases, cardiovascular diseases, lung diseases and neurodegenerative diseases and cancer (7). Therefore, a thorough understanding of the autophagy mechanism is particularly important in the diagnosis and treatment of diseases.

Autophagy refers to the process whereby damaged organelles, misfolded proteins and protein aggregates are packed into autophagosomes and transported to the lysosome for degradation (8,9). It mainly includes four stages: Initiation stage, autophagosome extension stage, autophagosome maturation stage and autophagosome degradation stage, and the regulation mechanism of each stage is complicated. The formation and renewal of autophagosomes involves evolutionary conserved genes called autophagy-related (ATG) genes. During the start-up phase, mechanistic target of rapamycin complex 1 (mTORC1) activates the ULK1 (also known as ATG1) complex [involving ULK1, ULK2, ATG13, FIP200 (also known as RB1CC1) and ATG101], and AMP-activated protein kinase AMPK. During the extension phase of autophagosomes, the ULK1 complex phosphorylates and activates the Beclin-1-VPS34 complex. This complex includes Beclin-1, VPS34 [Class III phosphatidylinositol 3-kinase (PI3K)] and other proteins, such as VPS15, ATG14L and Beclin 1 modulator 1, depending on their subcellular complexity the positioning (10). The ATG5-ATG12 complex binds to ATG16 in order to expand the autophagosome membrane, and members of the LC3 and GABARAP protein families bind to the lipid phosphatidylethanolamine and are subsequently recruited to the membrane. ATG4 binds to ATG7, combining LC3-I and PE to form LC3-II (also known as MAP1LC3B). LC3 is commonly used as an autophagy marker (11). Eventually, the autophagosome is fused with the lysosome, the contents are degraded, and the macromolecular precursor is recovered or used to promote metabolic pathways. Adaptor protein chelate 1 (also known as p62) targeting specific substrates to autophagosomes and LC3II is degraded together with other cargo proteins and can be used as a measure of autophagy flux (11).

Overview of ion channels. The ion channel of the biomembrane is a pathway for the transport of various inorganic ions across the membrane. It is mainly composed of transmembrane proteins and forms pores in the cell membrane to regulate the exchange of specific ions. The role of ion channels is mainly to maintain the steady state of ions inside and outside the cell and to transmit cell signals, while regulating the volume, proliferation, apoptosis, migration, invasion and adhesion of cells. Ion channels can be classified according to the channel opening and closing or gating mechanism (12). For example, ion channels can control the changes in ions inside and outside the cell through the combination of membrane voltage (voltage-gated), extracellular ligands (ligand-gated), or a combination of intracellular secondary messengers. In addition to the gate mechanism, ion channels can also be classified according to their selectively permeable ions (12). For example, there are various types of calcium (Ca^{2+}), potassium (K^{+}) and sodium (Na^{+}) ion channels. Calcium-permeable ion channels can regulate the levels of mitochondria, ER, lysosomes and cytosolic calcium. The ion channels are located on the intracellular organelle membrane or plasma membrane (13,14). Calcium penetration channels mainly include transient receptor potential (TRP) channels, storage operation channels (SOC), voltage-gated calcium channels, 2-pore segment channel (TPCN), mitochondrial permeability transition pores (MPTP), and mitochondrial calcium unidirectional transporters (MCU), IP3 and ryanodine receptors and other receptors. By regulating the driving force of Ca^{2+}, it provides Ca^{2+} in and out pathways, thereby regulating the changes in Ca^{2+} concentration intracellularly and extracellularly, and thus affecting calcium-dependent processes such as proliferation, apoptosis and autophagy (13-18). As an example, several members of the TRP family of ion channels, namely TRPC1, TRPC3, TRPC6, TRPV1, TRPV6, TRPM1, TRPM4, TRPM5, TRPM7 and TRPM8, show altered expression in cancer cells. The involvement of SOCs, MPTP, MCU and IP3 receptors and ryanodine receptors in the regulation of cell death has also been described.

Aside from Ca^{2+}-permeable ion channels, other ion channels also play a critical role in cell biological behavior. Sodium channels are considered as integral membrane proteins that mediate sodium influx into the cell or intracellular organelles. According to the gating mechanism, sodium channels can be divided into voltage-gated sodium channels family and epithelial sodium channels (19,20). Voltage-gated sodium channels are distributed in almost all cell types, while epithelial sodium channels are mainly located in the skin and kidneys. Voltage-gated sodium channels are responsible for membrane depolarization and regulating cell invasion and migration. Potassium channels mediate the flow of potassium ions down their electrochemical gradient. K^{+} channels are widely distributed in all kinds of cell types and are involved in the regulation of various physiological processes including maintenance of membrane potential, regulating cell proliferation and apoptosis. Based on structural criteria, conductance properties as well as activation mechanisms, potassium channels are divided into 4 classes: Voltage-gated, calcium-activated, inward-rectifier and 2-pore-domain potassium channels (21). Chloride channels mediate the flow of chloride ions across cell membranes and reside both in the plasma membrane and in intracellular organelles. Chloride channels are ubiquitously expressed and regulate a variety of fundamental cellular processes including apoptosis, volume regulation, cell cycle and intracellular organelle acidification (22). According to the gating mechanism, chloride ion channels can be divided into chloride voltage-gated channels, cystic fibrosis transmembrane conductance regulator, calcium activated chloride channels, volume-regulated anion channels and ligand gate control anion channel (22).

