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Acute Pancreatitis: A Multifaceted Set of Organelle and Cellular Interactions

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Abstract

Acute pancreatitis is an inflammatory disorder of the exocrine pancreas associated with tissue injury and necrosis. The disease can be mild, involving only the pancreas, and resolve spontaneously within days or severe, with systemic inflammatory response syndrome- associated extrapancreatic organ failure and even death. Importantly, there are no therapeutic agents currently in use that can alter the course of the disease. This article emphasizes emerging findings that stressors (environmental and genetic) that cause acute pancreatitis initially cause injury to organelles of the acinar cell (endoplasmic reticulum, mitochondria, and endolysosomal–autophagy system), and that disorders in the functions of the organelles lead to inappropriate intracellular activation of trypsinogen and inflammatory pathways. We also review emerging work on the role of damage-associated molecular patterns in mediating the local and systemic inflammatory response in addition to known cytokines and chemokine pathways. In the review, we provide considerations for correction of organelle functions in acute pancreatitis to create a discussion for clinical trial treatment and design options.

Keywords

Acute Pancreatitis; Autophagy; Mitochondria; Endolysosomal System; Stimulator of Interferon Genes; Damage-Associated Molecular Patterns; Unfolded Protein Response; Endoplasmic Reticulum Stress; Mitophagy; Macrophage

Acute Pancreatitis: A Disorder With Different Causes Requiring Solutions

Acute pancreatitis is an inflammatory disorder of the exocrine pancreas associated with tissue injury and necrosis.[1,2] The disease can be mild, involving only the pancreas, and

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Conflicts of interest

The authors disclose no conflicts.

resolve spontaneously within days, or severe, with systemic inflammatory response syndrome–associated extrapancreatic organ failure and even death. Importantly, there are no therapeutic agents currently in use that can alter the course of the disease. Current management consists of fluid resuscitation and supportive care.[2]

Acute pancreatitis has been reported as one of the most common reasons for inpatient hospital care in the United States, with an annual incidence of 13–45 cases per 100,000 people.[3,4] Gallstones and alcohol abuse are key causative factors in the mechanisms of pancreatitis; and the incidence varies between regions and sexes as a function of the prevalence of gallstone disease and alcohol abuse.[4] Gallstones migrating out of the gallbladder and causing transient obstruction of the pancreatic duct and exposure of the pancreas to biliary constituents still represent the most common cause of acute pancreatitis.[4,5] The second most common cause of acute pancreatitis is alcohol abuse.[4,5] Alcohol abuse as a cause of pancreatitis requires a significant amount of intake over a prolonged period (≥4–5 drinks per day over >5 years).[6] The mechanisms of alcohol-induced pancreatitis are complex and involve disorders of the acinar cell and ductal cells of the exocrine pancreas.[7–20]

Cigarette smoking is common with alcohol consumption and recent studies support a significant role for smoking and the combination of alcohol consumption with smoking.[18,21,22] These studies show that smoking is an independent risk factor for pancreatitis (acute, recurrent, and chronic) in addition to heavy alcohol abuse. There also is increasing recognition of the important role of hyper-triglyceridemia in acute pancreatitis. Hypertriglyceridemic pancreatitis is the third leading cause of acute pancreatitis.[23] Estimates suggest that 15%–20% of those with severe hypertriglyceridemia (triglyceride levels >1000 mg/dL) will develop acute pancreatitis.[24] The clinical course in these patients is more severe with a greater incidence of persistent multiorgan failure.[25,26] Of interest are recent studies showing increased severity of pancreatitis in patients with mild (triglyceride levels 150–199 mg/dL) and moderate (triglyceride levels 200–999 mg/dL) increases in serum triglycerides measured during an episode. Other more common causes of acute pancreatitis include complications of endoscopic retrograde cholangiopancreatography and an autoimmune etiology and are idiopathic.[4] Of note, recent literature also associates diabetes with an increased risk for development of pancreatitis.[27–29]

