Targeting Endoplasmic Reticulum Stress as an Effective Treatment for Alcoholic Pancreatitis

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Abbreviations:

AP, acute pancreatitis

CP, chronic pancreatitis

ER, endoplasmic reticulum

UPR, unfolded protein response

EPI, exocrine pancreatic insufficiency

PC, pancreatic cancer

DM, diabetes mellitus

CLDN2, clauding 2

CTRB1, chymotrypsin B1

CTRB2, chymotrypsin B2

ALDH2, aldehyde dehydrogenase-2

ADH1B, alcohol dehydrogenase-1B

ALD, alcoholic liver disease

ALT, alanine aminotransferase

AST, aspartate aminotransferase

LPS, lipopolysaccharides

CPA1, carboxypeptidase A1

TPP, thiamine pyrophosphate

ROS, reactive oxygen species

CFTR, cystic fibrosis transmembrane conductance regulator

IRE1, inositol-requiring kinase 1

PERK, protein kinase-like ER kinase

GRP78, 78-kDa glucose regulated protein

eIF2, eukaryotic translation initiation factor-2

XBP1, X box-binding protein 1

ERAD, ER-associated degradation

RIDD, IRE1-dependent RNA decay

ATF6, activating transcription factor 6

ATF4, activating transcription factor 4

CHOP, C/EBP homologous protein

GADD34, growth arrest and DNA damage-inducible protein 34

MANF, mesencephalic astrocyte-derived neurotrophic factor

hPAC, human pancreatic acinar cells

ERAD, ER-associated degradation

4-PBA, sodium phenylbutyrate

UDCA, ursodeoxycholic acid

TUDCA, tauroursodeoxycholic acid

CCK-8, cholecystokinin-8

GA, guanabenz acetate

TZD, trazodone

DBM, dibenzoylmethane

ALS, amyotrophic lateral sclerosis

OPMD, oculopharyngeal muscular dystrophy

HSPs, hereditary spastic paraplegias

SCI, spinal cord injury

AA 147, compound 147

AA 263, compound 263

CRAC, calcium release-activated calcium channel

AAV, adeno-associated virus

DA, nigral dopamine

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Abstract

Pancreatitis and alcoholic pancreatitis are serious health concerns, and there is an urgent need for effective treatment strategies. Alcohol is a known etiological factor for pancreatitis, including acute pancreatitis (AP) and chronic pancreatitis (CP). Excessive alcohol consumption induces many pathological stress responses; of particular note is endoplasmic reticulum (ER) stress and adaptive unfolded protein response (UPR). ER stress results from the accumulation of unfolded/misfolded protein in the ER and is implicated in the pathogenesis of alcoholic pancreatitis. Here we summarize the possible mechanisms by which ER stress contributes to alcoholic pancreatitis. We also discuss potential approaches targeting ER stress and UPR for developing *novel* therapeutic strategies for the disease.

Acute and chronic pancreatitis

Pancreatitis is a common inflammatory disorder of the pancreas and is associated with high mortality and healthcare burdens worldwide [1, 2]. It mainly consists of two forms: acute pancreatitis (AP) and chronic pancreatitis (CP). AP is the most frequent cause of gastrointestinal disorders requiring hospitalization in the US, and its associated inpatient care cost is about $2.6 billion annually [2-4]. Although less frequent, CP also causes significant morbidity and financial burden [3]. Additionally, the incidence of pancreatitis differs with age and gender. The risk of developing AP increases with age [5, 6], whereas CP is more common in middle-aged people [2]. Furthermore, AP does not appear to differ between men and women [6], but CP is more common in men than women [2, 7]. AP and CP share a significant portion of clinical manifestations and phenotypes but also have distinct morphological and imaging features.