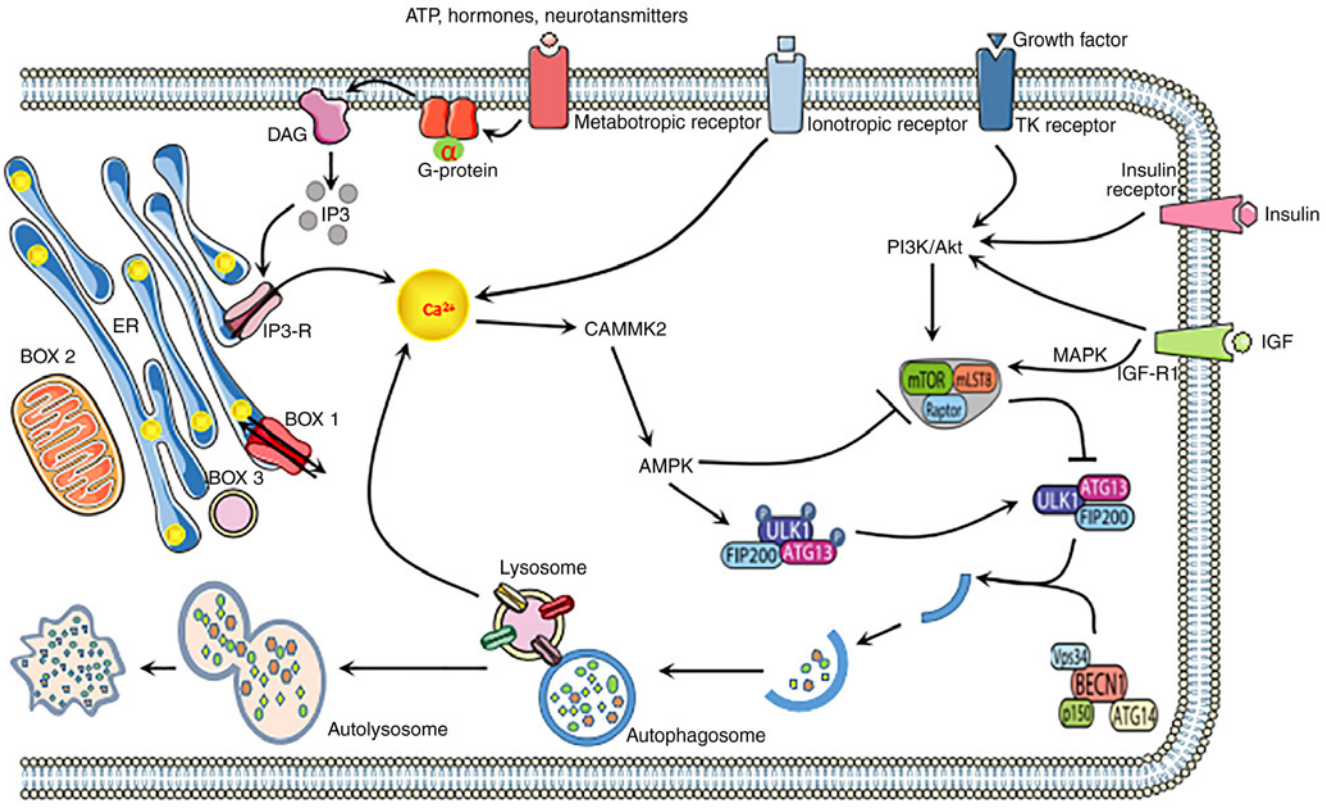

Figure 1. Calcium and calcium-permeable ion channels regulate autophagy. The inhibitory and stimulatory effects of Ca^{2+} on autophagy and the calcium penetration channels that may be involved in the regulation of autophagy are depicted. Insulin growth factor, insulin and growth factors activate their tyrosine kinase receptors and trigger intracellular pathways that inhibit autophagy. The activation of receptors in the plasma membrane of the cell can increase the level of inositol triphosphate in the cell and trigger the release of Ca^{2+} through the endoplasmic reticulum, thereby promoting autophagy through the CaMKK2-AMPK pathway. mTORC1 plays a central role in integrating all these signals to regulate autophagy. In addition, the activation of ULK1 by AMPK can also trigger autophagy. Ca^{2+}, calcium.

2. Role of ion channels in the regulation of autophagy

Calcium-permeable channels in the regulation of autophagy. In recent years, reports on ion channel-regulated autophagy have focused on calcium-permeable ion channels (23). Calcium is a ubiquitous intracellular messenger that affects almost every aspect of cellular life (24). The calcium-permeable ion channel, as a 'calcium signal toolkit', promotes the change in cytosolic calcium concentration by providing a Ca^{2+} entry pathway and regulating the driving force of Ca^{2+} entry. It also provides a way for Ca^{2+} to circulate in the cytoplasm and organelles. In this way, calcium-permeable channels indirectly control various calcium-dependent cellular processes, such as cell proliferation, apoptosis and autophagy. The complex role of Ca^{2+} in the regulation of autophagy has become apparent since 1993, when the first report on autophagy and intracellularly sequestered calcium was published (25). It was demonstrated that both a decrease and an increase in intracellular Ca^{2+} levels can inhibit autophagy in rat hepatocytes (24). Afterwards, Høyer-Hansen *et al* (26) demonstrated that Ca^{2+} mobilizing agents, namely vitamin D3, thapsigargin, ATP and ionomycin, stimulate autophagy via a signaling pathway involving CAMKK2/CaMKKβ (calcium/calmodulin dependent protein kinase 2), which directly activates AMPK to inhibit mTOR and induce the accumulation of autophagosomes to prove that the increase in free cytoplasmic calcium is an effective inducer of macroautophagy. However, the 'classical' Ca^{2+}-CAMKK2-AMPK pathway (both MTOR-dependent and MTOR-independent) is not a unique pathway for cytosolic calcium-induced autophagy. One study showed that Ca^{2+} signaling can induce autophagy independently of Ca^{2+}-mediated AMPK activation (27). It is reported that exogenous introduction of Ca^{2+} precipitated into mammalian cells as calcium phosphate will induce BECN1, ATG5 and phosphatidylinositol 3 kinase dependent autophagy (28). To date, the role of calcium in the regulation of autophagy is quite complex and controversial. Several reports indicate that calcium has an inhibitory effect on autophagy, in contrary to the calcium stimulation effect reported by others (29,30). A graphic overview of the mechanisms of calcium-permeable channel in autophagy regulation is presented in Figs. 1 and 2.