Medication-associated pancreatitis is a less common cause, probably accounting for fewer than 5% of cases, although multiple drugs have been associated with the development of pancreatitis.[30] Drugs with strong associations with the development of acute pancreatitis include azathioprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin-converting enzyme inhibitors, and mesalamine.[30] Although there has been considerable interest in the association between glucagon-like peptide 1 mimetics (aka incretin mimetics) used for the treatment of diabetes in causing pancreatitis, more thorough investigations show that the increased incidence in these cases is likely due to the underlying diabetes, which increases the risk of acute pancreatitis by 2–3 times, and not to treatment with these agents.[31–34]

Currently, the consensus is that only a minority of adult patients have pancreatitis resulting from genetic alterations. However, episodes of recurrent acute pancreatitis or unexplained

first episodes of acute pancreatitis in patients younger than 35 years have pathogenic genetic variants in nearly half of patients.[35] Further, of importance is the recent report that a genetic mutation in claudin 2 can augment the effect of alcohol drinking on the susceptibility for pancreatitis, pointing out the potential interactions between lifestyle factors and genetic susceptibility to pancreatitis.[36,37]

There are cases in which the cause is not easily discernable. One should not overlook the possibility of a malignancy that can occasionally present as acute pancreatitis, especially in patients older than 50 years.[30] In those cases with an unknown cause, especially if there is a recurrent episode, a more detailed examination of the pancreas with imaging procedures, including endoscopic ultrasound, and testing for genetic abnormalities are warranted.[35]

The diagnosis of acute pancreatitis is less common in the pediatric population and emerging data suggest that most pediatric cases are due to underlying genetic influences involving mutations in key digestive enzymes (hereditary pancreatitis) and genes in the cystic fibrosis family of mutations.[38,39]

The reason for this discussion is to emphasize that there are multiple causes of acute pancreatitis and that each cause could have unique mechanisms to initiate the disease. A limiting factor in investigating the early stages in the disease process is the rapid progression of the disease so that it is difficult to obtain information about the natural history of the disease process from its inception. Furthermore, it is rare to obtain pancreatitis tissues from patients because of the relative inability to sample pancreatitis tissues because of the location of the pancreas and concern that manipulations can worsen disease severity. Therefore, as discussed below, investigations of mechanisms of pancreatitis initiation and promotion have depended on experimental animal models and ex vivo human acinar tissue. The theme of this article as emphasized in the title is that recent evidence indicates interactions among cell types in the pancreas, organelles in the pancreatic acinar cell, and the inflammatory system that underlie the full manifestations of pancreatitis.

Roles of Acinar and Ductal Cells in Acute Pancreatitis

The exocrine pancreas is designed to carry out functions of digestion of meal macronutrients and neutralization of gastric acid entering the small intestine for optimal pH for digestive enzyme activity.[40] To accomplish these functions, the exocrine pancreas synthesizes, stores, and secretes digestive enzymes from the acinar cell; and the secreted digestive enzymes are transported to the small intestine by a ductal system secreting large amounts of bicarbonate-rich fluid. Disorders of the acinar cell and ductal epithelial cells can initiate pancreatitis; and these disorders can initiate and propagate and inflammatory response. Much of our understanding of the mechanism of pancreatitis has come from studies focused on the acinar cell in the initiation of the disease,[14,41] but more recently there has been increasing understanding of the role of the ductal epithelium in the initiation of acute pancreatitis.[9,16,42] However, the general consensus is that dysfunction in ductal water and bicarbonate secretion mediate pancreatitis through secondary effects on the acinar cell, which generates that pancreatitis response.[9]

Preclinical Animal Models and Ex Vivo Human Acinar Tissue Used for Mechanistic Insights

Because of the lack of safe access to human tissues, studies addressing pancreatitis disease mechanisms have largely used animal models. There are several rodent models of acute pancreatitis reproducing the spectrum of human disease manifestations.[43] These models have greatly advanced our understanding of the cell biology of the disease and the molecular factors involved and allowed testing of potential therapeutic interventions. The most widely used in vivo models of acute pancreatitis include those induced in rodents by administering supraphysiologic doses of cholecystokinin 8 (CCK), cerulein (an orthologue of CCK), or muscarinic agonists (ie, carbachol); treating with bile acids or L-arginine; and feeding mice a choline-deficient ethionine-supplemented diet. Treating isolated acini (functional units of acinar cells of the exocrine pancreas) with supraphysiologic doses of CCK (or cerulein) or with bile acid salts triggers early pathologic responses of acute pancreatitis (trypsinogen activation, dysregulated secretion, vacuole accumulation) and thus is considered an ex vivo disease model.