AP is characterized by sudden abdominal pain, elevated levels of pancreatic enzymes in the blood, and imaging evidence of pancreatic inflammation [8, 9]. Depending on the clinical features, AP can be classified into mild, moderate, or severe forms. The most common form of AP is mild AP, which can be self-healed within weeks. However, the moderate and severe forms

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can progress into necrotizing pancreatitis, which has a 20-40% mortality rate [10]. A variety of long-term sequelae have been reported that can persist beyond hospital admission of AP. AP may increase the risk of other pancreatic disorders, including CP, exocrine pancreatic insufficiency (EPI), pancreatic cancer (PC) and diabetes mellitus (DM). 17% of AP patients are re-admitted after the first episode for recurrent pancreatitis, and about 8% of patients progress to CP [11, 12]. Approximately one quarter to one third of AP patients develop EPI during the follow-up period [13, 14]. The prevalence of EPI following AP is higher with the severe form than with the mild form, and it is higher in patients with an etiology of alcohol than one of gallstones [14]. AP patients often develop prediabetes and/or DM after being discharged from the hospital [15, 16]. The diagnosis of AP increases the risk of PC, and a higher risk of PC is associated with an increased number of recurrent episodes of AP [17, 18].

CP is believed to result from the recurrence of AP, which leads to chronic pain, pancreatic atrophy, duct strictures and calcifications [19, 20]. Although less common than AP, CP significantly affects patients' quality of life due to irreversible and debilitating injuries to the function of the pancreas. CP is also associated with other pancreatic diseases. It has been reported that CP increases the risk of EPI [21, 22], PC [23, 24] and DM [25, 26]. The high disease burden of AP and CP underscores the importance of identifying predisposing factors, understanding pathogenesis and developing therapeutic intervention for these diseases.

Alcohol consumption and pancreatitis

Alcohol exposure is a known etiological factor for both AP and CP. Epidemiological studies have shown that excessive alcohol consumption is the second leading cause of AP after gallstones [1, 27] and is the most prevalent risk factor for CP [28]. Alcohol abuse is also a risk factor for the recurrence of AP and increases the chances of progression of AP to CP [11, 29]. Although alcohol can contribute to the initiation and progression of pancreatitis, only a small number of

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heavy alcohol drinkers develop the disease, suggesting that other disposing factors are involved in the development of alcohol-related pancreatitis [30-33].

The association between alcohol consumption and pancreatitis is evaluated predominantly by self-reported survey studies. Corrao et al. conducted a meta-analysis of studies published between 1966 and 1995 and showed that the risk of pancreatitis monotonically increased with increasing alcohol consumption [34]. Consistent with this finding, Irving et al. analyzed research published between 1980 and 2008 and confirmed a monotonic dose-response relationship between alcohol consumption and the risk of pancreatitis, with a threshold of 4 drinks daily that significantly increased the risk of pancreatitis [35]. Similarly, more recent studies indicated that prolonged use of alcohol with a threshold level of 4-5 drinks per day was required for an increased risk of pancreatitis [19, 36-39]. In addition, the amount of recently-consumed alcohol was shown to determine the severity of the first episode of acute alcoholic pancreatitis [40]. In the absence of long-term use, binge drinking alone did not increase the incidence of AP [41]. Regular consumption of alcohol at lower levels, however, appeared to have an inconsistent effect on pancreatitis. Some reported that low alcohol drinking (< 50 gram per day) increased the recurrence of AP and accelerated the progression of CP [42, 43]. Others even found that mild or moderate drinking was inversely associated with an increased risk of pancreatitis [44].

In contrast to prolonged heavy alcohol consumption that has been known as a risk factor for pancreatitis, alcohol abstinence has been shown to slow down the progression of pancreatitis and reduce the recurrence of AP. For example, withholding from drinking resolved abdominal pain and slowed the deterioration of pancreatic function in chronic heavy drinkers [45]. Abstinence after the first episode of AP minimized the number of recurrent attacks of AP [46]. Similarly, in an effort to determine the risk factors associated with recurrent pancreatitis, Pelli et al. showed that abstinence from alcohol protected against recurrence of AP [47].

Alcohol can also act as a co-factor to increase the sensitivity of the pancreas to the detrimental effect of other risk factors including environmental and dietary factors [48]. Cigarette

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smoking is an independent risk factor for a number of pancreatic disorders, including AP [49], CP [50] and PC [51, 52]. Alcohol drinking can accelerate the progression of cigarette smoking-related pancreatitis and vice versa, suggesting a synergistic interaction of alcohol and smoking in the development of the disease [53-56]. Hypertriglyceridemia, referring to an elevated blood level of triglycerides often resulting from high dietary fats, is another important cause for pancreatitis [57-59] and is present in many alcoholics [60, 61]. Excessive alcohol consumption has been suggested to be associated with hypertriglyceridemia-induced pancreatitis [62, 63].