The ubiquitously expressed inositol 1,4,5-triphosphate receptor (ITPR) is the main intracellular Ca^{2+} release channel and also the channel most reported for calcium-permeable channels as autophagy regulators. It is located on the membrane of the ER, mainly inositol 1,4,5-triphosphate (InsP3)-mediated calcium release from the ER (31). These reports indicate that the complex role of ITPR in the regulation of autophagy may lead to the activation and inhibition of this process (32,33). These complex effects mainly depend on the spatiotemporal characteristics of Ca^{2+} signals, including the presence of Ca^{2+} signal microdomains in calcium of ER-mitochondria and ER-lysosomes. In DT40 cells, basal autophagy is negatively regulated by ITPR-dependent Ca^{2+} signaling, which maintains

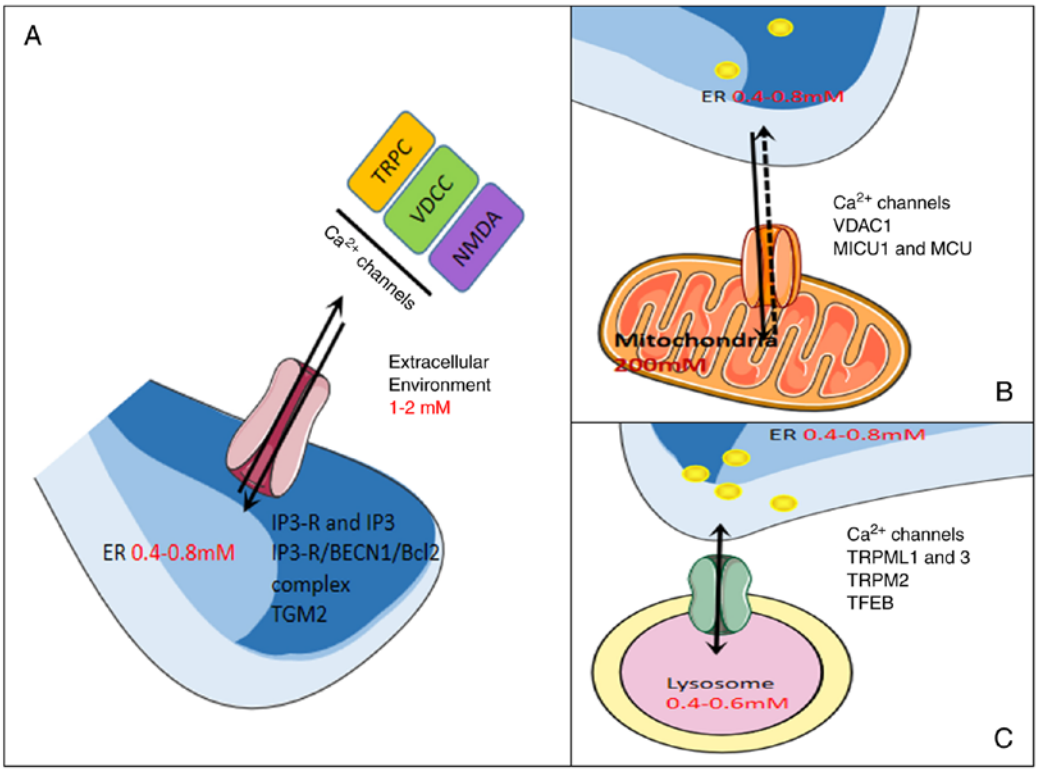

Figure 2. Communication of different cellular compartments of Ca^{2+} homeostasis. Intracellular Ca^{2+} is mainly stored in the ER (0.4-0.8 mM), but also in mitochondria (200 nM) and lysosomes (0.4-0.6 mM). These cell compartments and cytoplasm flow with each other. (A) Inositol 1,4,5-triphosphate receptor (also known as ITPR) in the ER membrane, which is the most important intracellular Ca^{2+} release channel. (B) Voltage-dependent anion channel 1 and mitochondrial calcium unidirectional regulator 1 in the outer and inner mitochondrial membranes. (C) Receptor lysosomal lipoprotein 1/3 and transient receptor potential calcium channels melatonin 2 and 3. In addition, there are plasma membrane channels that control the influx of Ca^{2+} from the extracellular environment. The dynamic changes in Ca^{2+} produced by these receptors and channels maintain the homeostasis of cells. ER, endoplasmic reticulum; Ca^{2+}, calcium.

elevated MTORC1 activity through an AMPK-independent pathway (34). Besides, some researchers have proposed another MTOR-independent mechanism, ITPR-mediated Ca^{2+} release from ER and subsequent Ca^{2+} absorption by mitochondria to maintain the basic needs of mitochondrial bioenergy and ATP production in resting cells. The lack of Ca^{2+} transfer will lead to a decrease in ATP production and AMPK activation, which in turn activates survival autophagy in a MTOR-independent manner (35). The transfer of Ca^{2+} from the ER to the mitochondria is proposed to occur through the ITPR on the ER to the voltage-dependent anion channel 1 (VDAC1) on the outer mitochondrial membrane. It then enters the matrix through the mitochondrial inner membrane mediated by a highly selective, low-affinity Ca^{2+} channel known as mitochondrial calcium unidirectional transporter (MCU). By controlling mitochondrial Ca^{2+} concentration, MCU plays a key role in regulating aerobic metabolism and cell survival. Tomar *et al* (36) confirmed the important role of MCU and MCUR1 in mitochondrial bioenergy and autophagy. The study showed that mouse cardiomyocytes and endothelial cells lacking MCUR1 severely impaired mitochondrial Ca^{2+} absorption and current flow through the MCU. The loss of MCU or MCUR1 will interfere with the MCU hetero-oligomeric complex, damage mitochondrial bioenergy, cell proliferation and migration, and trigger AMPK-dependent autophagy. In addition to ITPR, some other calcium-permeable channels have also been shown to participate in autophagy regulation. For example, the role of intracellular voltage-gated calcium channels in autophagy has been revealed. Tian *et al* (37) reported that the P/Q-type calcium channel CACNA1A/Cav2.1 (calcium voltage-gated channel subunit α1A) is located in the lysosome, and the loss of lysosome CACNA1A in the cerebellar cultured neurons leads to lysosome unable to merge with the endosome. It was shown that lysosomal fusion requires CACNA1A, instead of CACNA1A residing on the plasma membrane (37). Current evidence also supports the view that ryanodine receptor, TPCN, TRP channels and SOCE channels are also involved in the regulation of autophagy (15,16,38-40).

