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Autophagy in intestinal injury caused by severe acute pancreatitis

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Severe acute pancreatitis (SAP) is a potentially lethal disease with considerable morbidity and mortality. It is often accompanied by systemic inflammatory response syndrome, sepsis, and organ dysfunction.[1] It is generally believed that intestinal barrier dysfunction and bacterial translocation (BT) are the primary causes of systemic inflammation and sepsis complications in patients with SAP.[2] Recently, increasing evidence has shown that autophagy plays an important role in intestinal homeostasis. Autophagy can protect the intestinal mucosal barrier during SAP by degrading and recovering the cytoplasmic content of intestinal epithelial cells and damaged organelles, removing invading microorganisms, and participating in antigen presentation and lymphocyte development.[2,3] Therefore, regulating autophagy as a form of treatment for SAP may bring beneficial results.

Autophagy is defined as a catabolic process that is conserved among all eukaryotic organisms. Its main functions are to degrade cytoplasmic content and recover damaged organs and proteins to maintain intracellular homeostasis when cells face stress factors such as starvation. Apart from starvation, autophagy is critical in responding to a diverse range of stressors namely hypoxia, infection, endoplasmic reticulum stress, tissue remodeling, cellular debris breakdown, turnover of damaged organelles, tumor suppression, immune response, and cell death.[3,4] Our current knowledge on autophagy broadly differentiates it into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Among them, CMA is highly specific and has only been described in mammals so far.[4,5] The activation and execution of autophagy can be divided into two stages: (1) signal transmission with molecular switches that induce or turn off autophagy (protein kinase A, mitogen-activated protein kinase, and mammalian target of rapamycin [mTOR]) and (2) the morphologically detectable execution stage: initial (dependent on the Unc-51 like autophagy activating kinase 1 complex), nucleation (dependent on BECLIN1-PtdIns3KC3-ATG14L complex), extension and closure (dependent on Autophagy protein 12 [*Atg12*]-*Atg5* and light chain 3 [LC3]-phosphatidylethanolamine conjugate system), and cycling (dependent on *Atg9*).[4,6]

An intact gut mucosa serves as an effective barrier between the luminal bacterial microbiome as well as stool contents and the systemic circulation.[6] The intestinal mucosal barrier is mainly divided into biological barriers (intestinal microorganisms), immune barriers, and mechanical barriers (intestinal epithelial cells, gap junctions [GJs], and tight junctions [TJs]).[3,7] These barriers maintain host health in different ways, such as promoting the development and maturity of the immune system, limiting the direct contact of microorganisms with the intestinal mucosa, and reducing the possibility of freeing them from the intestinal lumen. In addition, adaptive immunity occurs through dendritic cells (DCs) that continuously sample the bacteria in the lumen to minimize the exposure of resident bacteria to systemic immunity and to keep the immunity of the intestinal mucosa "ignorant" to the microflora.[3,7] TJs between cells are gates or barriers that prevent hydrophilic molecules between adjacent cells from penetrating to the next cell. GJs channels provide direct communication between cells and promote physical adhesion between cells.[8]

Intestine is one of the remote organs that are damaged in the SAP process. It is not only a "victim" of SAP but also further promotes the deterioration of the disease. Intestinal BT is considered to be a central mechanism for the development of AP.[1] Microcirculation disorders, fluid loss in the third space, hypovolemia, visceral vasoconstriction, and ischemia-reperfusion injury can occur in SAP, which can cause intestinal reactive oxygen species (ROS). ROS in the intestine and the storm of inflammatory factors are the main reasons for the damage or obstacles to the mucosal function of the intestinal mucosal barrier. Impaired intestinal barrier function allows a large number of intestinal bacteria and endotoxins to enter the blood and lymph circulation and finally enter the entire internal organs, triggering a "second attack," and causing secondary

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pancreatic infection and sepsis.[2,5,9] Thus, it is very meaningful to protect the intestinal damage during SAP.

