


Interleukin-22 and acute pancreatitis

A review

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Abstract

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases, and it is divided into 3 types according to its severity: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis. The mortality in severe acute pancreatitis is approximately 15% to 30% due to multiorgan dysfunction and the lack of specific treatment. Interleukin-22 (IL-22) is a member of the Interleukin-10 family, and it can activate several downstream signaling pathways by binding to its receptor complex, thus it is involved in cell differentiation, proliferation, and apoptosis. Some studies have reported the elevated level of IL-22 in patients with AP, which suggests IL-22 may be involved in the pathogenesis of AP. And many studies have shown that IL-22 had a protective effect against AP. This article reviews the characteristics and mechanism of IL-22 and its role in AP to provide insight into the treatment of AP.

Abbreviations: AKT = protein kinase B, also known as PKB, AP = acute pancreatitis, ERK = extracellular regulatory protein kinase, IL-22 = interleukin-22, IL-22BP = IL-22 binding protein, MAP = mild acute pancreatitis, PAP = pancreatitis associated protein, SAP = severe acute pancreatitis, STAT = signal transducer and activator of transcription.

Keywords: acute pancreatitis, autophagy, interleukin-22, signal transducer and activator of transcription 3

1. Introduction

There are various factors that can trigger acute pancreatitis (AP), including gallstones, alcohol abuse, hyperlipidemia, trauma, infections, medication, and so on. The initial event in AP is premature activation of zymogens, which stimulate inflammation and cellular injury via autocrine and paracrine signaling pathways. Interleukin-22 (IL-22), which is produced mainly by activated CD4⁺ T cells, acts by binding to a heterodimeric receptor (consisting of IL-22R1 and IL-10R2), then it activates several signaling pathways and upregulates some genes expression, and it plays a key role in antimicrobial defense, tissue repair, and inflammation.

In the pancreas, IL-22 has been shown to reduce acinar cell apoptosis, enhance acinar cell regeneration, and limit inflammation and fibrosis. Recent studies have reported that IL-22 level is elevated in patients with AP and experimental models of AP. Administration of exogenous IL-22 has been shown to ameliorate AP by reducing pancreatic inflammation and tissue damage, and improving survival rate. Further studies are needed to elucidate the precise mechanism of IL-22 in AP and to evaluate its potential value as a therapeutic target for the treatment of this complex and multifactorial disease.

2. The characteristic of IL-22

2.1. The source of IL-22

IL-22 is a member of the IL-10 cytokine family and is secreted by immune cells. It was first identified in IL-9 treated mouse lymphoma cells^[1] and was initially called IL-10-related T cell-derived inducible factor. Its protein is composed of 179 amino acids in mice and 146 amino acids in humans,^[2] with 79% homology between the 2 species.^[3] The major source of IL-22 is CD4⁺ T cells, including Th22 cells, Th1 cells and Th17 cells, with a small proportion coming from CD8⁺ T cells, natural killer cells, $\gamma\delta$ T cells, and innate lymphocytes. Additionally, non-lymphocyte cells such as fibroblasts, mast cells, macrophages, and neutrophils may also produce IL-22 in response to various pathological stimulus. It has been reported that mast cells have been identified as the major source of IL-22 in patients with dermatitis and psoriasis.^[4]

IL-22 primarily acts on nonimmune cells expressing the homologous IL-22 receptor, which consists of IL-10R2 and IL-22R1 subunits and includes extracellular, transmembrane, and intracellular signaling regions. IL-10R2 is ubiquitous, whereas IL-22R1 is almost exclusively expressed in cells of

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non-hematopoietic origin, and its expression is abundant in the pancreas.^[5,6] IL-22R1 is also expressed in the skin, colon, small intestine, liver, and kidney. However, studies^[7] have reported that hematopoietic cells, especially circulating myeloid cells of primary Sjogren syndrome patients, also express IL-22R1, and IL-18 and IL-22R1 are correlated directly.