Other ion channels regulate autophagy. The accumulated data indicates that the complex regulation of other ion channels and autophagy opens up a new way to target autophagy in disease treatment. For example, the acid-sensitive ion channel 3 (ASIC3) in the sodium channel can regulate the apoptosis of chondrocytes in articular cartilage, and the overexpression of ASIC3 and hypoxia-inducible factor-1α (HIF-1α) can inhibit the cells in intervertebral disc degeneration by preventing the G1 cell cycle transition and activating the MAPK pathway of autophagy to promote cell apoptosis (41,42). In addition, non-selective cation channels (such as members of the TRP channel family) can also permeate Na^+ ions, suggesting that these channels may regulate autophagy through Na^+-dependent mechanisms. There are also studies that have proposed several potassium channels to regulate autophagy. According to reports, the opening of the ATP-sensitive K^+ (K^+ + ATP) channel induces autophagy in different cell types. For example, according to

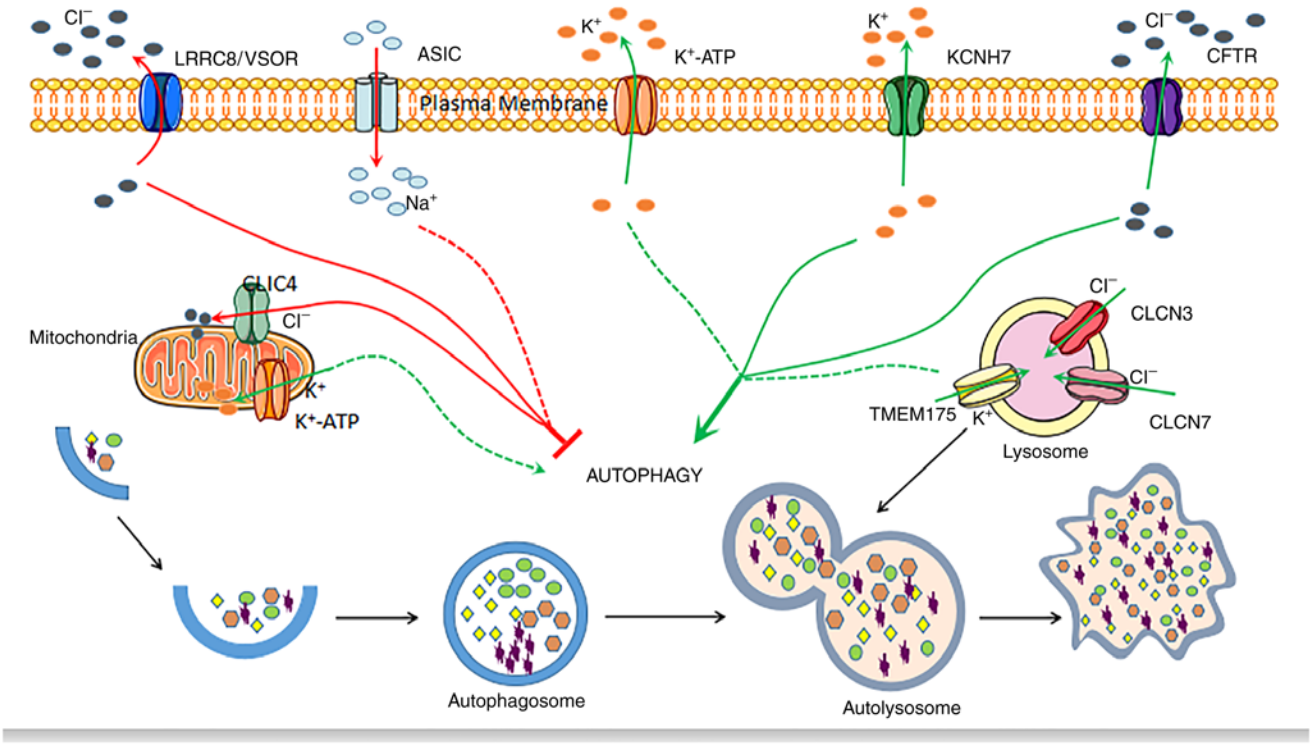

Figure 3. Other ion channels regulate autophagy. The inhibition and stimulation of autophagy by various ion channels other than calcium ion channels are eliminated. Ion channels that stimulate autophagy are shown in green, while ion channels that inhibit autophagy are shown in red.

Williams *et al* (43), minoxidil is a K^+ + ATP channel agonist that can enhance autophagy in PC12 cells, while K^+ + ATP channel blockers such as quinine sulfate and tosylamide can slow down autophagic substrate removal. One study suggested that KCNH7/Kv11.3/HERG3 (member 7 of potassium voltage-gated channel subfamily H) plasma membrane potassium channels are involved in the regulation of melanoma autophagy and aging (44). In detail, by stimulating the KCNH7 channel with the small molecule activator NS1643, AMPK-dependent signaling pathways in melanoma cell lines are activated to induce autophagy (44). There are few data on the role of chloride channels in the regulation of autophagy. In fact, the Cl-channel is very low in selectivity among anions and allows various anions to penetrate. A previous study showed that small interference RNA-mediated knockdown of CLIC4/mtCLIC (chloride intracellular channel 4) can enhance BECN1-dependent autophagy and apoptosis in human glioma U251 cells induced by starvation (45). In addition, Wang *et al* (46) reported that volume-sensitive outward rectification (LRRC8/VSOR) chloride channels can promote high glucose-induced cardiomyocyte apoptosis by inhibiting autophagy. The authors demonstrate that LRRC8/VSOR channel blockers induce autophagy through MTOR inhibition (46). In summary, the aforementioned data indicate the diversity and importance of ion channels in the regulation of autophagy. Today's limited data proves that ion channel dysfunction and autophagy dysregulation are associated with several diseases, and it is possible to consider ion channels and autophagy as potential therapeutic targets. A graphic overview of the mechanisms associated with other ion channels on autophagy regulation is presented in Fig. 3.

