

Harnessing autophagy: A potential breakthrough in digestive disease treatment

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Abstract

Autophagy, a conserved cellular degradation process, is crucial for various cellular processes such as immune responses, inflammation, metabolic and oxidative stress adaptation, cell proliferation, development, and tissue repair and remodeling. Dysregulation of autophagy is suspected in numerous diseases, including cancer, neurodegenerative diseases, digestive disorders, metabolic syndromes, and infectious and inflammatory diseases. If autophagy is disrupted, for example, this can have serious consequences and lead to chronic inflammation and tissue damage, as occurs in diseases such as Chron's disease and ulcerative colitis. On the other hand, the influence of autophagy on the development and progression of cancer is not clear. Autophagy can both suppress and promote the progression and metastasis of cancer at various stages. From inflammatory bowel diseases to gastrointestinal cancer, researchers are discovering the intricate role of autophagy in maintaining gut health and its potential as a therapeutic target. Researchers should carefully consider the nature and progression of diseases such as cancer when trying to determine whether inhibiting or stimulating autophagy is likely to be beneficial. Multidisciplinary approaches that combine cutting-edge research with clinical expertise are key to unlocking the full therapeutic potential of autophagy in digestive diseases.

Key Words: Autophagy; Digestive disease; Inflammatory bowel disease; Gastrointestinal cancer; Harnessing autophagy

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Core Tip: There are still many unanswered questions regarding the role of autophagy in the onset and development of diseases. Before induction or inhibition of autophagy can be into therapeutic protocols, the mysteries surrounding autophagy need to be solved through detailed experimental studies.

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INTRODUCTION

Autophagy, also known as autophagocytosis, is a conserved cellular degradation process that plays a role in the survival and maintenance of the cell by degrading cytoplasmic organelles, proteins, and macromolecules, and recycling the degradation products. Through a lysosome-dependent, regulated mechanism, autophagy removes unnecessary or dysfunctional components. Autophagy is crucial for maintaining cellular and organismal homeostasis[1,2], facilitating immune responses[3], preventing inflammation[4], adapting to metabolic, oxidative, and inflammatory stress conditions [5,6], supporting energy metabolism[1,7], contributing to various aspects of development[2,8-10], regulating cell proliferation[11], and tissue repair and remodeling[12]. Dysregulation of autophagy has been implicated in numerous diseases, including cancer, neurodegenerative disorders, digestive diseases, metabolic syndromes, and infectious and inflammatory diseases, highlighting its importance in overall health and disease prevention.

Autophagy is a generic term for all pathways by which cytoplasmic materials are released into the lysosomes in animal cells or into the vacuole in plant and yeast cells. The resultant degradation products can be reused in protein synthesis, energy production, and gluconeogenesis[12]. Autophagy refers to the formation of autophagosomes that surround the organelles and proteins that need to be degraded in the cells. The standard pathway of mammalian autophagy includes induction, formation of the phagophore, an isolation membrane, expansion of phagophore to form the autophagosome, and fusion of the autophagosome with the lysosome forming autolysosome where degradation occurs. Phagophores and autophagosomes are double-membraned structures[13,14]. Autophagosomes are formed on or near the endoplasmic reticulum (ER)[13,15]. However, some recent studies suggest that additional membrane sources such as the Golgi complex, mitochondria, and the plasma membrane also contribute to autophagosome formation[13,15-17]. Three-dimensional analysis of correlative light and electron microscopy by Takahashi *et al*[18] shows that ER is associated with all phagophores, 92% of autophagosomes, and 79% of autolysosomes suggesting that most autophagosomes remain on the ER after closure and even fuse with the lysosomes. They also reported that the ER is the organelle most frequently engulfed by phagophores and autophagosomes, with a percentage of 65%. Sometimes the content is undefinable although membranous, and sometimes it is non-membranous but only cytosol. Therefore, the electron microscopic features of the autophagosomes can vary in size and shape, reflecting the diversity of cellular cargo being degraded. Engulfed organelles, cytoplasmic components, cytosol (Figure 1), or pathogens can be observed in the autophagosomes.