In addition to the IL-22 receptor, IL-22 binding protein (IL-22BP) is another receptor of IL-22, and IL-22BP is encoded by 231 amino acids. The extracellular structure of IL-22BP is resembles that of IL-22R1, and there is a 34% homology in amino acid sequences between them.^[8,9] However, IL-22BP lacks intracellular and transmembrane domains, and it is mainly expressed in lymph nodes, spleen, thymus, and the digestive system (such as the stomach, intestine, pancreas, and esophagus). IL-22BP is capable of neutralizing IL-22 activity, and its stable expression in tissues and organs can prevent the pathological increase of IL-22. As a soluble receptor with higher affinity to IL-22 than IL-22R1, IL-22BP can competently inhibit the formation of the IL-22-IL-22R1 complex, thereby affects the function of IL-22. Studies have demonstrated that IL-22BP has a pro-inflammatory effect by interacting with IL-22 and affecting epithelial barrier function.^[10]

2.2. Biological function and mechanism of IL-22

IL-22 performs a range of functions by binding to its receptor complexes, including cell differentiation and mucosal defense and inflammatory, and its function varies by tissue and disease. IL-22 receptor complexes belong to the Class II cytokine receptor family. IL-22 binds to its receptor complexes and activates the classical Janus kinase 1/Tyrosine kinase 2 signaling, subsequently activates the signal transducer and activator of transcription 3 (STAT3), along the mitogen-activated protein kinase pathway, and protein kinase B (AKT or PKB) is also activated.^[11-15] Mitogen-activated protein kinase pathway comprises extracellular regulatory protein kinases, kinase p38, and c-Jun N-terminal kinases. In addition, STAT1^[16] and STAT5 are also targets of IL-22 signaling. STAT3 signaling pathway is the primary signal pathway of IL-22 and its phosphorylation on the serine residue 727 is unique to interleukin.

IL-22 targets cells present in the skin, pancreas, liver, kidney, lungs, and other organs, and it plays significant roles in infections, tissue regeneration, tumors, and autoimmune diseases. A study shows the critical role of IL-22 in regulating intestinal cell homeostasis and promoting epithelial regeneration in inflammatory bowel disease.^[17] It is noteworthy that IL-22 promotes epithelial regeneration, innate defense, and membrane mucus production, with similar effects in healthy individuals and inflammatory bowel disease patients.^[18] Study^[19] in mice with necrotizing enteritis have shown that IL-22 can ameliorate intestinal inflammation by promoting epithelial regeneration. In the liver, IL-22 can regulate STAT3/ERK/Akt signaling pathways, then increases the anti-inflammatory/pro-inflammatory-Kupffer cells ratio, consequently delays the occurrence of liver fibrosis,^[20] and IL-22 alleviates acetaminophen-induced liver injury by enhancing autophagy,^[21] bacteria engineered to produce IL-22 reduced ethanol-induced steatohepatitis.^[22] During intestinal rotavirus infection, production of the IL-22 induced a protective gene expression program in intestinal epithelial cells.^[23] IL-22 exhibits a protective effect in ovalbumin-induced asthma mouse model by inhibiting the inflammatory cell infiltration and the airway hyperresponsiveness.^[24] Studies show that IL-22 alleviates acetaminophen-induced kidney injury by inhibiting mitochondrial dysfunction and inflammatory response.^[25] Additionally, IL-22 activates myocardial STAT3 signaling pathway and prevents myocardial ischemia-reperfusion injury.^[26]