Autophagy acts as a double-edged sword in the gut. The various roles of autophagy in regulating homeostasis and inflammation are extremely significant in the context of the intestinal mucosa, where most of the stressors are likely to converge.[3] According to current researches, autophagy is controlled by almost all types of pattern recognition receptors and is also regulated by cytokines and receptors of innate immunity and adaptive immunity. This means that autophagy actively or passively participates in several regulatory pathways, whether in chronic inflammation of the intestine or SAP, which is why researchers are particularly interested in its role in the intestinal mucosa.[4,5] At present, the main functions of autophagy in intestinal mucosal homeostasis are as follows. (1) Eliminate invading microorganisms and toxins. Autophagy can be initiated during the process of host cells taking up bacteria or macrophages actively engulfing bacteria. Other studies reported that *Atg5* contributed to antibiosis, especially by increasing susceptibility to infection and controlling dissemination of *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Salmonella*.[8,10] Moreover, autophagy facilitates the binding of endogenous antigens with major histocompatibility complex-II molecules that are recognized by a cluster of differentiation 4^+ T cells.[4] Autophagy can also sense viral RNA and DNA in the cytoplasm through retinoic acid inducible gene I and cyclic guanosine monophosphate-anti-microbial peptide synthetase, thereby inhibiting the production of type I interferon (IFN-I). The effect is to enhance the resistance of the intestine to the virus.[3,7] (2) Protect the TJs and GJs vesicle turnover of the intestine. Change in paracellular TJs proteins is the main factor that increases intestinal permeability in SAP.[1] Studies have shown that autophagy can increase the TJs barrier function in Caco-2 intestinal stem cells (IECs) by enhancing Claudin-2 (a cation-selective pore-forming protein that plays an important role in TJs and the intestinal barrier) protein's lysosomal degradation.[7] Autophagy can also degrade other abnormal TJ proteins to prevent the release of intestinal toxins and pro-inflammatory cytokines.[1,2] It was recently shown that defects in mitochondria and ER functions induce intestinal permeability, promoting *Escherichia coli* internalization and transcytosis across the epithelium, and these are counteracted by selective autophagy-mediated elimination of intracellular bacteria, which is so-called xenophagy.[8] However, uncontrolled autophagy can destroy the structure of TJs proteins because of excessive degradation, ultimately leading to apoptosis.[2] (3) Maintain the secretion of Paneth cells (PC) and goblet cells. A study showed that autophagy can maintain the secretory function of PC.[6] Many autophagy-related genes, including nucleotide-binding oligomerization domain 2, autophagy-related protein16L1 (ATG16L1), leucine-rich repeat kinase 2, and X-box binding protein 1, exert various effects on PC.[11] Moreover, autophagy controls the development and function of goblet cells, and the $ATG16L1^{T300A}$ polymorphism alters goblet cell morphology.[10] Autophagy deficiency (eg, *Atg5*, *Atg7*, and LC3) in goblet cells reduced mucin production by affecting ROS generation and calcium release from the ER.[8] (4) Balance the immune response of the intestine. Macrophages, DCs, T cells, B cells, and natural killer cells are the important components of the intestinal mucosal immune system. A growing body of evidence has emerged supporting the view that autophagy mediates the crucial functions of triggering and modulating innate and adaptive immune responses such as antigen presentation, cytokines secretion, and antimicrobial peptide production.[3] Autophagy can affect the cytoskeleton or organization of DCs and can also indirectly affect the activation of T cells. The reduction in autophagy levels leads to reduced antigen sampling and interleukin-10 (IL-10) secretion, increased DCs maturation, and increased T-cell proliferation and production of pro-inflammatory type of DCs, which will cause the overgrowth of intestinal bacteria and increase the risk of bacteria being freed from the intestinal cavity.[3,8] (5) Regulate ROS and inflammation. Autophagy, especially mitophagy, by eliminating damaged or superfluous mitochondria, plays a major role in limiting ROS accumulation. Mutations in the autophagy-related genes or autophagy deficiency have an impact on ROS levels via the impaired elimination of dysfunctional mitochondria in several cell types.[6] Understanding the role of autophagy and oxidative stress in SAP-induced intestinal mucosal injury is critical for the development of new therapeutic strategies.[1] Excessive inflammation is also a key factor in intestinal damage. High-mobility group box-1 (HMGB1), the key inflammatory mediator, has a confirmed association with SAP. Studies observed that HMGB1 inhibition ameliorated the disruption of TJs and autophagy exhibited in SAP and adjusted oxidative stress to maintain the internal environment.[2] Kim *et al*[6] showed that ATG16L1-deficient macrophages exhibited Toll/IL-1 receptor domain-containing adaptor or inducing IFN-β dependent activation of the inflammasome, resulting in the production of high amounts of the inflammatory cytokines such as IL-1β and IL-18. Thus, it has been demonstrated that autophagy can modulate cytokine-induced programmed cell death in intestinal epithelium, limiting intestinal inflammation.[8] (6) Produce antifibrosis effects. Autophagy mainly promotes the degradation of fibroblast collagen to exert antifibrotic effects. When autophagy is inhibited, it will aggravate fibrosis. But the degree of fibrosis is related to the level of autophagy in different organ environments. Other studies observed that autophagy seems to inhibit intestinal fibrosis by modulating the function of the innate immune system and the mesenchymal activity.[3,12] (7) Balance intestinal epithelial cells (ISCs) regeneration. The critical role of autophagy in maintaining ISC functions under different physiological conditions has been discovered only in recent years. Recent work has suggested that deletion of the *Atg5* gene in intestinal epithelial cells results in accumulation of mitochondria and ROS in leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5) ISCs and impaired their capacity to induce intestinal regeneration following irradiation. Subsequently, researchers show that loss of *Atg7* induces the p53-mediated apoptosis of $Lgr5^+$ ISCs.[13] Wu *et al*[7] also pointed out that intrinsic autophagy supported ISCs maintenance and promoted the recovery of IECs after radiation-induced injuries. It is suggested that autophagy may play an important role in inducing the self-renewal of ISCs in intestines.[2,10]