In recent years, cytoplasmic and extracellular ion concentrations and ion channel types, which mediate ion flux across cell membranes, have become important regulators of basic autophagy and induced autophagy. The dysfunction of ion channels may cause the dysregulation of autophagy, which in turn leads to a series of diseases. Therefore, ion channels and autophagy can be regarded as potential therapeutic targets. However, there is still limited information about the molecular nature of autophagy-regulated channels and their regulatory mechanisms, and the most important ones are reports of calcium ions and calcium channels regulating autophagy. The existing data on ion channels participating in the autophagy regulatory pathway was discussed in the present review.

3. Interaction between diseases, ion channels and autophagy

Calcium and calcium channels in liver disease regulate autophagy. The liver can provide the nutrients used by the body's organs. When the body is under starvation conditions, it will induce autophagy in the liver to help maintain the homeostasis of the whole body. One study showed that during starvation, glucagon stimulates the InsP3R1-CaMKII pathway, which mediates the phosphorylation of O-linked β-N-acetylglucosamine (O-GlcNAc) transferase (OGT) at a post-translational level (47). ULK protein is a target to fine-tune liver autophagy. During starvation, glucagon stimulates the InsP3R1-CaMKII pathway, thereby mediating OGT phosphorylation. This approach uses post-translational levels of ULK protein as a target to fine-tune liver autophagy and provide substrates for gluconeogenesis and ketogenic to maintain systemic glucose homeostasis (47). In addition, autophagy caused by nutrient deficiency or starvation can also be inhibited by BAPTA-AM (BAPTA is a selective Ca^{2+} chelator, and its

acetyl methyl ester derivative is BAPTA-AM), which indicates that other autophagy-inducing conditions, such as starvation or rapamycin, may also activate autophagy through the Ca^{2+} signaling pathway. In this study, to demonstrate whether calreticulin was stimulated by ER stress, the authors generated an ER stress murine model via intraperitoneal administration of an ER stress inducer, tunicamycin, and determined the hepatic expression of calreticulin. Researchers found that the overexpression of calreticulin stimulates the formation of autophagosomes and increases autophagic flux. These findings indicate that a calreticulin-based mechanism couples endoplasmic reticulum stress with autophagy activation, thereby reducing cellular stress. This may be achieved by reducing the formation of abnormally folded proteins (48).Under ER stress conditions, calreticulin induces autophagy by interacting with microtubule-associated protein 1A/1B-light chain 3 (LC3). Further studies have shown that calreticulin-mediated autophagy activation and decrease in ER stress require an area that interacts with the LC3 in calreticulin (48).

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. NAFLD involves the accumulation of excess lipids in hepatocyte cytoplasmic lipid droplets, which can develop into nonalcoholic steatosis, fibrosis and HCC. Furthermore, elevated free fatty acids, especially saturated fatty acids, such as palmitic acid, may play an important role in the lipotoxic mechanism of NAFLD (49). Saturated fatty acids can induce autophagy dysfunction and ER stress, increase intracellular calcium, and ultimately lead to hepatocyte apoptosis (50,51). Studies on the mechanism of autophagy impairment in fatty liver disease have determined that the increase in intracellular calcium is a mediator of autophagy dysfunction. Park *et al* (52) demonstrated that saturated free fatty acids (FFA) induce increased cytosolic calcium in liver cells, thereby inhibiting autophagy. It was determined that obesity and lipotoxicity can induce a chronic increase in cytosolic calcium levels in liver cells, thereby interfering with the fusion between autophagosomes and lysosomes, which can weaken liver autophagy flux. Subsequently, Czaja (53) found that in obese mice, the decrease in autophagy can be reversed by calcium channel blockers, resulting in a decrease in steatohepatitis. In addition, zinc (Zn) deficiency is the most commonly found nutritional manifestation of fatty liver disease. Zn is known to stimulate liver lipid oxidation, but research by Wei *et al* (54) demonstrated that zinc is an effective promoter of fat phagocytosis, which can significantly decrease the accumulation of lipid in hepatocytes and activate fat phagocytosis through the Zn^{2+}/MTF-1/PPARα and Ca^{2+}/CaMKKβ/AMPK pathways. The aforementioned results provide new insights into Zn nutrition and its potential beneficial role in preventing fatty liver disease. In addition, calcium can also be used to control autophagy in liver injury to protect the liver from inflammation. LPS is known to induce liver injury and promote hepatocyte autophagy (55). CD38 is an enzyme that produces NAADP, which is the most effective intracellular Ca^{2+} mobilization signal molecule (56). In a study by Rah *et al* (57), it was found that administration of NAADP to mice can alleviate LPS/GalN-induced liver injury by enhancing the autophagy process, which revealed that CD38 and Ca^{2+}-activated messenger NAADP are important regulators of hepatocyte autophagy. Although the downstream targets of Ca^{2+} signaling pathway mediated by NAADP-mediated autophagy have not yet been found, the Ca^{2+} signaling pathway mediated by CD38/NAADP triggered the autophagy process, induced the expression of autophagy-associated genes and protects the liver from injury caused by LPS (57).