Regarding human acinar tissue, we recently published a study comparing responses in human cadaveric pancreatic acini with those in rodents.[14] We found similar organelle structures and components by electron microscopy, proteomic analysis, and immunohistochemistry and acinar cell secretory responses to the muscarinic agonist carbachol. When we provoked a pancreatitis response ex vivo with high doses of carbachol or with known pancreatitis-causing agents such as bile acid or tauro-lithocholic acid 3-sulfate, acini from the 2 species similarly responded with mitochondrial depolarization, disordered autophagy, and pathologic endoplasmic reticulum (ER) stress. Furthermore, we found inappropriate conversion of preformed trypsinogen to the activated trypsin state, a hallmark of pancreatitis responses from dysfunctional autophagy, and production of proinflammatory cytokines. All these pathobiologic responses are the same as those observed in rodent tissues.[14] Thus, at least with respect to acinar cell pancreatitis responses ex vivo, we found no differences between rodent and human tissues.

Organelle Machinery of the Acinar Cell: From Homeostasis to Dysfunction in Pancreatitis

The central physiologic role of the pancreatic acinar cell is to synthesize, transport, store, and secrete digestive enzymes. It relies on normal functions of acinar cell organelles including the ER, mitochondria, and endolysosomal–autophagy system. Recent studies have shown that the functions of these organelles are deranged in pancreatitis and underlie the mechanisms involved in the generation of acute pancreatitis.

ER Functions and Ca^{2+} Signaling and Homeostasis

One of the major ER functions (with mitochondrial participation) is regulation of Ca^{2+} signaling for secretion and homeostasis in the acinar cell, whereas disorders of Ca^{2+} signaling and homeostasis lead to pathology and pancreatitis responses. Within a typical eukaryotic cell, ionized calcium in cytosol ($[Ca^{2+}]i$) is roughly 100 nmol/L, which is

approximately 12,000-fold lower compared with the extracellular fluid (as in circulating blood). This gradient is maintained through various calcium pumps and intracellular calcium storage organelles such as the ER.[44–46] Hormones and neurotransmitters, such as acetylcholine and CCK, that are involved in inducing acinar cell secretion release small amounts of Ca^{2+} from the ER, which results in the transient and oscillatory pattern of increases in $[Ca^{2+}]i$. Increases in $[Ca^{2+}]i$ during physiologic stimulation leads to transient and oscillatory patterns of $[Ca^{2+}]i$.[43–46] Physiologic responses such as secretion occur with these transient increases because Ca^{2+} is rapidly taken back to the ER and/or removed from the acinar cell by Ca^{2+} pumps. Also, the mitochondria take up Ca^{2+} during the transient increase for promoting adenosine triphosphate (ATP) generation. Ca^{2+} homeostasis is dysregulated in pancreatitis.[46] The common change seen in pancreatitis models, such as those induced by supraphysiologic doses of cerulein or bile acids, is the loss of physiologic $[Ca^{2+}]i$ oscillations, which are replaced by the sustained increase of $[Ca^{2+}]i$. The sustained increase in $[Ca^{2+}]i$ occurs because the pancreatitis-causing stimuli largely deplete the ER calcium stores, and the depletion promotes the entry of calcium into the pancreatic acinar cell through store-operated calcium channels, the most abundant of which is mediated by a protein called Orai1.[47] The sustained increase in $[Ca^{2+}]i$ causes mitochondrial Ca^{2+} overload, resulting in the loss of mitochondrial membrane potential and ability to make ATP.[48]