However, IL-22 has a dual function, it demonstrates pathogenicity effect besides its protective effect on tissues and organs. In psoriasis, the significantly elevated plasma IL-22 levels are

correlated with the disease severity, and skin-infiltrated T and natural killer cells are the sources of IL-22 in psoriasis,^[27] while ultraviolet B facilitates skin inflammation by increasing keratinocyte's responsiveness to IL-22,^[28] IL-22 aggravates lupus nephritis by promoting macrophage infiltration.^[29] The elevated expression of IL-22 is also involved in the occurrence and development of malignant tumors. Research has shown that IL-22 promoted the migration and invasion ability of oral squamous cells without increasing their viability.^[30] Another study revealed that IL-22 mediate chemotactic migration of breast cancer cells and macrophage infiltration of bone microenvironment, which achieved through enhancing sphingosine-1-phosphate/sphingosine-1-phosphate receptor signaling,^[31] and IL-22 promoted proliferation and invasion of osteosarcoma cells by activation of STAT3.^[32] Protopsaltis et al^[33] reported that IL-22 could induce endothelial cell proliferation, survival, chemotactic and neo-vascularization in choroid transplantation mice, and blocking IL-22 with antibodies could inhibit tumor angiogenesis, which suggesting that IL-22 maybe a potential therapeutic target for blocking tumor angiogenesis.

3. The mechanism of IL-22 in AP

3.1. Relationship between IL-22 and AP

AP is an inflammation characterized by pancreatic edema, hemorrhage, and necrosis, resulting from the self-digestion of pancreatic tissue due to various causes. Lipase, amylase, phospholipase, and the inflammatory mediators are involved in AP, with or without associated organ dysfunction. The mechanism of pancreatic enzyme activation, aggravating or protective factors are extensively studied. IL-22 is involved in various pancreatic disease processes, such as pancreatic inflammation, pancreatic fibrosis, pancreatic cancer. Research has demonstrated that serum IL-22 levels are significantly elevated in both human and animal models with AP, indicating the association of IL-22 in the occurrence and progression of AP.

A study^[34] found that the increased serum IL-22 levels in AP was not related to the severity of the disease, however, another study^[35] demonstrated that serum IL-22 levels in AP patients had a positive correlation with disease severity, further research is necessary. Xue et al^[36] suggested that IL-22 is involved in the pathogenesis of AP, and activation of the aromatic hydrocarbon receptor can induce the expression of IL-22, which has a protective effect on mice with AP.

3.2. Protective effect and mechanism of IL-22 in AP

Pancreatic acinar cells physiologically synthesize trypsinogen in an inactive form, pancreatic fluid enters the duodenum via the Oddi sphincter, and enterokinases secreted by duodenal mucosa can activate them. Abnormal activation of pancreatic enzymes leads to pancreatic acinar injury in AP, which involves the activation of inflammatory cascade, endoplasmic reticulum stress, and impaired autophagy.^[37,38] Some studies have shown that IL-22 can alleviate acinar cell damage in AP induced by caerulein. Additionally, activation of the Aryl hydrocarbon receptor protects mice from AP by inducing expression of IL-22.^[36] And administration of IL-22 before AP prevented the AP induction in a mild acute pancreatitis (MAP) model, and IL-22 knockout mice had less acinar cell injury but increased inflammatory cell infiltration.^[39] However, in severe acute pancreatitis (SAP) models, IL-22 administration during AP significantly ameliorated the pancreas injury. These researches suggested that IL-22 has protective effect on AP, but the specific mechanisms in MAP and SAP may be different. The specific mechanism of IL-22 in AP is unclear up to now, it may be related to STAT3, autophagy, PAP and so on, and we summarize as follows.

3.2.1. Activating the STAT3 pathway. AP animal model can be induced by caerulein, arginine or intraductal infusion of 5% taurocholic acid separately. Many studies have been conducted to explore the mechanism of IL-22 in patients with AP and AP mice model. IL-22 activates multiple signaling pathways through binding to receptors, and then performs important physiological functions. STAT3 is the predominant signaling pathway of IL-22, and it is known to be activated in acinar cells. STAT3 is activated by Janus kinase, and is involved in various cell physiological functions such as cell proliferation, apoptosis, and differentiation.