The risk of alcohol pancreatitis can also be altered by genetic modifiers. The *CLDN2* (Clauding 2) gene encodes a tight junction protein-regulating cation and water transport of epithelial cells, and it is normally expressed in pancreatic duct cells but not acinar cells [64, 65]. In a genome-wide study, a *CLDN2* risk allele, which is associated with an abnormal expression of CLDN2 protein in pancreatic acinar cells, was identified as a risk factor that interacted with alcohol consumption to accelerate the progression of chronic pancreatitis [66]. In another genome-wide association study, an inversion of the *CTRB1-CTRB2* (chymotrypsin B1 and B2) locus led to the imbalanced expression of CTRB1 and CTRB2 and an increased risk for both alcoholic CP and non-alcoholic CP [67].

Racial/ethnic differences are another susceptibility factor that can alter the risk of alcoholic pancreatitis. A population study using nationwide inpatient samples of the racially diverse US population between 1988 and 2004 demonstrated that Black people had the highest frequency of alcohol-related pancreatitis [68]. Another study using data collected by the North American Pancreatitis Study Group from 2000 to 2014 found that Black people were more likely to be diagnosed with CP than White people, likely because of alcohol consumption and smoking being more frequent in Black people [69]. In a number of studies conducted in the Asian population, a dose-response relationship between alcohol and pancreatitis was revealed [70-72]. The impact of ethnicity on the risk of alcoholic pancreatitis in these Asian studies was suggested to be related to the genetic polymorphism of alcohol metabolism enzymes; as genetic variant alleles of the

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aldehyde dehydrogenase-2 gene (ALDH2*2) and alcohol dehydrogenase-1B gene (ADH1B*2), which are associated with the accumulation of toxic acetaldehyde after alcohol drinking, were predominantly found in East Asians [73-76].

Animal and cell culture models for alcoholic pancreatitis

Epidemiologic studies have indicated that alcohol can act as a mild initiator or a robust modifier to sensitize the pancreas to the insult of other risk factors during the development of pancreatitis. To understand the mechanisms underlying the pathogenesis of alcohol-related pancreatitis, many animal and cell culture models have been established. These experimental models have recapitulated the clinical features of alcohol-related pancreatitis, facilitated our understanding of the pathology, and provided opportunities to test potential therapeutic treatments for the disease.

Consistent with epidemiologic studies, alcohol alone, either by acute exposure [77] or by chronic feeding [78-80], is not sufficient to induce pancreatitis-like features in rodent models. Recent studies have used chronic exposure combined with binge drinking and showed that alcohol, when acting as both the initiation and susceptibility factor, can cause pancreatic injuries which mimic pancreatitis. Binge alcohol exposure by intragastric intubation for 10 consecutive days (5 g/kg/day, 25% ethanol w/v) caused pancreatic edema, acinar cell death and moderate fibrosis in C57BL mice [81]. Mice receiving a liquid alcohol diet for two weeks followed by binge alcohol exposure by oral gavage for 3 days (5g/kg/day, 25% ethanol w/v) displayed more severe injuries and inflammation in the pancreas [82]. A 10-day feeding of a liquid alcohol diet plus a single binge ethanol exposure was found to lead to pancreatic edema and inflammation in C57Bl/6 mice [83, 84]. The chronic plus binge model may be of clinical relevance because it is similar to the drinking pattern of many alcoholic patients who have a history of chronic alcohol consumption and tend to have heavy episodic drinking [85-87]. In fact, the chronic plus binge exposure has also been used in animal models for alcoholic liver disease (ALD), as it has been shown to cause significant

elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and hepatic histological features, which bear a closer resemblance to the symptoms of early ALD patients, compared to chronic alcohol feeding or a single binge alone [83, 88, 89]