Blocking Orai1-mediated Ca^{2+} channels by genetic and pharmacologic means prevents mitochondrial failure and largely alleviates pancreatitis responses. The results suggest that aberrant global and sustained increases in $[Ca^{2+}]i$ contribute to the pathogenesis of acute pancreatitis and that pharmacologic approaches aimed at decreasing $[Ca^{2+}]i$ can be developed for the treatment of patients with pancreatitis.[47]

Another critically important function of the ER is protein synthesis and new protein folding and export.[49] Of note, ER is highly developed in acinar cells to fulfill their main function of producing and secreting large amounts of protein. When misfolded secretory proteins are sensed at their sites of synthesis, cells first respond by activating an adaptive “unfolded protein response” that generally decreases new protein synthesis and up-regulates levels of chaperones that mediate new protein folding and export.[49] The transcription factor spliced X protein-1 (sXBP1) plays a central role in the unfolded protein response. Nunnari and Suomalainen[50] demonstrated that complete genetic deletion of XBP1 results in defects exclusively in secretory organs such as the pancreas and salivary glands. The deletion led to apoptosis of acinar cells during embryogenesis, resulting in an atrophic pancreas at birth. We found that when XBP1 is inhibited by heterozygous (ie, not complete) deletion, there is inhibition of the secretory response to neurohumoral stimulation and that there is acinar cell injury and an increase in the expression of transcription factor CCAAT-enhancer-binding protein homologous protein (CHOP) associated with acinar injury and pancreatitis responses.[14,51] The role of CHOP has been examined in other tissues and shown effects on mitochondrial pathways and inflammatory signaling.[52,53] We found that inhibition of CHOP in acinar cells prevents cell death responses.[51]

Protein folding involves ER-based chaperones and formation of disulfide groups between cysteine residues in proteins using oxidoreductase enzymes in the ER.[12,45,46,54,55] Optimal

performance for disulfide bond formation requires a normal redox state in the ER.[49] Our studies show that the redox state is altered by alcohol feeding, which makes the ER environment more oxidative.[12,55] However, ER maintains homeostasis even with an altered redox state; the main protective mechanism is through sXBP1, which upregulates the folding systems in the ER despite its altered redox states.[12,46,47,54,55] Conversely, with decreased sXBP1 expression by genetic means, acinar injury and pancreatitis responses ensue.[12,14,51]

Most interestingly, we recently reported that although ethanol feeding up-regulates sXBP1, the addition of smoking results in inhibition of the sXBP1 response, associated with an increase in CHOP and pancreatitis responses, in particular acinar cell death.[51] These findings are important to our understanding of the effects of alcohol and smoking on the pancreas and explain epidemiologic studies indicating that smoking promotes alcoholic pancreatitis.[6,18,21,22,48,49] It is likely that redox alterations in the ER are responsible for the changes in sXBP1 and CHOP because treatment with the antioxidant N-acetylcysteine prevents the increase in CHOP and acinar death responses.[51]

Mitochondria are responsible for a range of cellular functions; their major physiologic role is generation of ATP.[50,51] Mitochondria also are critical in regulating cell survival.[52] In terms of pathobiologic responses of pancreatitis, mitochondrial membrane permeabilization is a universal trigger of apoptosis and necrosis. It is mediated by persistent opening of the mitochondrial permeability transition pore (MPTP), a multiprotein nonspecific channel traversing the inner and outer mitochondrial membrane.[52–54] In its “open” conformation, MPTP allows unregulated entry of solutes less than 1500 Da (including water) into the matrix, resulting in mitochondrial depolarization and inhibition of mitochondrial ability to synthesize ATP, leading to loss of cellular functions and necrosis. Various stresses, such as mitochondrial Ca^{2+} overload and excessive reactive oxygen species generation, cause MPTP opening. The MPTP backbone is organized around the mitochondrial resident protein cyclophilin D (CypD); and CypD inhibition by genetic, molecular, or pharmacologic means blocks MPTP opening. Blocking MPTP prevents mitochondrial failure and necrosis.