Research^[40] indicates that the STAT3/pancreatitis-associated protein 1 (PAP1) pathway has a protective effect on caerulein-induced AP by crossing STAT3 mice with Pdx1-promoter Cre transgenic mice. Moreover, IL-22 can ameliorate lung injury caused by arginine induced SAP through STAT3 pathway,^[41] and IL-22 protects intestinal mucosal barrier in SAP through decreasing colonic mucosal permeability, activating pSTAT3/Reg3 pathway, and restoring fecal microbiota abundance.^[42] It has also been reported^[43] that IL-22 enhanced the expression of antimicrobial peptides and antiapoptotic genes by activating STAT3 signaling pathway, and attenuated L-arginine-induced AP and intestinal mucosa injury in mice.

3.2.2. Autophagy. Autophagy is an evolutionally conserved cytoplasmic degradation process, and basal autophagy can maintain the physiological function of pancreatic acinar cell.^[44] Autophagy comprises 2 steps: the formation of autophagosomes and subsequent fusion of the autophagosome with lysosome to form an autolysosome.

Studies have shown that, due to the dysfunction of key organelle, autophagy is impaired in AP. Autophagy-lysosome fusion is affected, leading to the accumulation of autophagosomes, and excessive autophagy causes premature trypsinogen activation and acinus injury.^[45-48] However, inhibiting autophagy can relieve the AP severity,^[49] and autophagy regulation can ameliorate systemic organ injury and alter the progression of L-arginine or caerulein induced AP in mice.^[50] Studies have indicated that activating the nuclear factor- κ B pathway enhances autophagy of pancreatic acinus cells in AP, and inhibiting this pathway decreases the severity of AP.^[51] Feng et al^[52] found that IL-22 inhibited the autophagy pathway and then ameliorated caerulein-induced AP by combining B-cell lymphoma-2(Bcl-2) and Bcl-XL with Beclin-1, and IL-22 could be a promising drug in the future for the treatment of pancreatitis.

3.2.3. Others. PAP is an acute phase protein produced during AP, comprising PAP2, PAP1, and PAP3, also known as Reg3 α , Reg3 β , and Reg3 γ , respectively. They play an important role in apoptosis, regeneration, inflammation, immunity, etc. This secreted protein has a molecular weight of 16kDa, which is undetectable in normal pancreatic tissues, but it is highly expressed in AP. A study has revealed that PAP can function as a protective agent by inhibiting local and systemic inflammation during AP.^[53] Studies on PAP/HIP knockout mice revealed that while acinar damage was reduced in caerulein-induced MAP, inflammatory infiltration was more severe. Conversely, administration of recombinant PAP/HIP to PAP/HIP (-/-) mice reduced pancreatic inflammation and apoptosis, activated STAT3 and enhanced suppression of cytokine signaling 3 levels.^[54] Another research has shown that the cerulein-induced reduction in cell viability and increase in apoptosis are reversed by overexpression of PAP-1 in PAP-1-transfected cells.^[55] Reg3 levels of IL-22-deficient mice were significantly reduced in caerulein-induced AP, and IL-22 might regulate Reg3 expression in acinar cells via STAT3.^[39]

4. Conclusion

AP, especially SAP, is still a very challenging disease in clinical practice, and its etiology and mechanism were not very clear

up to now. In this paper, we analyzed the biological characteristics of IL-22 and its mechanism in AP. Previous studies have shown that IL-22 has a protective effect on AP animals' models, although the mechanism of MAP and SAP may not be the same. The possible mechanism of IL-22 in AP was investigated from STAT3, autophagy, and PAP. Further investigation of the mechanism of IL-22 in AP is necessary, and this may lead to more favorable outcomes for AP patients, particularly those with SAP.

