Published in final edited form as:
Curr Opin Gastroenterol. 2014 September ; 30(5): 495–499. doi:10.1097/MOG.0000000000000097.

The Conspiracy of Autophagy, Stress and Inflammation in Acute Pancreatitis

Jason C. Hall and **Howard C. Crawford**
Department of Cancer Biology, Mayo Clinic, Jacksonville Florida

Abstract

Purpose of review—Acute pancreatitis (AP) is associated with alcohol abuse, gallstones and bacterial infection. Its basic etiology is tissue destruction accompanied by an innate inflammatory response, which induces epithelial stress pathways. Recent studies have focused on some of the integral cellular pathways shared between multiple pancreatitis models that also suggest new approaches to detection and treatment.

Recent findings—Several models of pancreatitis have been associated with stress responses, such as endoplasmic reticulum (ER) and oxidative stress together with the induction of a defective autophagic pathway. Recent evidence reinforces the critical role of these cellular processes in pancreatitis. A member of the the Toll-Like Receptor family, TLR4, which is known to contribute to disease pathology in many models of experimental pancreatitis, has been found to be a promising target for treatment of pancreatitis. Interestingly, a direct activator of TLR4,, the bacterial cell wall component in Gram negative bacteria lipopolysaccharide (LPS), contributes to the onset and severity of disease when combined with additional stressors, such as chronic alcohol feeding, however recent studies have shown that acute infection of mice with live bacteria is alone sufficient to induce acute pancreatitis.

Summary—In the last several months, the convergent roles of acinar cell stress, autophagy and proinflammatory signaling initiated by the toll-like receptors have been emphatically reinforced in the onset of acute pancreatitis.

Keywords

Autophagic flux; Salmonella; Endoplasmic reticulum stress; gallstones

Introduction

Acute pancreatitis, the sudden inflammation of the pancreas, is the most common cause of digestive system related hospitalization in the United States [1]. Acute pancreatitis ranges in severity from mild interstitial pancreatitis to a more severe condition associated with rampant necrosis and concomitant multi-organ failure. Symptoms may include intense

Author of correspondence: Howard C. Crawford, Address: 4500 San Pablo Road, Jacksonville, FL 32224, Telephone: 904-953-6657, crawford.howard@mayo.edu.

Conflicts
None

abdominal pain together with increases in circulating digestive enzymes, a result of pancreatic acinar cell damage and death. The onset of acute pancreatitis is commonly associated with alcohol abuse or ductal obstruction caused by gallstones, with ~30% of cases remaining idiopathic in nature [2,3]. While a potentially deadly disease on its own, multiple bouts of acute pancreatitis can lead to unresolvable chronic pancreatitis, which is in turn a risk factor for the formation of pancreas cancer [2].

Several animal models of acute pancreatitis have been utilized over the last few decades to elucidate the cellular pathways whose dysregulation contributes to acute pancreatitis in human patients. For instance, chronic alcohol feeding on its own is not sufficient to induce pancreatitis in rodents, consistent with a low incidence of alcoholics developing pancreatitis [4,5]. However, alcohol sensitizes the pancreas to a subsequent insult, such as exposure to bacterial LPS, high fat diet or the pancreatic secretagogue cerulein [6–8]. A major contribution of chronic alcohol abuse appears to be the induction of endoplasmic reticulum (ER) and oxidative stress on the pancreatic acinar cell which can lead to an induction of autophagy [9]

Macroautophagy (henceforth, “autophagy”) is a process by which damaged organelles and large molecules are destroyed, as a mechanism to both relieve cellular stress and to provide nutrients to aid in cell survival[10]. The process involves the formation of an “autophagosome” to which accumulated dysfunctional cargo are delivered. The final stage of autophagy involves the fusion of the autophagosome with the lysosome where the contents are degraded to their molecular components and recycled. In some situations, however, the “autophagic flux” is impaired; that is, autophagy has commenced, but the contents of the autophagosome are not degraded due to lysosomal dysfunction or a failure of autophagosome/lysosome fusion [11]. This could lead to the accumulation of defective organelles and mis-folded proteins. Defective autophagic flux is a common observation in experimental pancreatitis and is responsible for intracellular digestive enzyme activation [11].This inadvertent activation of destructive enzymes had been hypothesized to lead to parenchymal autodigestion and cell death. Recent evidence has suggested that premature activation of digestive enzymes does increase cellular damage, but is neither necessary nor sufficient to induce pancreatitis [12].