Of note, individual mitochondria interact with each other forming a tubular–circular dynamic network, which largely determines mitochondrial activity.[55] Processes of mitochondria fission and fusion are highly regulated and enable the cell to adapt to metabolic stresses. Disorders of acinar cell mitochondrial dynamics occur in pancreatitis, resulting in inadequate ATP production, increased mitochondrial reactive oxygen species, and impaired Ca^{2+} transport.[56]

Mitochondrial dysfunction occurs across various models of pancreatitis.[19,56–59] Its main manifestation is persistent opening of MPTP, resulting in loss of mitochondrial membrane potential and mitochondrial fragmentation. Mechanisms of MPTP opening in experimental pancreatitis are model specific. In models induced by high doses of cerulein, the aberrant increases in $[Ca^{2+}]i$ lead to mitochondrial Ca^{2+} overload, resulting in MPTP opening.[58] Conversely, MPTP opening in arginine-induced pancreatitis is mediated by inhibition of ATP synthase[56] and in alcohol-induced pancreatitis is mediated by a decrease in the ratio of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide plus hydrogen resulting from oxidative alcohol metabolism.[19] Importantly, independent of the underlying

mechanisms, MPTP opening in all models of pancreatitis is CypD dependent. CypD genetic or pharmacologic inactivation prevents mitochondrial depolarization, resulting in restoration of mitochondrial function and greatly decreased local (pancreatic), systemic, and distant (pulmonary) pathologic responses in various experimental models of pancreatitis.[19,56–59]

Endolysosomal–Autophagy System

Autophagy (macroautophagy) is the principal cellular pathway for degradation and recycling of organelles, lipids, and long-lived proteins. It begins with sequestration of the material destined for degradation into autophagosomes, which then fuse with lysosomes forming the autolysosomes in which cargo is degraded by lysosomal hydrolases.[60,61] Impaired autophagy is a characteristic feature of various models of experimental pancreatitis, caused by the decreased ability of lysosomes to degrade cargo and a concomitant increase in autophagosome formation.[56,62–65] Experimental pancreatitis is associated with severe defects in lysosomes.[41,57,62,63,66] These include defective processing (maturation) of cathepsins and major lysosomal proteases, manifested by a lower level of fully processed and accumulated intermediate forms of cathepsins.[65] Concomitantly, cathepsins' enzymatic activities decrease in lysosome-enriched pancreatic subcellular fractions from animals with pancreatitis.[65,67] Pancreatitis causes alterations in the localization of lysosomal vacuolar proton ATPase, which maintains acidic pH in the lysosomal lumen.[68] Levels of lysosomal-associated membrane proteins (LAMPs), which are critical for maintaining the structure and function of lysosomes, dramatically decrease across various experimental models of nonalcoholic and alcoholic pancreatitis.[69] Accumulation in acinar cells of abnormally large autolysosomes containing poorly degraded cargo, a key manifestation of defective autophagy, has long been recognized as an early marker of pancreatitis.[62]

Studies using genetic models targeting the endolysosomal–autophagy system provide mechanistic insights into the role of this system in maintaining pancreatic function and homeostasis. The role of autophagy was analyzed in detail in mice with pancreas-specific knockouts of key mediators of autophagosome formation, the autophagy-related proteins (ATG) ATG5 or ATG7.[70,71] $Atg5^{\Delta pan}$ and $Atg7^{\Delta pan}$ mice developed spontaneous pancreatitis, with trypsinogen activation, fibrosis, inflammation, acinar-to-ductal metaplasia, and pancreas atrophy. In addition, the impaired lysosomal function in LAMP2-null mice resulted in spontaneous pancreatitis, starting with acinar cell vacuolization and progressing to severe pancreas damage characterized by trypsinogen activation, macrophage-driven inflammation, and acinar cell death.[69] Further, LAMP2 deficiency increased the severity of experimental pancreatitis induced by cerulein treatment.[69] Importantly, administration of trehalose, a natural disaccharide known to enhance autophagy, largely prevented trypsinogen activation, necrosis, and other parameters of pancreatic injury in mice in arginine- and cerulein-induced pancreatitis models.[56] Together, these findings show the essential role of dysfunction of the endolysosomal- autophagy system in pancreatitis development and suggest pharmacologic approaches to enhance autophagy efficiency for human pancreatitis treatment.