Author contributions

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References

- [1] Dumoutier L, Louahed J, Renaud JC. Cloning and characterization of IL-10-related T cell-derived inducible factor (IL-TIF), a novel cytokine structurally related to IL-10 and inducible by IL-9. *J Immunol.* 2000;164:1814–9.
- [2] Nagem RA, Colau D, Dumoutier L, et al. Crystal structure of recombinant human interleukin-22. *Structure.* 2002;10:1051–62.
- [3] Dumoutier L, Van Roost E, Colau D, et al. Human interleukin-10-related T cell-derived inducible factor: molecular cloning and functional characterization as an hepatocyte-stimulating factor. *Proc Natl Acad Sci USA.* 2000;97:10144–9.
- [4] Mashiko S, Bouguermouh S, Rubio M, et al. Human mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis. *J Allergy Clin Immunol.* 2015;136:351–9.e1.
- [5] Aggarwal S, Xie MH, Maruoka M, et al. Acinar cells of the pancreas are a target of interleukin-22. *J Interferon Cytokine Res.* 2001;21:1047–53.
- [6] Gurney AL. IL-22, a Th1 cytokine that targets the pancreas and select other peripheral tissues. *Int Immunopharmacol.* 2004;4:669–77.
- [7] Ciccia F, Guggino G, Rizzo A, et al. Interleukin (IL)-22 receptor 1 is over-expressed in primary Sjogren's syndrome and Sjogren-associated non-Hodgkin lymphomas and is regulated by IL-18. *Clin Exp Immunol.* 2015;181:219–29.
- [8] Dumoutier L, Lejeune D, Colau D, et al. Cloning and characterization of IL-22 binding protein, a natural antagonist of IL-10-related T cell-derived inducible factor/IL-22. *J Immunol.* 2001;166:7090–5.
- [9] Kottenko SV, Izotova LS, Mirochnitchenko OV, et al. Identification, cloning, and characterization of a novel soluble receptor that binds IL-22 and neutralizes its activity. *J Immunol.* 2001;166:7096–103.
- [10] Abood RN, McHugh KJ, Rich HE, et al. IL-22 binding protein exacerbates influenza, bacterial super-infection. *Mucosal Immunol.* 2019;12:1231–43.
- [11] Pan H, Hong F, Radaeva S, et al. Hydrodynamic gene delivery of interleukin-22 protects the mouse liver from concanavalin A-, carbon tetrachloride-, and Fas ligand-induced injury via activation of STAT3. *Cell Mol Immunol.* 2004;1:43–9.
- [12] Pickert G, Neufert C, Leppkes M, et al. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J Exp Med.* 2009;206:1465–72.
- [13] Lejeune D, Dumoutier L, Constantinescu S, et al. Interleukin-22 (IL-22) activates the JAK/STAT, ERK, JNK, and p38 MAP kinase pathways in a rat hepatoma cell line. Pathways that are shared with and distinct from IL-10. *J Biol Chem.* 2002;277:33676–82.
- [14] Wang S, Yao Y, Yao M, et al. Interleukin-22 promotes triple negative breast cancer cells migration and paclitaxel resistance through JAK-STAT3/MAPKs/AKT signaling pathways. *Biochem Biophys Res Commun.* 2018;503:1605–9.
- [15] Chen W, Zhang XY, Fan JJ, et al. Tethering Interleukin-22 to Apolipoprotein A-I ameliorates mice from acetaminophen-induced liver injury. *Theranostics.* 2017;7:4135–48.
- [16] Bai L, Fang H, Xia S, et al. STAT1 activation represses IL-22 gene expression and psoriasis pathogenesis. *Biochem Biophys Res Commun.* 2018;501:563–9.