Although autophagy was previously thought to be a non-selective degradation mechanism that indiscriminately degrades cytoplasmic components, more recent research has shown that it can be selective in some situations[19]. Depending on which organelle is removed, selective autophagy has different names. For example, if the target cargo is the mitochondria, the process is called mitophagy, if the target cargo is the nucleus, it is called nucleophagy[20]. With most of these names such as ER-phagy, lysophagy, and lipophagy, it is easy to recognize which cellular element is involved in the cargo. Some names such as xenophagy (target is cellular pathogens)[21], allophagy (target is paternal organelles)[22], aggrephagy (target is abnormal protein aggregates)[23] do not give a clear idea of what the content of the cargo is.

Autophagy is broadly divided into macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy. The term autophagy often refers to macroautophagy[19]. The degradation of cargo by macroautophagy enables the recycling of the resultant macromolecules to maintain cellular homeostasis. The substrates of cytoplasmic macroautophagy are entrapped in the autophagosome, a temporary organelle with double membrane that eventually fuses with lysosomes and vacuoles[2,24]. CMA is a type of selective autophagy that focuses on proteins for lysosomal destruction. The supply of free amino acids generated after protein degradation is the main function of this pathway. In addition, CMA influences glucose and lipid metabolism and controls cell metabolism, which in turn influences the body's overall energy metabolism[25]. In microautophagy, autophagic tubing facilitates both the rupture of vesicles and access to the cytoplasmic lumen by directly engulfing the cytoplasmic cargo[26]. In this way, eukaryotic cells directly degrade a variety of autophagic cargoes through a lysosomal degradation process[27]. It contributes to the maintenance of cell survival and homeostasis[26].

A collection of proteins known as class III phosphatidylinositol3-kinase, also known as Vps34, and BH3 domain protein Beclin-1 (BECN1) interacting with B-cell lymphoma 2 (Bcl-2) make up the intracellular machinery of autophagy. Both proteins are required for the development of autophagosomes[28]. The mammalian target of the rapamycin signaling pathway, a serine/threonine kinase involved in various pathways of cell survival, can initiate signal transduction[29].

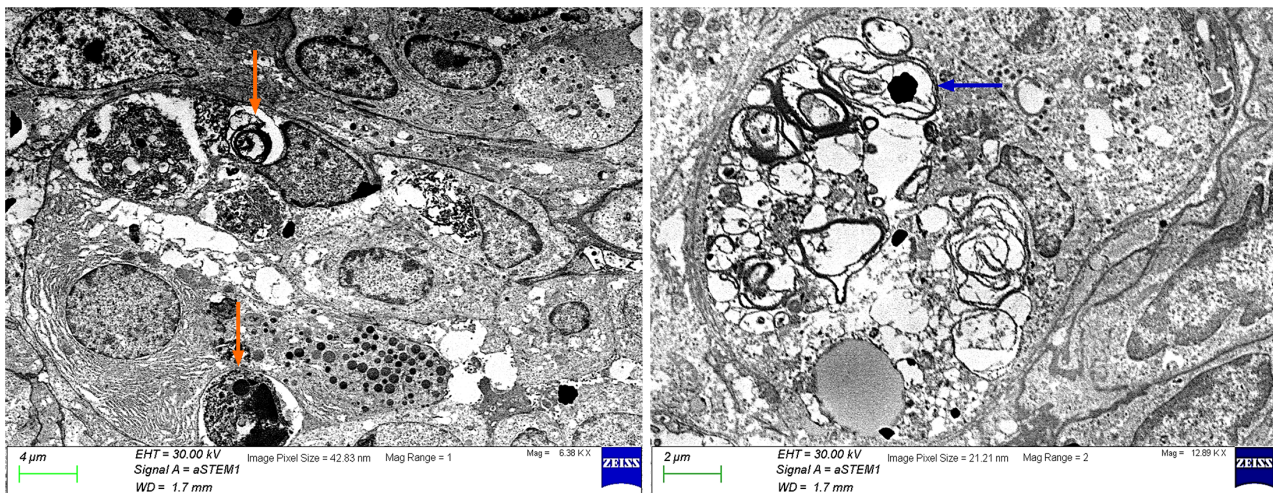


Figure 1 Many autophagosomes in the cytoplasm of pancreas acinar cells in acute pancreatitis are observed (two of those are marked by orange arrows). Double-membrane structure is clearly seen in some areas (marked by a blue arrow).