Alcohol can also act as a co-factor to sensitize the pancreas to the adverse effects of other susceptibility factors in the progression of pancreatitis. One physiologically relevant animal model for alcohol-related pancreatitis is the co-exposure of cholecystokinin (CCK) analogs and alcohol. CCK is an intestine hormone and is one of the most commonly used models to induce mild AP in rats [90-93] and a more severe form in mice [94-97] at a dose that is at least 10 times higher than the physiological condition. CCK analog-induced AP can recapitulate pathologic features of human AP caused by scorpion venom and cholinergic toxins [98-101]. The co-treatment of alcohol can either reduce the threshold concentration of CCK analogs that is required to elicit a pancreatitis response or intensify the pathologic response of the pancreas. Pandol et al. (1999) demonstrated that alcohol exposure sensitized rats to pancreatitis induced by CCK-8 at the physiological concentration, which by itself did not cause pancreatitis [92]. Quon et al. (1992) showed that chronic feeding of an alcohol diet exacerbated CCK analog caerulein-induced pancreatitis in rats, marked by greater increases in serum lipase level, interstitial edema and acinar vacuolization compared to that of animals treated with caerulein alone [102]. Repeated use of caerulein over time induced pathological features of the pancreas in rodents that mimicked human CP [103-105]. Alcohol exposure accelerated the progression of caerulein-induced CP in rats [105] and mice [106].

Another clinically relevant animal model is lipopolysaccharides (LPS)-induced alcoholic pancreatitis in rodents [107]. LPS are endotoxins derived from gram negative bacteria in the gut, which can be released to the blood to cause LPS-associated toxicity [108]. There has been reported a higher plasma level of LPS in alcoholics [109, 110] and an association between plasma endotoxin concentrations and the severity of human AP [111]. In rat models, LPS and alcohol exposure have been shown to cause a more severe pancreatic injury than LPS alone [107, 112]. Withdrawal of alcohol after manifestation of LPS-induced pancreatitis in rats resulted in the resolution of

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pancreatic lesions, including fibrosis and cell death, whereas continued alcohol administration aggravated the injury [113]. In a rat model of alcoholic AP, alcohol increased the expression of LPS-induced proinflammatory factors in acinar cells, including TNFα, IL-6, IL-10 and IL-18 [114]. The elevated expression of these inflammatory mediators was also observed in human AP and recurrent AP patient samples, suggesting an involvement of inflammation in alcoholic pancreatitis [114].

There are other susceptibility factors that have been identified in experimental models and have been shown to be associated with alcoholic pancreatitis. Hyperlipidemia and pancreatic duct obstruction, which cause minimal pancreatic damage individually, induced clinically relevant pancreatitis in rats when combined with alcohol feeding [115]. Genetic mutations, as exemplified by a pathogenic human p.N256K *CPA1* (Carboxypeptidase A1) mutant when expressed in mice, caused protein misfolding, ER stress and progressive CP, which was aggravated by alcohol exposure [116]. A severe pancreatitis phenotype manifested in knock-out mice for nuclear factor erythroid 2 like 2 (NRF2), a regulator of cellular antioxidant response and ethanol metabolism, was worsened by acute binge alcohol exposure, suggesting an involvement of oxidative stress or ethanol metabolites in alcoholic pancreatitis [117].

In addition to animal models, many *in vitro* models have been proposed to address the mechanisms underlying the pathology of alcoholic pancreatitis. The exocrine compartment of the pancreas is mainly composed of acinar and ductal cells. The pancreatic acinar cells are the functional unit of exocrine pancreas, constituting about 80% of the pancreas. Their function is to synthesize, store and secrete digestive enzymes. Acinar cells are believed by many to be the initiation site of pancreatic injury, as molecular and cellular events linked to acinar cell dysfunction have been shown to occur early in pancreatitis [118-121]. Similar to animal models, pancreatic acinar cells when treated by alcohol alone, but not in combination with other stressors *in vitro*, appeared to display minimal damages. Chronic alcohol exposure at a clinically relevant concentration (50 mM equivalent to 230 mg/dl, 96 hours) reduced the cellular uptake of thiamine pyrophosphate

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(TPP) in rat primary acini, rat pancreatic AR42J acinar cells [122] and mouse pancreatic 266-6 acinar cells [123], indicative of alcohol's damaging effects on pancreatic thiamine-dependent functions [124-126]. Alcohol exposure at the concentrations from 200 – 800 mg/dl for 6 hours caused mild apoptosis of AR42J cells and a minimal effect on the activity of lipase or amylase [127]. Lugea et al. (2017) showed alcohol treatment (50 mM equivalent to 230 mg/dl) for 4 days decreased the viability of AR42J cells only in combination with cigarette smoke extracts but not by itself [128]. In CCK-8-stimulated primary mouse pancreatic acini, alcohol treatment altered Ca^{2+} homeostasis [129], increased reactive oxygen species (ROS) production [130] and reduced CCK-8-evoked amylase secretion [131]. In rat pancreatic acini, alcohol treatment exacerbated the pathological intra-acinar protease activation induced by muscarinic agonist carbachol [132].