Of note, tissue specimen analysis from patients with pancreatitis shows manifestations of endolysosomal–autophagy system disorders in human disease similar to those in rodent models.[56,64,65,72]

Interrelations Between Acinar Cell Organelle Disorders in Pancreatitis

Several studies indicate that organelles in the acinar cell form an interconnected system and that pathology of one organelle can lead to failure of the entire network. For example, blocking autophagy by genetic ablation of ATG5 or ATG7 or by genetic deletion of the inhibitor of nuclear factor kB kinase subunit a result in ER stress and accumulation of dysfunctional mitochondria unable to generate ATP.[64,70,71] Conversely, restoring mitochondrial function by CypD genetic ablation alleviates ER stress and increases performance of the endolysosomal–autophagy system in experimental pancreatitis.[56] As another example, XBP1 deficiency causing ER stress also causes mitochondrial dysfunction manifest by decreased oxidative phosphorylation. Abnormal increases in $[Ca^{2+}]i$ from ER calcium depletion and excessive Ca^{2+} influx into the acinar cell cause mitochondrial depolarization and failure and defects in endocytosis.[73] Although these examples show interaction between organelles of the acinar cell, the complete extent of the mechanisms of interaction is yet to be shown.

In sum, these studies indicate that acinar cell organelle dysfunctions play a key role in the pathogenesis of acute pancreatitis, and that there are interactions between organelles so that dysfunctions in one can lead to disorders of others. Future work should focus on determining the mechanisms of these interactions because it is likely that interventions to prevent the spread of disorders across organelles will limit the severity of the disease.

How Do Injury Signals from Acinar Cells Cause Local and Systemic Inflammation?

Accumulating evidence indicates that acinar cell organelle damage triggers the inflammatory response of pancreatitis, although the underlying mechanisms remain to be investigated. As an example, autophagy blockade through disruption of genes encoding ATG5, ATG7, LAMP2, or inhibitor of nuclear factor κB kinase subunit α stimulates activation in acinar cells of proinflammatory transcription factors, such as nuclear factor κB and signal transducer and activator of transcription 3, resulting in up-regulation of cytokines and chemokines and inflammatory cell infiltration in the pancreas.[71,72] The mechanisms of these processes likely involve increases in reactive oxygen species owing to defective clearance of damaged or depolarized mitochondria or ER dysfunction. Organelle damage also can mediate inflammasome formation in pancreatitis.[71]

Acute pancreatitis is associated with significant acinar cell death.[41] Dying and necrotic cells release damage-associated molecular patterns (DAMPs) and other molecules that stimulate and activate inflammatory responses.[74–76] DAMPs, such as the high mobility group box 1 (HMGB1) chromatin protein released from damaged cells, have been shown to play an important role in experimental pancreatitis[77]; and circulating HMGB1 levels have been correlated with severity of clinical acute pancreatitis.[74,78] However, intracellular HMGB1

mitigates the inflammatory response and pancreatic damage,[79] suggesting that DAMPs released extracellularly activate inflammatory signals and exacerbate acute inflammation locally and in distant sites, whereas intracellular localization of HMGB1 is anti-inflammatory.

In addition to HMGB1, DNA released from dying and necrotic cells is a well-described DAMP. In fact, DNA released from necrotic cells has been shown to be a potent activator of the innate immune system involving dendritic cells and macrophages.[75,80,81] Moreover, DNA in the circulation contributes to autoimmune disease such as systemic lupus erythematosus[82] and is associated with severity of clinical acute pancreatitis.[78] Pathogen- and host-derived DNA activates cyclic guanosine and adenosine mono-phosphate synthase and generates the second-messenger cyclic guanosine and adenosine monophosphate, which activates stimulator of interferon genes (STING) signaling and generation of interferon type I.[83,84] STING activation in macrophages by DNA derived from dying acinar cells and generation of proinflammatory cytokines including inter-feron β and tumor necrosis factor α was recently reported in experimental acute pancreatitis and exacerbated the disease.[85] In the absence of STING signaling, macrophages did not mount the observed interferon β response to dying acinar cells, indicating the direct link between acinar cell death-released DNA and immune activation leading to the generation of proinflammatory cytokines. These findings are consistent with reports of STING activation and DNA sensing from dying and necrotic cells that promote inflammatory diseases.[86]