ROLE OF AUTOPHAGY IN CELL SURVIVAL

Autophagy has been described as a novel mechanism for cell death as well as a stress-adaptive mechanism to support cell survival. In stressful conditions, autophagy ensures that the cells receive the metabolic substrates required for energy for cell growth and survival[30,31]. If carbon sources such as amino acids and glucose are insufficient to maintain the rate of protein synthesis or to provide sufficient amounts of ATP needed to sustain metabolic reactions, cells turn on autophagy to rapidly degrade obsolete and depleted fractions and recycle the available biomolecule library. Through negative feedback, autophagy can be induced to provide energy and building blocks to restore homeostasis while eliminating oxidative damage. From this perspective, cells also need autophagy to overcome oxidative stress[5]. Autophagy delays cell death by removing mitochondria, ER components, peroxisomes, and proteins damaged by oxidative stress. There is a close relationship between autophagy and oxidative stress[32-34]. Accordingly, defects of autophagic genes lead to increased production of reactive oxygen species (ROS) and accumulation of damaged organelles and DNA which in turn promote metabolic reprogramming and induce tumorigenesis[35]. Cancer cells have an increased metabolism for proliferation, and they usually need to grow under hypoxic conditions until angiogenesis is adequately established. As a result, cancer cells, especially those with RAS mutations, which are one of the most common mutations in all malignancies, are highly dependent on and dependent on autophagy[36].

Because the baseline level of autophagy is important for maintaining normal cellular homeostasis which allows physiological turnover of damaged organelles, and cytoplasmic content, it should be tightly regulated. Large-scale degradation is important in autophagic function, but it also carries some risk because unregulated degradation of the cytoplasm is likely to be lethal[37]. The most important lesson is probably that autophagy can be harmful either in excess or insufficient amounts. This is complicated by the fact that autophagy plays a dual role in both cytoprotection and cell death. Since silencing of autophagy-related gene (ATG) results in cell death occurring more rapidly rather than gradually, autophagy is thought to play a cytoprotective role in response to most forms of cellular stress[38,39]. Conversely, if ATG1 is upregulated, the resulting upregulation of autophagy can lead to apoptotic cell death[40]. The mechanisms linking autophagy and apoptosis are not fully understood; however, it is known that many signals that induce activation of apoptosis also induce autophagy, while signals that inhibit apoptosis also inhibit autophagy[41-44]. In addition, several apoptotic proteins such as Bcl-2-associated X protein, NOXA, and NIX modulate autophagy, and several autophagic proteins are implicated in intrinsic and extrinsic apoptosis[44]. The coordinated regulation of 'self-digestion' by autophagy and 'self-killing' by apoptosis may underlie various aspects of development, tissue homeostasis, and disease pathogenesis[37].

CROSSTALK BETWEEN AUTOPHAGY AND THE DIGESTIVE SYSTEM

It is well known that cells in the digestive system, like every part of the body, rely on autophagy to maintain their function and health. For example, basal autophagy metabolizes cytoplasmic components to prevent the accumulation of degenerated proteins and organelles in hepatocytes, thereby preventing hepatocellular degeneration[13]. Loss of ATG7 in mouse hepatocytes has been shown to lead to an accumulation of edematous and deformed mitochondria, an increase in the number of peroxisomes and lipid droplets, and the formation of protein aggregates[45]. The mutant mice suffering from severe hepatomegaly develop hepatitis[46]. In addition, spontaneous benign tumorigenesis is observed in the livers of mice with systemic mosaic deletion of ATG5 or with ATG7-specific disruption in hepatocytes[35].

Similar to the liver, basal autophagy is also important for the maintenance of beta cell volume and function in the endocrine pancreas[13]. Autophagy is necessary to maintain the structure, mass, and function of pancreatic beta cells.

Impairment of autophagy leads to insulin deficiency and hyperglycemia as the turnover and function of cellular organelles are impaired[46].