Pancreatic ductal cells, which are responsible for transporting the acini-produced digestive enzymes into the duodenum and secreting bicarbonate-rich fluid to neutralize stomach acid, have also been proposed to be involved in the pathology of pancreatitis [133-135]. Alteration of ductal cell function may cause insufficient transportation or precipitation of digestive enzymes in the ducal lumen, which may lead to obstruction and damage. Sarles et al. (1965) showed the formation of mucoprotein plugs in the pancreatic ducts was an early lesion in the pathology of alcohol-induced chronic calcifying pancreatitis [136]. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel protein highly expressed in pancreatic duct cells, was found to be associated with CP [137]. Maleth et al. (2015) showed ethanol exposure reduced the expression of CFTR, and disrupted the folding of CFTR at endoplasmic reticulum (ER) in a number of human pancreatic cell lines and pancreatic tissues of mice and guinea pigs [138]. In addition, CFTR knockout mice developed more severe pancreatitis when given ethanol than *WT* control mice [138].

Endoplasmic reticulum (ER) stress and unfolded protein response (UPR) in alcohol-related pancreatitis

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The endoplasmic reticulum (ER) is an intracellular compartment that plays a major role in protein folding and processing, and calcium storage and release, and it also serves as the first step of secretory pathway followed by the Golgi apparatus [139, 140]. Cellular stress factors, such as deficiencies in protein processing, disturbance in calcium level or the redox state, result in the accumulation of unfolded/misfolded proteins within the ER, which is known as ER stress and triggers an adaptive response known as unfolded protein response (UPR). UPR can either resolve the ER stress when the stress is reversible or cause cell death when the stress is irreversible. The pancreatic acinar cells are particularly vulnerable to ER stress because of their primary function, which is to synthesize and secrete digestive enzymes for food digestion, largely depending on ER functionality. ER stress and UPR signaling have been shown to be activated in a variety of experimental models of pancreatitis, including arginine-induced AP [141], caerulein- and taurocholate-induced AP [142], and CP induced by repeated episodes of caerulein [143]. The occurrence of ER stress and the activation of UPR signaling during the initiation of pancreatitis suggest that ER stress plays an important role in the development of pancreatitis. The involvement of ER stress in pancreatitis is also shown in the human studies as an autosomal dominant mutation (p. R116C) in human cationic trypsinogen gene, which is associated with hereditary pancreatitis, induces the accumulation of misfolded trypsinogen, ER stress and UPR signaling [144-147]. Although alcohol exposure only caused minimal pancreatic injury in animals with intact UPR functions [128, 148], loss of function of a UPR regulator X-box binding protein 1 (Xbp1) resulted in altered ER structure, acinar cell damage and pancreatitis-like features in alcohol-exposed animals, pointing to a critical protective role of UPR in alcoholic pancreatitis [80, 149].

UPR signaling is the major cellular response induced by ER stress, and it consists of three distinct but also interconnected intracellular signal transduction pathways (Fig. 1). These pathways are initiated by three ER-resident transmembrane sensor proteins: inositol-requiring kinase 1 (IRE1 both α and β isoforms), protein kinase-like ER kinase (PERK) and activating transcription factor 6 (ATF6 both α and β isoforms)[150-152]. These transmembrane sensor proteins

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have an ER luminal sensor domain and a cytosolic effector domain, thereby transmitting the protein folding status inside ER to other cellular compartments via intracellular signaling pathways. In non-stressed cells, all the sensor proteins remain inactive by binding to an ER chaperone 78-kDa glucose-regulated protein (GRP78) through their N-terminus [153, 154]. Under the conditions of ER stress, GRP78 dissociates from these sensor proteins to initiate their activation [153, 154]. The activated UPR signaling pathways attempt to stop improper translation, facilitate protein folding and therefore maintain ER homeostasis. However, if the ER stress is not resolved, UPR triggers cell death [155-157].