- [17] Zhang X, Liu S, Wang Y, et al. Interleukin-22 regulates the homeostasis of the intestinal epithelium during inflammation. *Int J Mol Med*. 2019;43:1657–68.
- [18] Patnaude L, Mayo M, Mario R, et al. Mechanisms and regulation of IL-22-mediated intestinal epithelial homeostasis and repair. *Life Sci*. 2021;271:119195.
- [19] Mihi B, Gong Q, Nolan LS, et al. Interleukin-22 signaling attenuates necrotizing enterocolitis by promoting epithelial cell regeneration. *Cell Rep Med*. 2021;2:100320.
- [20] Su SB, Qin SY, Xian XL, et al. Interleukin-22 regulating Kupffer cell polarization through STAT3/Erk/Akt crosstalk pathways to extenuate liver fibrosis. *Life Sci*. 2021;264:118677.
- [21] Mo R, Lai R, Lu J, et al. Enhanced autophagy contributes to protective effects of IL-22 against acetaminophen-induced liver injury. *Theranostics*. 2018;8:4170–80.
- [22] Hendrikx T, Duan Y, Wang Y, et al. Bacteria engineered to produce IL-22 in intestine induce expression of REG3G to reduce ethanol-induced liver disease in mice. *Gut*. 2019;68:1504–15.
- [23] Zhang B, Chassaing B, Shi Z, et al. Prevention and cure of rotavirus infection via TLR5/NLRC4-mediated production of IL-22 and IL-18. *Science*. 2014;346:861–5.
- [24] Wang J, Gao S, Zhang J, et al. Interleukin-22 attenuates allergic airway inflammation in ovalbumin-induced asthma mouse model. *BMC Pulm Med*. 2021;21:385.
- [25] Shen Y, Jin X, Chen W, et al. Interleukin-22 ameliorated acetaminophen-induced kidney injury by inhibiting mitochondrial dysfunction and inflammatory responses. *Appl Microbiol Biotechnol*. 2020;104:5889–98.
- [26] Takahashi J, Yamamoto M, Yasukawa H, et al. Interleukin-22 directly activates myocardial STAT3 (Signal Transducer and Activator of Transcription-3) signaling pathway and prevents myocardial ischemia reperfusion injury. *J Am Heart Assoc*. 2020;9:e014814.
- [27] Wolk K, Witte E, Wallace E, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Eur J Immunol*. 2006;36:1309–23.
- [28] Kim Y, Lee J, Kim J, et al. The pathogenic role of interleukin-22 and its receptor during UVB-induced skin inflammation. *PLoS One*. 2017;12:e0178567.
- [29] Hu L, Hu J, Chen L, et al. Interleukin-22 from type 3 innate lymphoid cells aggravates lupus nephritis by promoting macrophage infiltration in lupus-prone mice. *Front Immunol*. 2021;12:584414.
- [30] Komine-Aizawa S, Aizawa S, Takano C, et al. Interleukin-22 promotes the migration and invasion of oral squamous cell carcinoma cells. *Immunol Med*. 2020;43:121–9.
- [31] Kim EY, Choi B, Kim JE, et al. Interleukin-22 mediates the chemotactic migration of breast cancer cells and macrophage infiltration of the bone microenvironment by potentiating S1P/S1PR signaling. *Cells*. 2020;9:131.
- [32] Li P, Shi X, Xu Y, et al. Interleukin-22 promotes osteosarcoma cell proliferation and invasion via STAT3 activation. *Med Sci Monit*. 2018;24:7802–8.
- [33] Protosaltis NJ, Liang W, Nudleman E, et al. Interleukin-22 promotes tumor angiogenesis. *Angiogenesis*. 2019;22:311–23.
- [34] Vasseur P, Devaure I, Sellier J, et al. High plasma levels of the pro-inflammatory cytokine IL-22 and the anti-inflammatory cytokines IL-10 and IL-1ra in acute pancreatitis. *Pancreatol*. 2014;14:465–9.
- [35] Zhang JL, Chen WD, Wang XY. Expression and significance of IL-22 in serum of patients with acute pancreatitis. *J Hepatobiliary Surg*. 2010;29:214–6. in Chinese