This article reviews recent studies that have reinforced the importance of these stress pathways, together with activation of proinflammatory signaling originating from damaged acinar cells. Molecules that are hallmarks and drivers of acute pancreatitis have been explored, suggesting new therapeutic options. Finally mouse models of pancreatitis induced by Salmonella infection have been developed.

ER stress and autophagy

Experimental pancreatitis in mouse models has established a connection between pancreatitis and the induction of an autophagic response that has impaired autophagic flux [13,14]. This defective autophagic response has been experimentally linked to the intracellular activation of trypsinogen [11], which, was thought to be the primary mechanism of the onset of acute pancreatitis. However, mice with genetic trypsinogen

ablation are still susceptible to acute pancreatitis, though they are more protected from acinar cell damage [12]. Cellular debris resulting from a necrotic response was once thought to be a primary incitement for the inflammatory response, though now this is more likely a result of other pathways within the epithelium that control cytokine production from the acinar cells, including NFkB [15] and EGFR [16].

This leaves the question of whether defective autophagy plays a different active role in pancreatitis onset or if it, too, is merely a symptom of the disease. A probable answer to this question comes from Karin and colleagues who created a mouse model in which Inhibitor of Kappa B Kinase alpha (IKKα) is genetically ablated from the pancreas [17]. IKKs are major regulators of the NFκB pathway, which has been repeatedly linked to pancreatitis pathology[18–21]. IKKα knockout mice develop an acute pancreatitis phenotype marked by a significant increase in serum lipase and amylase, but with no significant change in trypsin activation in the tissue, reinforcing that promiscuous trypsin activity is not necessary for pancreatitis onset. Instead, acinar cells in the IKKα mutant mice die via apoptosis together with compensatory regenerative and an inflammatory response [17]. Eventually, the mice progress to a chronic pancreatitis phenotype.

Surprisingly, pancreatitis induced by ablation of IKKα is independent of both its kinase activity and regulation of NFκB signaling. Instead, IKKα ablation induces autophagy with a defective autophagic flux, presumably due to a previously undiscovered function of the IKKα protein in complex with the autophagy regulator ATG16L2 [17]. p62, a chaperone protein that brings ubiquitinated cargo to the autophagosome for destruction and, in the process, is degraded itself. Impaired autophagic flux in IKKα mutant mice causes the accumulation of p62 and its ubiquitinated cargo, which together form protein aggregates. Interestingly, genetic ablation of p62 from the IKKα null background relieves the ER and oxidative stress as well as the pancreatitis phenotype, suggesting that p62 aggregates play an active role in inducing pancreatitis. Importantly, both IKKα loss and p62 accumulation was noted in human chronic pancreatitis samples, suggesting that this pathway may be relevant to the onset of pancreatitis in patients. Together with numerous other studies implicating defective autophagic flux in pancreatitis onset, this study strongly suggests that p62 accumulation may be the primary causation in these models as well. This and other studies examining known and novel autophagy-associated proteins suggest a variety of potential biomarkers for pancreatitis assessment[22].

In a study suggestive of a new target for pancreatitis treatment, T-cell protein tyrosine phosphatase (TCPTP) is found to be induced in acinar cells during acute pancreatitis [23]. Genetic ablation of TCPTP reduced the severity of acute pancreatitis as measured by serum levels of digestive enzymes. TCPTP ablation also abrogated the induction of NFκB activity and expression of proinflammatory cytokines. In the course of examining the NFκB pathway, this study also shows that cerulein treatment induces both the expression and phosphorylation of IKKα, both of which are abrogated in the TCPTP knockout background. Significantly, TCPTP knockout animals also show decreased ER stress and cell death response [23], implicating some of the same pathways as the IKKα knockout study.