In recent years, many researchers have worked hard to find new therapeutic targets to successfully treat hepatocellular carcinoma (HCC), and there are also therapeutic strategies that study the interaction mechanism between calcium signaling and autophagy. The earliest research was conducted by Shi *et al* (58), who found that Trichokonin VI (TKVI), a peptaibol from Trichoderma pseudokoningii SMF2, induced growth inhibition of HCC cells in a dose-dependent manner. TK VI induces the influx of Ca^{2+} across the cell membrane or the release of intracellular Ca^{2+} stores, resulting in increased cytoplasmic calcium activation of Bak and calpain, which induces two types of cell death, including calcium-calpain-Bax in HepG2 mediated apoptosis and calcium-Bak-mediated autophagy (58). It is suggested that the increase in intracellular calcium level in HCC mediates the autophagy of HCC cells, thereby inducing cell apoptosis. 5-fluorouracil (5-FU) is the most widely used chemotherapeutic agent for the gastrointestinal tract, breast cancer, head and neck cancer and ovarian cancer. Accumulating evidence suggests that various cancer cells including colon cancer (59), pancreatic cancer (60) and gastric cancer cells (61) can induce autophagy through 5-FU. It is known that increased SOCE associated with upregulation of Stim1, Orai1 or TRPC1 expression has been observed in several different types of tumors (62-64), indicating that SOC is a potential therapeutic target for the treatment of cancer. In liver cancer, recent studies have shown that inhibition of TRPC1 by regulating SOCE can inhibit cell proliferation (65,66). A study showed that with increased expression of Orai1 in liver cancer tissues, 5-FU can inhibit Ca^{2+} entry by down-regulating Orai1-mediated SOCE, and by inhibiting the activation of PI3K/AKT/mTOR signaling pathway, causes 5-FU in HepG2 cells to induce autophagic cell death and enhances the chemical sensitivity of liver cancer cells to 5-FU (67). Based on the fact that changes in mitochondrial dynamics and cytosolic calcium may occur at the same time, the study by Huang *et al* (68) provides a new idea. The study by Huang *et al* found that in HCC cells, mitochondrial fission through STIM1-mediated storage-operated Ca^{2+} entry (SOCE) significantly enhances cytoplasmic Ca^{2+} signaling, and increased cytoplasmic calcium signaling promotes mitochondrial fission, forming a positive feedback loop. It is mitochondrial fission and the cytoplasmic calcium signaling pathway that form a positive feedback loop, and promote the autophagy of liver cancer cells through the Ca^{2+}/CAMKK/AMPK signaling pathway (68).

Calcium and calcium channels in pancreatic diseases regulate autophagy. Acute pancreatitis (AP) is the most common pancreatic disease, which is mainly caused by a variety of factors. It is usually accompanied by inflammation, edema, bleeding and even necrosis of its own tissues or remote organs (69-71). During the onset of AP, under the stimulation of cholecystokinin (CCK), bile acids, alcohol metabolites or some other reason, the influx of Ca^{2+} was significantly increased (71-74). It was determined that storage-operated Ca^{2+} entry (SOCE) is a key pathogenic step in AP development

and can lead to trypsin activation, inflammation and vacuoles (73,74). Recent studies have shown that Orai1 is the main SOCE channel in pancreatic acinar cells. After the ER Ca^{2+} reservoir is emptied, its opening interacts with stromal interaction molecule 1 (STIM1) (75-78). Research by Zhu *et al* (79) found that caerulein (CCK receptor agonist) triggers SOCE by inducing the interaction between STIM1 and Orai1, thereby activating calcineurin (CaN), which activates activated T cells nuclear translocation and dephosphorylation of nuclear factor and transcription factor EB (TFEB), thereby promoting the transcriptional activation of multiple chemokine genes and autophagy-associated genes (79). These findings suggest that TFEB may play a vital role in the long-term effect of SOCE/CaN on autophagy and vacuoles in AP development. In addition, the inhibition of SOCE or CaN decreases the formation of autophagosomes and the severity of vacuoles, edema and inflammation, which supports the hypothesis that CaN is a key regulator of autophagy and inflammation in AP. In summary, CaN-mediated TFEB activation regulates the autophagy of SOCE in AP. Moreover, there is another statement about the signaling pathway that triggers and promotes acute pancreatitis (AP), namely, the pathogenesis of AP has been associated with abnormal increases in cytosolic Ca^{2+}, mitochondrial dysfunction, impaired autophagy and ER stress (80).

Accumulated evidence indicates that interleukin-1β (IL-1β) is important in AP (81,82). IL-1β can stimulate the autophagy of macrophages and induce ER stress (83-86). Among them, ER is an important organelle for calcium storage and can regulate intracellular Ca^{2+} homeostasis. ER stress may cause the ER to release calcium into the cytoplasm (87). Additionally, it has been thought that Ca^{2+} plays an important role in many aspects of the cellular processes involved in pancreatitis (88). Studies have also shown that there is a connection between intracellular Ca^{2+} signaling and autophagy, indicating that elevated free cytoplasmic Ca^{2+} can lead to autophagy activation (89,90). Based on the aforementioned analysis, Xu *et al* (91) hypothesized that IL-1β caused ER stress, resulting in the release of Ca^{2+} into the cytoplasm, and subsequent activation of trypsinogen by AP autophagy damage. The data indicate that IL-1β can induce autophagy damage to acinar cells, and this effect is time-dependent. Besides, studies have shown that ER can release Ca^{2+} into the cytoplasm in response to IL-1β stimulation, and cause a transient oscillation signal of Ca^{2+} mediated by the InsP3 signaling pathway, which increases the cytoplasmic Ca^{2+} in acinar cells. After inhibiting Ca^{2+} signal, the expression of LC3-II and trypsinogen activation were both decreased. In addition, capsaicin is an effective stimulant for TRPV1. Díaz-Laviada and Rodríguez-Henche (92) demonstrated that capsaicin increases intracellular calcium, produces reactive oxygen species, disrupts mitochondrial membrane transition potential, and activates transcription factors such as NFκB and STATS, and triggers AMP-dependent kinases in cell death (AMPK) and autophagy pathways trigger apoptosis in human pancreatic cancer cells (92).