The most important link between autophagy and the intestinal epithelium is centered on Paneth cells. *In vivo* studies have shown that autophagy or ATG genes play a role in maintaining the normal function of Paneth cells. ATG16L1 hypomorphic mice, which express a very low level of ATG16L1, exhibit structurally abnormal and disorganized Paneth cell granules[47]. ATG5- and ATG7-deficient mice have also shown morphological abnormalities of Paneth cells[48]. The lineage between autophagy and Paneth cells expresses several microbial pattern recognition receptors (PRRs), including nucleotide-binding oligomerization domain-containing protein 2, (NOD2) and Toll-like receptors[49,50], which can stimulate the release of granule contents of Paneth cells[51,52]. The antimicrobial proteins produced by Paneth cells can protect against pathogens and alter the composition of the commensal microbiota[53]. Increased ER stress in autophagy deficiency can lead to abnormalities in Paneth cell and goblet cell functions, and damage the barrier of normal intestinal antimicrobial and mucous proteins, thereby causing continuous inflammatory stimulation and promoting the occurrence of inflammatory bowel diseases (IBDs)[54].

PRRs induce autophagy, and *via* autophagic adaptors, autophagy provides a mechanism for the clearance of intracellular microorganisms. Autophagy controls inflammation by regulating interactions with innate immune signaling pathways, by removing endogenous inflammasome agonists, and by affecting the secretion of immune mediators[55]. In many cases, signaling associated with inflammation may also regulate autophagy. Recent studies suggest that in addition to excessive inflammation, alterations in immune response, and imbalance of gut flora, abnormal autophagy may be associated with IBDs. Single-nucleotide polymorphisms (SNPs) of various genes related to autophagy are associated with susceptibility to IBDs[54].

CROSSTALK BETWEEN AUTOPHAGY AND INTESTINAL DISORDERS

Autophagy has shown promise to understand and treat numerous diseases, including digestive diseases, infectious and inflammatory diseases, and cancers. From IBD to gastrointestinal cancer, researchers are discovering the complex role of autophagy in maintaining gut health and its potential as a therapeutic target. Chron's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD characterized by damage to the intestinal epithelium which forms a barrier between luminal contents and the mucosal immune system. Modulation of tight junctions, leading to increased permeability of the barrier, has been associated with IBDs[56]. The intestinal epithelium disrupted by altered tight junction expression allows more microbiota or luminal antigens to cross the barrier, leading to stimulation of local immune cells, production of chemokines, and subsequent infiltration of immune cells. One of the main mechanisms of chronic long-term inflammation in UC is the excessive inflammation caused by these events[57]. Autophagy and its regulatory mechanisms are involved in both homeostasis and repair of the intestine. They support intestinal barrier function in response to cellular stress by regulating tight junction proteins and protecting against cell death[58,59]. Previous studies have shown that autophagy can increase the expression of occluding *via* terminating its BECN1-mediated endocytosis[60], conversely, it can downregulate claudin-2 *via* lysosomal degradation or TNF-mediated inhibition[59,61,62]. Previous studies have demonstrated that occludin expression is reduced in the colonic mucosa of UC patients and is positively related to intestinal mucosal healing[63].

The association between the polymorphisms of specific autophagy genes including ATG16L1, immunity-related GTPase family M protein, and leucine-rich repeat kinase 2, and susceptibility to CD has been described extensively in the literature[58,64]. For example, the SNP of the ATG16L1 gene are important risk factors for the pathogenesis of CD and are closely associated with CD[65]. Genetic polymorphisms in NOD2 are also associated with the highest risk of developing CD and remain the greatest genetic risk factor[66]. ATG16L1 inhibits pro-inflammatory signaling downstream of NOD2 [67]. Recent studies have shown that NOD2 acts as a sensor for intracellular bacteria by triggering autophagy through interaction with ATG16L1[68]. Interestingly, NOD2 and ATG16L1 have only been associated with CD, but not UC[69]. However, mutations in the X-box binding protein 1 gene, which is involved in the unfolded protein response, as risk factors for both UC and CD[70,71].

Although defects in autophagic genes lead to increased production of ROS and accumulation of damaged organelles and DNA which in turn promote metabolic reprogramming and induce tumorigenesis[35], research indicates that autophagy can either promote or suppress tumor growth, depending on the context. In some cases, autophagy acts as a tumor suppressor, facilitating the clearance of damaged organelles and protein aggregates that might otherwise promote oncogenesis. Conversely, in certain circumstances, autophagy can promote tumor survival and support cancer growth by providing nutrients and alleviating metabolic stress.