The common links of cellular stress and an induced autophagic response in pancreatitis models raises the question what the relevant effects of these responses are to disease onset and progression. Impaired autophagic flux has been implicated in increasing the inflammatory response [14]. The strong association between autophagy and pancreatitis suggests that activation of the process should be examined regardless of the inciting agent. For instance, it was recently shown that low extracellular pH sensitizes acinar cells to cerulein-induced damage by inducing an autophagic process that leads to the degradation of connexin 32 (Cx32)[24], a protective gap junctional channel protein. The importance of autophagy in the induction of pancreatitis is still being examined, with each new finding leading to new potential methods to manage this disease

TLR activation and Bacterial Infection

Bacterial infection has been implicated repeatedly in acute pancreatitis onset[25]. Infection has also been implicated in alcoholic pancreatitis as lipopolysaccharide (LPS) levels are often elevated in the serum of chronic alcoholics [26]. LPS signals through the toll like receptors (TLRs) which can activate proinflammatory responses in part by activating caspase-1 release of IL1β and the NFκB pathway[27,28]. The most prominent TLR-induced response originates from the inflammatory cells, inducing a macrophage influx into the pancreas and other organs. However, acinar cells are also known to express TLRs and to respond to LPS [29,30]. Treatment of mice with bacterial LPS has been shown to insufficient to induce pancreatitis in animals, although it can contribute to pancreatitis onset when combined with other stimuli including alcohol or cerulein administration [6,8]. In a study of LPS/cerulein induced acute pancreatitis, Hoque et al. demonstrate that treatment with lactate abrogates TLR4 signaling in macrophages via activation of the G-protein coupled receptor GPR81 [28]. Most importantly, lactate treatment of mice after the incitement of pancreatic damage very effectively reduces acinar cell necrosis and tissue inflammation, strongly suggesting lactate as an effective treatment of acute pancreatitis, a notion supported by a recent clinical trial [31,32].

In a similar study, Xue et al, found that the administration of the carbon monoxide releasing molecule CORM-2 was able to strongly ameliorate both cerulein-induced acute pancreatitis and choline-deficient diet supplemented with ethanolamine (CDE)-induced hemorrhagic acute pancreatitis, after the onset of damage [33]. Impressively, CORM-2 treatment virtually eliminated the morbidity and extensive lung damage induced by the CDE diet, in addition to blocking progressive pancreatic damage. Similar to lactate, CORM-2 blocked TLR4 activation on macrophages by LPS in vitro. Furthermore, CORM-2 treatment reduced TLR4/MD2 (which together constitute the active TLR signaling receptor) expression on the cell surface in vitro and after acute pancreatitis onset in vivo. Bone marrow transplant of wild type mice with TLR4 knockout bone marrow protected wild type mice from cerulein-induced pancreatitis and CORM-2 treatment did not increase protection from damage in the transplanted mice, suggesting that inflammatory cell TLR4 is the relevant target for CORM-2. Using this knowledge and recognizing the potential toxicity of systemic administration of CORM-2 to pancreatitis patients, the authors then demonstrate that CORM-2 primed Cd11b+ cells (monocytes/macrophages) protected against cerulein induced acute pancreatitis when adoptively transferred in the course of cerulein treatments.

Though LPS treatment usually requires an additional stimulant to induce pancreatitis, two recent studies, including one from our laboratory, show that live bacterial infection is sufficient to induce pancreatitis in mice [34,35]. Both studies demonstrate that acute and sustained Salmonellae infection can initiate a systemic and complex inflammatory response, leading to acute and chronic pancreatitis phenotypes, respectively. Both studies also show that the bacteria can directly colonize the pancreas, and can invade acinar cells. Interestingly, Gonzalez-Escobedo, et al. show that Salmonellae biofilms can associate with gallstones for up to a year in mice [35]. It is tempting to hypothesize that this persistent infection may contribute directly to the connection between gallstones and pancreatitis, in addition to damage caused by ductal obstruction.

One major difference between live bacterial infection and LPS treatment is the inflammatory response elicited by the two treatments. LPS induces only a minor neutrophil response, whereas live bacterial infection is accompanied by a robust neutrophil response [34], possibly in the response to the direct colonization of the tissue by the bacteria. Neutrophils are well known to cause oxidative stress in the parenchymal tissues they infiltrate[36], possibly mimicking the ER and oxidative stress induced by chronic alcohol feeding or cerulein treatment needed to complement LPS activation of TLR4. The inflammatory response also includes macrophage and myeloid suppressor cell infiltration which are known to contribute to disease pathology [33,37]. Also, the inflammation in the live infection is strikingly more focal than with LPS treatment, suggestive of a reaction to the direct invasion of the Salmonellae into some acinar cells [34].