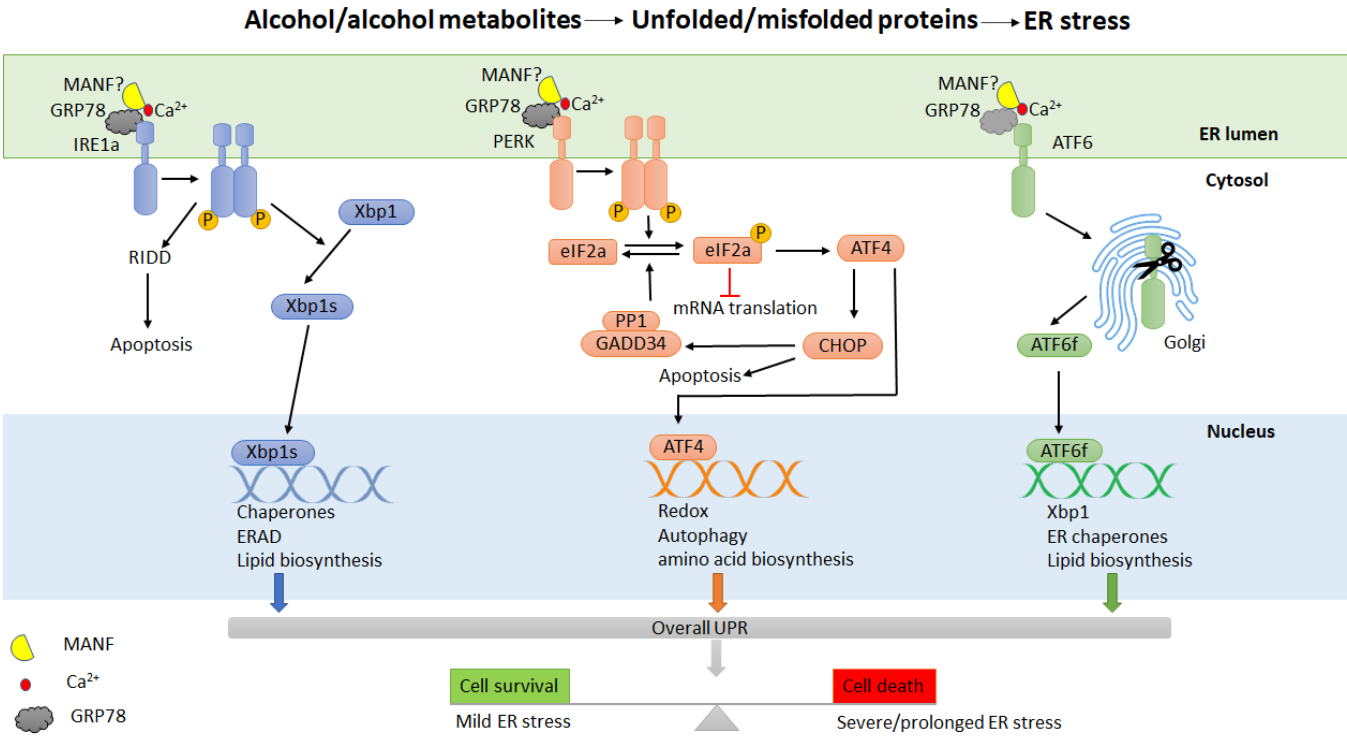

Figure 1: Alcohol exposure and ER stress. Alcohol and its metabolites may cause ER stress and induce a cellular adaptive response known as the unfolded protein response (UPR) in the pancreas. UPR is controlled by three transmembrane sensor proteins: inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). Under non-stressed conditions, these sensor proteins bind to GPR78 and possibly MANF in a calcium-dependent manner. Alcohol exposure results in the accumulation of unfolded or

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misfolded proteins in the ER, which in turn causes the release of GRP78/MANF to activate UPR. The activation of UPR regulates transcriptional and translational programs to either restore protein folding, promote protein degradation, or induce cell death.