DNA also can be sensed by Toll-like receptors, such as Toll-like receptor 9, and activate inflammasome pathways (eg, nucleotide-binding oligomerization domain-like receptor protein 3) and promote inflammation in acute pancreatitis.[87] Thus, inflammation in acute pancreatitis might be triggered by nuclear components released from damaged and dying acinar cells through different mechanisms described earlier. Additional mechanisms that initiate inflammation include cytokines and chemokines initially released by acinar cells in response to injury that have been extensively reviewed recently.[63,88]

Summary

Figure 1 presents a summary of this article in showing environmental stressors and genetic factors known to increase the risk for pancreatitis. As pointed out earlier, some risk factors act in combination to promote the disease as exemplified to alcohol abuse and smoking; and it is likely that genetic alterations also can increase susceptibility when combined with a lifestyle factor such as alcohol abuse.[37] Although not completely explored, stressors such as gallstones and the effect their passage has on reflux of bile acids into the pancreas could act through increased calcium influx to cause mitochondrial de-energinization.[89–91]

This article addresses the effect of acinar cell stressors on the function of intracellular organelles and their dysfunction during disease development and focuses on mitochondria, ER, and autophagy. An important point to stress is that our studies show that once one of the organelles fails, the others likely follow.[58,65,71] This observation has significance related to development of therapeutics. Pancreatitis is an inflammatory disease, which is local for milder disease and involves distant organs for more severe disease.[88,92,93] This review

presents newly developed information about the inflammatory mechanisms related to DAMPs. An important observation with relevance to therapeutic application is that the inflammatory response can promote further acinar cell injury, including necrosis, creating a feed-forward process to create more inflammation.[94] Thus, early intervention to address the mechanisms discussed in this article is expected to prevent the feed-forward inflammation and necrosis process.

Gaps and Future Directions to Improve Outcome in Patients with Acute Pancreatitis

This review points out that stressors that cause pancreatitis initially cause organelle disorders in the acinar cell of the pancreas leading to a subsequent inflammatory response that is localized to the pancreas in milder disease or systemic in severe disease. Further, this review shows key pathobiologic processes that are the foundation for therapeutics development.

The key questions that remain are whether treatments are needed to address more than 1 organelle disorder simultaneously (eg, resolving autophagy and mitochondrial failure at the same time) and whether treatment must be initiated at the earliest stages of the disease to prevent the full manifestation of pancreatitis. It will be important to identify the mechanisms whereby organelle dysfunctions and pathologic interactions between organelles promote cell death (necrosis) and generate pancreatitis responses—inflammation in particular. Further, there could be a consideration for treating organelle failure and the inflammatory cascade simultaneously. Some of these questions can be addressed in preclinical models to provide better clinical strategies for the field.

However, much of our progress will come from observing responses to agents in human clinical trials with an emphasis on timing of delivery and methods of measurement of organelle function and inflammatory pathways, possibly during different stages of the disease. That is, there could be therapies during the early stage that reestablish organelle homeostasis and treatments later in the disease that address inflammation and the systemic in-flith an e response, which could be more important.

Progress will come from keeping these concepts in mind during trial designs, including exploratory measures performed to continue to advance our understanding, and using this information for subsequent trial designs and measurements.

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Abbreviations used in this paper:

ATG	autophagy-related protein
ATP	adenosine triphosphate

$[Ca^{2+}]i$	ionized calcium in cytosol
CCK	cholecystokinin-8
CHOP	CCAAT-enhancer-binding protein homologous protein
CypD	cyclophilin D
DAMP	damage-associated molecular pattern
ER	endoplasmic reticulum
HMGB1	high mobility group box 1
LAMP	lysosomal-associated membrane protein
MPTP	mitochondrial permeability transition pore
STING	stimulator of interferon genes
sXBP1	spliced X protein-1