Autophagy can regulate the cell cycle thus influence cell proliferation[11,72]. Although the mechanisms underlying the interaction between autophagy and cell proliferation are not clear, various cell cycle proteins regulate autophagy, and autophagy in turn can modulate the expression of cell cycle proteins[11]. Basal autophagy in normal cells prevents carcinogenesis but basal autophagy in tumor cells promotes tumor growth and cancer progression[73]. Disruption of autophagic cell quality control can lead to tumor development. Tumor growth is also related to the supply of nutrients to the cells through the activation of autophagy. Therefore, both inhibition and activation of autophagy contribute to tumor development and growth through different pathways[20]. Recent data suggest that autophagy may promote cancer cell proliferation by degrading cyclin A2 to prevent G2/M cell cycle arrest. Autophagy also regulates cyclin D1 to promote proliferation. Cyclin D1 is frequently overexpressed in cancer cells[74,75]. Current evidence suggests that cyclin D1 is not degraded by autophagy. It is not known whether autophagy-induced promotion/maintenance of cyclin D1 and/or degradation of cyclin A2 is a universal mechanism to promote cancer cell proliferation by autophagy[73]. Reduction of

cyclin D1 and suppression of proliferation in cancer cells can be induced by inhibition of autophagy *via* downregulation of autophagy genes such as RB1-inducible coiled-coil protein 1/focal adhesion kinase family interacting protein of 200 kDa[76], BECN[77], and ATG4B[78]. By contrast, one study reported that knockdown of ATG4B in colorectal cancer cells inhibited cyclin D1 expression, cell proliferation, and tumor growth but increased autophagy flux[79]. In addition, the autophagosome marker light chain 3-II protein is overexpressed in advanced colorectal cancer compared to normal surrounding tissues[80]. Furthermore, the expression of BECN1, a regulatory protein of autophagy, is increased in colorectal and gastric cancers without any significant association with invasion, metastasis, and stage[81].

Altered expression and/or mutations of autophagy genes including BECN, ATG10, and ATG5 have been reported in human gastric and colorectal cancers[82]. Downregulation of several autophagy genes including BECN1, ATG3, and ATG5 result in suppression of proliferation[83,84]. Increased autophagy activity has been found in human colorectal cancer[82,85]. Autophagy may play a role in the development and/or progression of colorectal cancer.

Taken together, autophagy can both suppress and promote cancer progression and metastasis at different stages. This complicates therapeutic intervention and makes it necessary to evaluate the type of tumor cell, its genetic background, the stage of tumor progression, and the tumor microenvironment to achieve the desired effect of autophagy modulation and avoid potential disease exacerbation[6].

CONCLUSION

In recent years, the complicated relationship between dysfunction of autophagy and digestive disorders has become increasingly evident. Autophagy, a self-degradation process, serves as a guardian of gut homeostasis, clearing damaged organelles, combating microbial invaders, and regulating inflammation. If autophagy is disrupted, for example, this can have serious consequences and lead to chronic inflammation and tissue damage, as occurs in diseases such as CD and UC. Targeting autophagy pathways holds immense potential for modulating immune responses, reducing inflammation, and restoring intestinal tissue integrity. Multidisciplinary approaches that combine cutting-edge research with clinical expertise are key to unlocking the full therapeutic potential of autophagy in digestive diseases. Researchers should carefully consider the nature and progression of diseases such as cancer when attempting to determine whether autophagy inhibition or stimulation is likely to be beneficial. For instance, autophagy acts as a tumor suppressor, facilitating the removal of damaged organelles and toxic protein aggregates that could otherwise promote oncogenesis. Conversely, in certain microenvironments or under specific genetic alterations, autophagy can promote tumor survival and fuel cancer growth by providing nutrients and mitigating metabolic stress. Nevertheless, translating autophagy research from the laboratory to the clinic presents its own set of challenges. While preclinical studies have yielded promising results, clinical trials must navigate the complexities of patient heterogeneity, treatment resistance, and off-target effects. Additionally, ensuring the safety and efficacy of autophagy-modulating therapies requires meticulous oversight and rigorous evaluation.

FOOTNOTES

Author contributions: Esrefoglu M designed the overall concept of the manuscript and solely contributed to the writing and editing of the manuscript and reviewing the literature.

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