Induction of an inflammatory response is critical to disease establishment. However, Salmonella invasion of acinar cells can potentially activate some of the epithelial responses associated with other experimental pancreatitis models. *Salmonella* infection induces activation of a process known as “xenophagy” where the autophagic response is brought to bear to destroy the pathogen [38]. p62 assembles on the microbes to direct them to the autophagosome. This response involves the phosphorylation of p62 and the induction of Nrf2, an indicator of oxidative stress. Thus, bacterial invasion of the acinar cells is capable of evoking a cell autonomous response similar to what is found in in more reductive models of pancreatitis. It will be interesting to examine if *Salmonella* infection also induces an impaired autophagic flux in acinar cells together with stress and other pro-inflammatory pathways.

Conclusions

Acute pancreatitis is strongly associated with the activation of the pro-inflammatory NFκB pathway[21], often through activation of TLR4 on both inflammatory and acinar cells, in collaboration with cellular stress and a defective autophagic flux in the acinar cells. Systemic TLR4 activation by LPS is sufficient to induce an inflammatory response that includes extensive infiltration into the pancreas, but not sufficient to induce the acinar cell stress responses that are equally complicit in disease pathology[34]. On the other hand, targeting TLR4 activity is emerging as a very effective method of ameliorating pancreas damage even after disease onset [28,33], suggesting that, even though its activation is not sufficient to induce pancreatitis, it is necessary.

Coxsackievirus has long been known to be an infectious agent that, by itself, is capable of inducing pancreatitis in patients and animal models, in part due to its direct infection of the pancreatic cells[39]. Consistent with other pancreatitis models, coxsakievirus infection induces autophagy within the cells the virus infects [40]. Now we know that *Salmonella* infection is capable of direct invasion of pancreas cells and capable of inducing a pancreatitis response. Future studies will determine of *Salmonella*-induced xenophagy is also required for pancreatitis onset or whether inflammatory cells attacking the infected acinar cells is sufficient to produce sufficient cellular stress.

Doubtless, the last year has left us with intriguing questions regarding the pathology of acute pancreatitis. For instance, does blocking the inflammatory responses with lactate or CORM-2 also ameliorate the defective autophagic flux in the models tested? Can restoration of normal autophagic flux restore tissue homeostasis? Do gallstones contribute to recurrent pancreatitis by harboring a persistent *Salmonella* infection? Does antibiotic therapy fully resolve *Salmonella* induced disease after it is initiated? Answering these questions will guide us down an intriguing path to understanding how inflammatory and autophagy signaling conspire to determine the fate of pancreatitis and how we may be able to effectively break up this conspiracy.

Acknowledgements

Supported by National Institutes of Health (NIH) grants R01CA 159222 and R01CA136754 to H.C.C

Abbreviations

TLR	Toll-like receptor
LPS	lipopolysaccharide
IKK	Inhibitor of kappa B Kinase
NFκB	Nuclear Factor kappa B
TCPTP	T-cell Protein Tyrosine Phosphatase
CORM2	Carbon Monoxide Releasing Molecule 2
ER	Endoplasmic Reticulum

References and recommended reading

Papers of particular interest, published within the annual period of review, (18 months/ 2012–2013) have been highlighted as:

• of special interest

•• of outstanding interest

1. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, et al. Burden of gastrointestinal disease in the united states: 2012 update. Gastroenterology. 2012; 143(5):1179–1187. e1171–e1173. [PubMed: 22885331]

2. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013; 144(6):1252–1261. [PubMed: 23622135]
3. Testoni PA, Caporuscio S, Bagnolo F, Lella F. Idiopathic recurrent pancreatitis: Long-term results after ercp, endoscopic sphincterotomy, or ursodeoxycholic acid treatment. Am J Gastroenterol. 2000; 95(7):1702–1707. [PubMed: 10925971]
4. Li J, Guo M, Hu B, Liu R, Wang R, Tang C. Does chronic ethanol intake cause chronic pancreatitis?: Evidence and mechanism. Pancreas. 2008; 37(2):189–195. [PubMed: 18665082]
5. Dufour MC, Adamson MD. The epidemiology of alcohol-induced pancreatitis. Pancreas. 2003; 27(4):286–290. [PubMed: 14576488]
6. Fortunato F, Gates LK Jr. Alcohol feeding and lipopolysaccharide injection modulate apoptotic effectors in the rat pancreas in vivo. Pancreas. 2000; 21(2):174–180. [PubMed: 10975712]
7. Tsukamoto H, Towner SJ, Yu GS, French SW. Potentiation of ethanol-induced pancreatic injury by dietary fat. Induction of chronic pancreatitis by alcohol in rats. Am J Pathol. 1988; 131(2):246–257. [PubMed: 3358454]
8. Ponnappa BC, Marciniak R, Schneider T, Hoek JB, Rubin E. Ethanol consumption and susceptibility of the pancreas to cerulein-induced pancreatitis. Pancreas. 1997; 14(2):150–157. [PubMed: 9057187]
9. Deegan S, Saveljeva S, Gorman AM, Samali A. Stress-induced self-cannibalism: On the regulation of autophagy by endoplasmic reticulum stress. Cell Mol Life Sci. 2013; 70(14):2425–2441. [PubMed: 23052213]
10. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet. 2009; 43:67–93. [PubMed: 19653858]
11. Mareninova OA, Hermann K, French SW, O'Konski MS, Pandol SJ, Webster P, Erickson AH, Katunuma N, Gorelick FS, Gukovsky I, Gukovskaya AS. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. J Clin Invest. 2009; 119(11):3340–3355. [PubMed: 19805911]
12. Sah RP, Dudeja V, Dawra RK, Saluja AK. Cerulein-induced chronic pancreatitis does not require intra-acinar activation of trypsinogen in mice. Gastroenterology. 2013; 144(5):1076–1085. e1072. [PubMed: 23354015]
13. Gukovsky I, Pandol SJ, Mareninova OA, Shalbueva N, Jia W, Gukovskaya AS. Impaired autophagy and organellar dysfunction in pancreatitis. J Gastroenterol Hepatol. 2012; 27(Suppl 2): 27–32. [PubMed: 22320913]
14. Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: Common features in the pathogenesis of pancreatitis and pancreatic cancer. Gastroenterology. 2013; 144(6):1199–1209. e1194. [PubMed: 23622129]
15. Huang H, Liu Y, Daniluk J, Gaiser S, Chu J, Wang H, Li ZS, Logsdon CD, Ji B. Activation of nuclear factor-kappab in acinar cells increases the severity of pancreatitis in mice. Gastroenterology. 2013; 144(1):202–210. [PubMed: 23041324]
16. Ardito CM, Gruner BM, Takeuchi KK, Lubeseder-Martellato C, Teichmann N, Mazur PK, Delgiorno KE, Carpenter ES, Halbrook CJ, Hall JC, Pal D, et al. Egf receptor is required for kras-induced pancreatic tumorigenesis. Cancer cell. 2012; 22(3):304–317. [PubMed: 22975374]
17. Li N, Wu X, Holzer RG, Lee JH, Todoric J, Park EJ, Ogata H, Gukovskaya AS, Gukovsky I, Pizzo DP, VandenBerg S, et al. Loss of acinar cell ikkalpha triggers spontaneous pancreatitis in mice. J Clin Invest. 2013; 123(5):2231–2243. [PubMed: 23563314]
18. Chen X, Ji B, Han B, Ernst SA, Simeone D, Logsdon CD. Nf-kappab activation in pancreas induces pancreatic and systemic inflammatory response. Gastroenterology. 2002; 122(2):448–457. [PubMed: 11832459]
19. Vaquero E, Gukovsky I, Zaninovic V, Gukovskaya AS, Pandol SJ. Localized pancreatic nf-kappab activation and inflammatory response in taurocholate-induced pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2001; 280(6):G1197–G1208. [PubMed: 11352813]
20. Lawrence T. The nuclear factor nf-kappa b pathway in inflammation. Cold Spring Harb Perspect Biol. 2009; 1(6)
21. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. Current Opinion in Gastroenterology. 2013; 29(5):523–530. [PubMed: 23892538]