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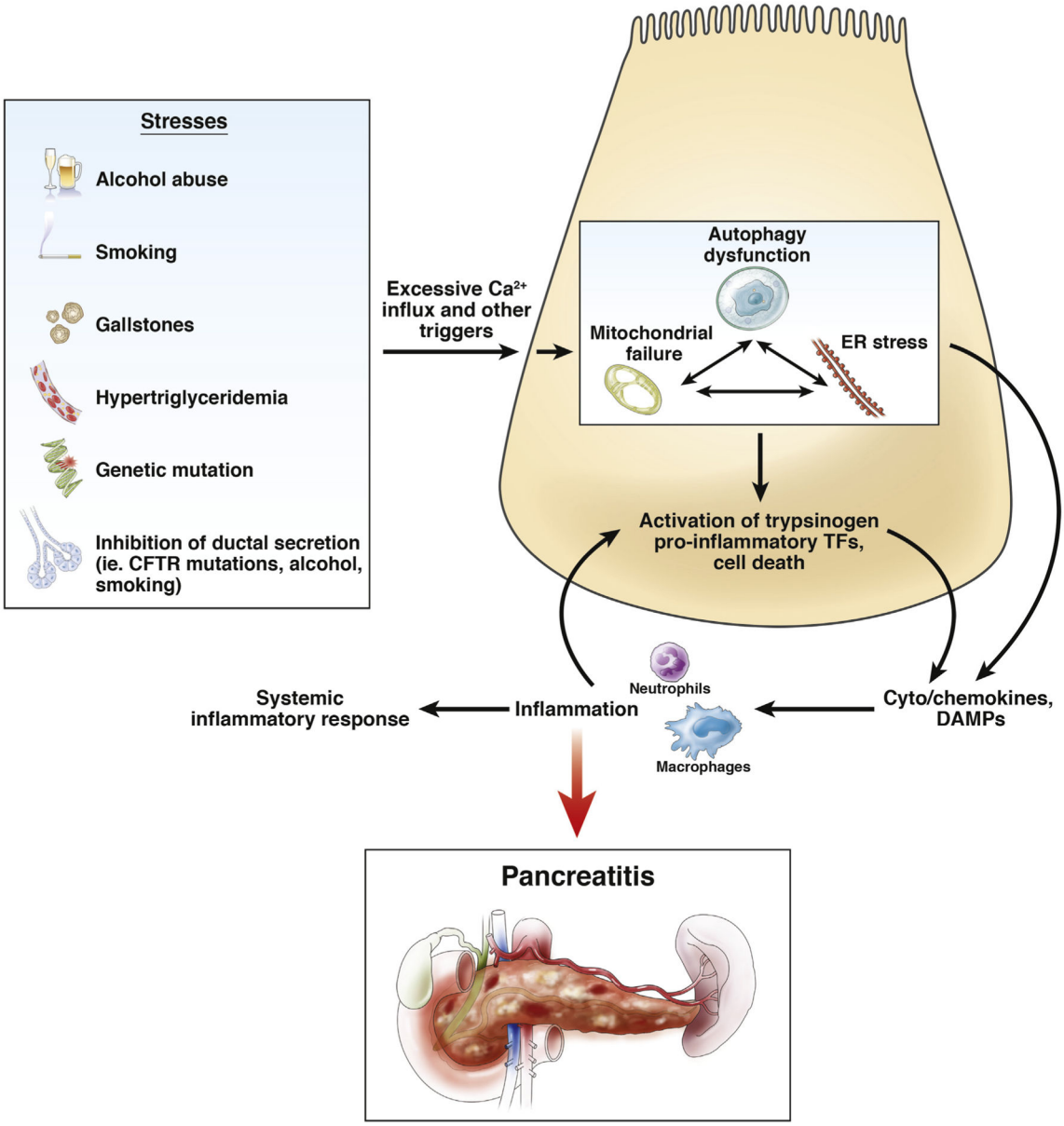

Figure 1.

Summary of environmental stressors and genetic factors known to increase the risk for pancreatitis. CFTR, cystic fibrosis transmembrane conductance regulator; TFs, transcription factors.