- [36] Xue J, Nguyen DT, Habtezion A. Aryl hydrocarbon receptor regulates pancreatic IL-22 production and protects mice from acute pancreatitis. *Gastroenterology*. 2012;143:1670–80.
- [37] John DS, Aschenbach J, Krüger B, et al. Deficiency of cathepsin C ameliorates severity of AP by reduction of neutrophil elastase activation and cleavage of E-cadherin. *J Biol Chem*. 2019;294:697–707.
- [38] Biczó G, Vegh ET, Shalbueva N, et al. Mitochondrial dysfunction, through impaired autophagy, leads to endoplasmic reticulum stress, deregulated lipid metabolism, and pancreatitis in animal models. *Gastroenterology*. 2018;154:689–703.
- [39] Huan C, Kim D, Ou P, et al. Mechanisms of interleukin-22's beneficial effects in acute pancreatitis. *World J Gastrointest Pathophysiol*. 2016;7:108–16.
- [40] Shigekawa M, Hikita H, Kodama T, et al. Pancreatic STAT3 protects mice against caerulein-induced pancreatitis via PAPI1 induction. *Am J Pathol*. 2012;181:2105–13.
- [41] Qiao YY, Liu XQ, Xu CQ, et al. Interleukin-22 ameliorates acute severe pancreatitis-associated lung injury in mice. *World J Gastroenterol*. 2016;22:5023–32.
- [42] Jin M, Zhang H, Wu M, et al. Colonic interleukin-22 protects intestinal mucosal barrier and microbiota abundance in SAP. *FASEB J*. 2022;36:e22174.
- [43] Bai JX, Bai JY, Yang M. Interleukin-22 attenuates AP-associated intestinal mucosa injury in mice via STAT3 activation. *Gut Liver*. 2021;15:771–81.
- [44] Antonucci L, Fagman JB, Kim JY, et al. Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. *Proc Natl Acad Sci USA*. 2015;112:E6166–74.
- [45] Mareninova OA, Hermann K, French SW, et al. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. *J Clin Invest*. 2009;119:3340–55.
- [46] Gukovskaya Anna S, Gukovsky I, Algül H, et al. Autophagy, inflammation, and immune dysfunction in the pathogenesis of pancreatitis. *Gastroenterology*. 2017;153:1212–26.
- [47] Wang S, Ni HM, Chao X, et al. Impaired TFEB mediated lysosomal biogenesis promotes the development of pancreatitis in mice and is associated with human pancreatitis. *Autophagy*. 2019;15:1954–69.
- [48] Fortunato F, Burgers H, Bergmann F, et al. Impaired autolysosome formation correlates with Lamp-2 depletion: role of apoptosis, autophagy, and necrosis in pancreatitis. *Gastroenterology*. 2009;137:350–60.e5.
- [49] Yang H, Ma S, Guo Y, et al. Bidirectional effects of pyrrolidine dithiocarbamate on severe acute pancreatitis in a rat model. *Dose Response*. 2019;17:1559325819825905.
- [50] Wan J, Chen J, Wu D, et al. Regulation of autophagy affects the prognosis of mice with severe acute pancreatitis. *Dig Dis Sci*. 2018;63:2639–50.
- [51] Yang S, Bing M, Chen F, et al. Autophagy regulation by the nuclear factor κB signal axis in acute pancreatitis. *Pancreas*. 2012;41:367–73.
- [52] Feng D, Park O, Radaeva S, et al. Interleukin-22 ameliorates Cerulein-induced pancreatitis in mice by inhibiting the autophagic pathway. *Int J Biol Sci*. 2012;8:249–57.
- [53] Zhang H, Kandil E, Lin YY, et al. Targeted inhibition of gene expression of pancreatitis-associated proteins exacerbates the severity of acute pancreatitis in rats. *Scand J Gastroenterol*. 2004;39:870–81.
- [54] Gironella M, Folch-Puy E, LeGoffic A, et al. Experimental acute pancreatitis in PAP/HIP knock-out mice. *Gut*. 2007;56:1091–7.
- [55] Yu JH, Lim JW, Kim H. Pancreatitis-associated protein-1 suppresses apoptosis in cerulein-stimulated pancreatic acinar cells in response to nuclear factor-κB activation. *J Physiol Pharmacol*. 2019;70:849–57.