In view of the importance of autophagy in various diseases, researchers have great interest in developing potential treatments to regulate this pathway. The disaccharide trehalose, which increases the efficiency of autophagy, reduces pancreatic injury and AP severity in animal models and holds promise as a potential therapeutic agent in AP.[5] Chloroquine (CQ) and its derivatives have been widely used to inhibit autophagy *in vitro* with the benefit of relatively low toxicity. In the dextran sulfate sodium-induced murine colitis model, CQ administration significantly retarded colon length shortening, inflammatory cell infiltration, tissue damage, and body weight loss.[7] Similarly, it was reported that glutamine enhances autophagy in IECs both under basal and stress-induced conditions by regulating mTOR and mitogen-activated protein kinase/p38 pathways, thus limiting stress-induced cellular apoptosis.[8] In addition, recent studies suggested that bone marrow-derived mesenchymal stem cells suppressed autophagy in multiple organs (including the pancreas, small intestine, and lungs) to protect against SAP-induced multiple-organ injury.[14] In the future, with the deepening of related research, we believe that more targeted drugs will be developed.

Patients who survive the SAP process often have some sequelae, such as diabetes, pancreatic exocrine insufficiency, and chronic pancreatitis. At the same time, the high incidence of AP also highlights the urgent need for new treatment methods. The role of autophagy in various diseases has shown exciting results and has become a new research field. However, the mechanism of autophagy in intestinal homeostasis and the potential effects during SAP still require more researches. We hope this review provide a comprehensive perspective revealing the role of autophagy modulators in diseases and opening up a new world for the treatment of SAP.

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Conflicts of interest

None.

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