Calcium and calcium channels in gastric diseases regulate autophagy. Gastric cancer (GC) is the fifth most common cancer in the world and ranks third in the cause of death (93). Although the diagnosis and treatment of early GC have been developed, the long-term survival rate of patients with advanced GC is still low (94). Therefore, understanding the basic mechanisms of GC will help elucidate specific molecular targets and develop more effective therapies for the disease. Currently, there is increasing evidence that TRPM2 function is particularly critical in many cellular events by inducing several intracellular pathways (such as oxidative stress signaling, MAPK and autophagy events), including insulin secretion, cytokine production and cell metabolism, temperature-steady state and cell death. In the study by Almasi *et al* (95) it was demonstrated that TRPM2 channel-mediated autophagy regulation maintains mitochondrial function through JNK signaling pathway and promotes the survival of GC cells. The results indicate that TRPM2 regulates autophagy through mechanistic targets of c-Jun N-terminal kinase (JNK)-dependent and rapamycin-independent pathways. In the absence of TRPM2, the downregulation of the JNK signaling pathway impairs autophagy, eventually leading to the accumulation of damaged mitochondria and the death of gastric cancer cells. Acid-sensitive ion channels (ASICs) are insensitive cation channels on the media of the epithelial Na^+ channel/phenylephrine superfamily and are activated by extracellular protons (96,97). According to reports, ASICs can activate autophagy (98,99). In a study by Zhang *et al* (100), it was confirmed that ASIC1 and autophagy were activated in the gastric cancer tissues and cells of patients. ASIC1 regulates autophagy through ATG5 activation. At the same time, in the mouse xenograft model established, ASIC1 or ATG5 knockdown inhibited the growth of cancer cells, while ASIC1 shRNA inhibited tumor volume and prolong the survival time of animals. Therefore, the downregulation of ASIC1 can inhibit GC by inhibiting autophagy (100).

Helicobacter pylori (*H. pylori*) is a common pathogenic bacterium that causes stomach diseases and exhibits severe stomach diseases, including gastritis and gastric malignancies (101). The secreted vacuolar cytotoxin A (VacA) is a key bacterial virulence factor that is inserted into the host cell membrane and essentially acts as a chloride channel (102). It can target mitochondria and may penetrate VacA, resulting in loss of mitochondrial membrane potential, thereby causing mitochondrial autophagy (103). Inhibiting the autophagy of the host's macrophages is one of the strategies used by several pathogen cells (including *H. pylori*) to escape killing. Studies have pointed out that VacA will inhibit the lysosomal calcium channel MCOLN1/TRPML1, resulting in increased lysosomal calcium levels, thereby disrupting the transport events between lysosomes and autophagosomes, late endosomes and plasma membranes, leading to large enzyme-like organelles and autophagic vesicles aggregate, and the autophagic flux is severely damaged, which ultimately promotes the survival of bacteria in the cell (104); the latest research has also confirmed such results (105). For the treatment of *H. pylori*, recent research suggests that vitamin D3 has an ideal anti-*H. pylor*i effect, and can even resist antibiotic-resistant strains (106). Cells treated with vitamin D3 activate the PDIA3 receptor to restore the lysosomal degradation function and promote the nuclear translocation of the PDIA3-STAT3 protein complex, and subsequently upregulate the MCOLN3 channel, resulting in enhanced release of lysosomal Ca^{2+} and lysozyme. The body acidification is normal, and the restored lysosomal degradation function eliminates *H. pylori* through the autolysosome pathway.