22. Zhang L, Zhang J, Shea K, Xu L, Tobin G, Knapton A, Sharron S, Rouse R. Autophagy in pancreatic acinar cells in caerulein-treated mice: Immunolocalization of related proteins and their potential as markers of pancreatitis. Toxicol Pathol. 2014; 42(2):435–457. [PubMed: 23640381]
23. Bettaieb A, Xi Y, Hosein E, Coggins N, Bachaalany S, Wiede F, Perez S, Griffey SM, Sastre J, Tiganis T, Haj FG. Pancreatic t cell protein-tyrosine phosphatase deficiency ameliorates cerulein-induced acute pancreatitis. Cell Commun Signal. 2014; 12(13)
24. Reed AM, Kolodecik TR, Husain SZ, Gorelick FS. Low ph enhances connexin32 degradation in the pancreatic acinar cell. Am J Physiol Gastrointest Liver Physiol. 2014
25. Schmid SW, Uhl W, Friess H, Malfertheiner P, Buchler MW. The role of infection in acute pancreatitis. Gut. 1999; 45(2):311–316. [PubMed: 10403749]
26. Vonlaufen A, Xu ZH, Daniel B, Kumar RK, Pirola R, Wilson J, Apte MV. Bacterial endotoxin: A trigger factor for alcoholic pancreatitis? Evidence from a novel, physiologically relevant animal model. Gastroenterology. 2007; 133(4):1293–1303. [PubMed: 17919500]
27. Rock KL, Latz E, Ontiveros F, Kono H. The sterile inflammatory response. Annu Rev Immunol. 2010; 28:321–342. [PubMed: 20307211]
28. Hoque R, Farooq A, Ghani A, Gorelick F, Mehal WZ. Lactate reduces liver and pancreatic injury in toll-like receptor- and inflammasome-mediated inflammation via gpr81-mediated suppression of innate immunity. Gastroenterology. 2014
29. Sharif R, Dawra R, Wasiluk K, Phillips P, Dudeja V, Kurt-Jones E, Finberg R, Saluja A. Impact of toll-like receptor 4 on the severity of acute pancreatitis and pancreatitis-associated lung injury in mice. Gut. 2009; 58(6):813–819. [PubMed: 19201771]
30. Li Y, Zhou ZG, Xia QJ, Zhang J, Li HG, Cao GQ, Wang R, Lu YL, Hu TZ. Toll-like receptor 4 detected in exocrine pancreas and the change of expression in cerulein-induced pancreatitis. Pancreas. 2005; 30(4):375–381. [PubMed: 15841051]
31. Buxbaum J, Yan A, Yeh K, Lane C, Nguyen N, Laine L. Aggressive hydration with lactated ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol. 2014; 12(2):303–307. e301. [PubMed: 23920031]
32. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, Smith B, Banks PA, Conwell DL. Lactated ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011; 9(8):710–717. e711. [PubMed: 21645639]
33. Xue J, Habtezion A. Carbon monoxide-based therapy ameliorates acute pancreatitis via tlr4 inhibition. J Clin Invest. 2014; 124(1):437–447. [PubMed: 24334457]
34. Delgiorno KE, Tam JW, Hall JC, Thotakura G, Crawford HC, van der Velden AW. Persistent salmonellosis causes pancreatitis in a murine model of infection. PLoS One. 2014; 9(4):e92807. [PubMed: 24717768]
35. Gonzalez-Escobedo G, La Perle KM, Gunn JS. Histopathological analysis of salmonella chronic carriage in the mouse hepatopancreatobiliary system. PLoS One. 2013; 8(12):e84058. [PubMed: 24349565]
36. Hampton MB, Kettle AJ, Winterbourn CC. Inside the neutrophil phagosome: Oxidants, myeloperoxidase, and bacterial killing. Blood. 1998; 92(9):3007–3017. [PubMed: 9787133]
37. Liou GY, Doppler H, Necela B, Krishna M, Crawford HC, Raimondo M, Storz P. Macrophage-secreted cytokines drive pancreatic acinar-to-ductal metaplasia through nf-kappa b and mmps. J Cell Biol. 2013; 202(3):563–577. [PubMed: 23918941]
38. Ishimura R, Tanaka K, Komatsu M. Dissection of the role of p62/sqstm1 in activation of nrf2 during xenophagy. FEBS Lett. 2014; 588(5):822–828. [PubMed: 24492006]
39. Huber S, Ramsingh AI. Coxsackievirus-induced pancreatitis. Viral Immunol. 2004; 17(3):358–369. [PubMed: 15357902]
40. Sesti-Costa R, Silva GK, Proenca-Modena JL, Carlos D, Silva ML, Alves-Filho JC, Arruda E, Liew FY, Silva JS. The il-33/st2 pathway controls coxsackievirus b5-induced experimental pancreatitis. J Immunol. 2013; 191(1):283–292. [PubMed: 23733876]

Key Points

- Defective autophagic flux in acinar cells is associated with most pancreatitis models.
- TLR4/NFκB signaling in macrophages is complicit in pancreatitis initiation.
- TLR4 signaling is a viable therapeutic target for pancreatitis treatment.
- While bacterial lipopolysaccharide can exacerbate, but not initiate pancreatitis in mouse models, *Salmonella* infection alone is sufficient to induce the disease.