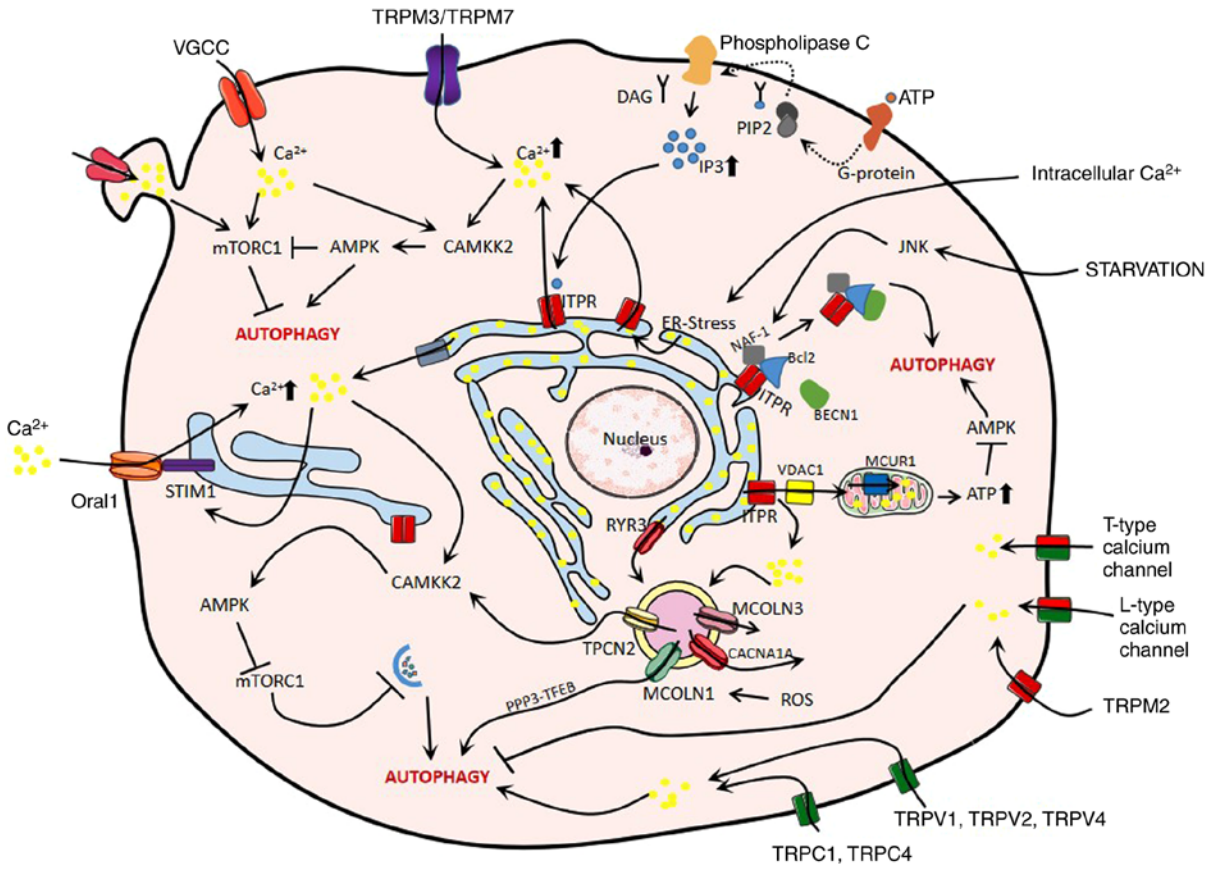

Figure 4. Calcium and calcium channels regulate autophagy in diseases of the digestive system. The inhibitory and stimulating effects of Ca^{2+} on autophagy and calcium permeation channels involved in the regulation of autophagy in the digestive system are depicted. The figure shows the main pathways connecting extracellular and intracellular signals that regulate ion channels and/or ion flow through cellular components of the disease. Changes in (Ca^{2+}) can be induced by increased ion entry in the extracellular environment or release of Ca^{2+} from the ER. Changes in (Ca^{2+}) c can be induced by increased ion entry in the extracellular environment or release of Ca^{2+} from the ER. The most important signal transduction pathways connecting Ca^{2+} and autophagy are the Ca^{2+}-CaMKK2-AMPK pathway and the mTORC1 pathway. The increase in (Ca^{2+}) c can activate the CaMKK2-AMPK pathway, leading to autophagy in an mTOR-dependent or -independent manner. In addition, other changes in mitochondrial Ca^{2+} signaling may also lead to mitochondrial phagocytosis, and Ca^{2+} overload may induce cell death through the mitochondrial pathway. The Ca^{2+} present in lysosomes is not only important for maintaining basal autophagy flux, but is also important to be altered by cells when autophagy is induced. Besides, the cell also activates c-Jun N-terminal kinase, which phosphorylates Bcl-2 and releases BECN1 to induce autophagy. Ca^{2+}, calcium; ER, endoplasmic reticulum.

Calcium and calcium channels in intestinal diseases regulate autophagy. Despite many treatment and screening attempts, colorectal cancer (CRC) remains the main life-threatening malignant tumor (107). Autophagy is known to be associated with various clinical diseases, such as CRC. Emerging research shows that in human cancer, STIM1/Orai1-mediated SOCE is crucial in regulating autophagy-associated mechanisms. A recent study reported that in colorectal cancer cells, the SOCE inhibitor SKF-96365 induces cytoprotective autophagy (108). Calcium antagonist SKF-96365 decreases the concentration of Ca^{2+} by inhibiting SOCE in human colorectal cancer cells, while decreasing the colon cancer cell line through the calcium/calmodulin-dependent protein kinase IIγ (CaMKIIγ)/AKT signaling cascade Akt activity. The present study highlights the unique role of STIM1/Orai1-mediated SOCE in regulating autophagy. In addition, studies have shown that once activated by integrin-mediated adhesion, the hERG potassium channel will form a macromolecular complex with the p85 regulatory subunit of PI3K and regulate the PI3K-Akt pathway, resulting in Akt phosphorylation (109). The latest research on ion channels regulating autophagy affects CRC indicates that clarithromycin (Cla) exerts antiproliferative activity and regulates autophagy through hERG1-dependent PI3K/Akt pathway and p53 regulation, thereby enhancing chemotherapeutic drugs' antitumor effect (110).

Discussion

Autophagy has been studied in detail as a key factor in cell physiology and pathology, which has revealed many intracellular signal transduction pathways and the strict regulation of autophagy by molecules. Among them, the field of interaction between ion channels and autophagy needs further development. Thus far, accumulated data prove that calcium, calcium-permeable ion channel dysfunction and autophagy are associated with several diseases. Thus, calcium, calcium-permeable ion channel and autophagy are potential therapeutic targets. Calcium and calcium-permeable ion channels are considered as autophagy regulators, opening up a new way for targeting autophagy in the treatment of digestive tract diseases. In cancer, changes in ion channel expression are associated with several cancer-associated processes, including autophagy. For example, the TRPV1 channel that targets tumor suppressor (overexpressed in pancreatic cancer and actively regulates autophagy) may be used to

regulate autophagy and tumor cell apoptosis. In different digestive tract diseases, the regulation of autophagy by calcium and the calcium permeable channel is also different. For example, saturated FFA in NAFLD induce increased cytosolic calcium in liver cells, thereby inhibiting autophagy, and the use of calcium channel blockers can reverse this phenomenon, leading to a decrease in steatohepatitis. In HCC, inhibiting the entry of Ca^{2+} mediated by Orai1 can enhance the chemical sensitivity of HepG2 liver cancer cells to 5-FU. For different digestive tract diseases, a deeper understanding of the interaction between calcium, calcium-permeable ion channels and autophagy will be of great value for the diagnosis and treatment of digestive system diseases in the future.

Overall, the data in the present review clearly demonstrate the diversity and particular importance of calcium ion channels in the regulation of autophagy. However, little is known about the mechanism of action of autophagy through calcium channel in the occurrence and development of digestive system diseases and its application in disease treatment. A graphic overview of the calcium and calcium channel-associated mechanisms of autophagy regulation in digestive diseases is presented in Fig. 4. The present review discussed the association between digestive system diseases and autophagy, and reveals the role of autophagy in digestive system diseases, that is, the regulatory mechanism, in order to provide more theoretical basis for the diagnosis and treatment of digestive system diseases.

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Authors' contributions

JL and XXY wrote the manuscript. WXS, ZJ, JHD, YXH, QD and QSL collected the literature. JYX primarily revised and finalized the manuscript. RX revised the manuscript for clarity and style. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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