IRE1 is the most evolutionarily conserved ER stress sensor protein with dual protein kinase and RNase activities [158-160]. At the onset of ER stress, dissociation of GRP78 activates IRE1, which involves dimerization and trans-autophosphorylation of IRE1 kinase domains, followed by the activation of the RNase domain in the cytosol. Activated IRE1 regulates the splicing of transcription factor X box-binding protein 1 (XBP1) to generate a more stable and active form known as Xbp1s [161]. XBP1s translocates to the nucleus and mediates the expression of a group of target genes in protein folding, ER-associated degradation (ERAD) and phospholipid synthesis, thereby acting as an adaptive response that promotes the folding capacity of ER to alleviate ER stress [151, 162, 163]. In addition, activated IRE1 also regulates a subset of RNAs leading to cell death through a process known as IRE1-dependent RNA decay (RIDD) [164-166]. Both IRE1 and XBP1 are essential in secretory cells, including pancreatic acinar cells [167, 168]. IRE1α conditional knock-out mice have lower pancreas mass and abnormally structured pancreatic acinar cells but showed no difference in the level of amylase expression and secretion [168]. Conditional disruption of Xbp1 caused decreased production of digestive enzymes and zymogen granules, altered ER structure and extensive apoptosis in mouse pancreatic acinar cells [167, 169]. In a mouse model for alcoholic pancreatitis, alcohol exposure activated IRE1/Xbp1-mediated UPR and only caused minimal pancreas damage in *WT* mice, while *Xbp1*$^{+/-}$ mice displayed significant acini necrosis, inflammation and reduction in zymogen granules and amylase levels, indicative of a protective role of XBP1 against alcohol-induced damages in the exocrine pancreas [170].

PERK is an ER-resident kinase that is composed of cytosolic and kinase domains [171, 172]. Similar to IRE1, the activation of PERK also involves dimerization and trans-autophosphorylation. Activated PERK phosphorylates the α-subunit of the translation initiation factor eIF2 (eukaryotic

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translation initiation factor-2) to reduce global protein synthesis [171-173]. This reduces the amount of protein entering the ER and alleviates ER stress. The phosphorylation of eIF2α by PERK also results in the selective translation of activating transcription factor 4 (ATF4), which regulates the expression of genes involved in protein folding, amino acid metabolism and autophagy [174, 175]. ATF4 also modulates the expression of proapoptotic molecules, including the transcription factor C/EBP homologous protein (CHOP) and growth arrest and DNA damage-inducible protein (GADD34) [176-178]. GADD34 plays a role in a feedback loop to dephosphorylate eIF2α by interacting with protein phosphatase 1 (PP1), which reverses translational inhibition and induces cell death [156, 179]. PERK is highly expressed in a number of tissues, including the exocrine and endocrine pancreas [180]. PERK knock-out (*Perk*$^{-/-}$) mice displayed reduced expression of major digestive enzymes, abnormal ER morphology and apoptosis of acinar cells and increased number of stellate cells [180, 181]. The loss of acinar cells and proliferative response of stellate cells in *Perk*$^{-/-}$ mice are also often observed in patients with chronic alcoholic pancreatitis [182]. In addition, the pancreatic acinar cell-specific *Perk* knock-out mice exhibit AP-like features, such as cell death and the inflammatory response [183].

ATF6 is an ER-localized membrane-bound transcription factor. Under ER stress, ATF6 is translocated to Golgi and cleaved proteolytically to release the transcriptionally active N-terminal domain, which enters the nucleus and activates the transcription of several UPR-related genes, including GRP78, Xbp1 and CHOP [161, 184, 185]. ATF6 has been shown to play an essential role in modulating the ER function particularly in chronic stress [186, 187]. High expression levels of ATF6, CHOP and Xbp1 have been observed in human CP pancreatic tissues, together with histological and cellular characteristics of CP, suggesting that ATF6/Xbp1/CHOP signaling may be involved in the development of CP [188]. In a CP model induced by caerulein injection in PRSS1 transgenic mice, ATF6 was shown to regulate the apoptosis of pancreatic acinar cells and the progression of CP [188].

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The timing and intensity of the activation of the three UPR signaling pathways are different in response to a particular ER stressor [157, 189, 190]. Alcohol exposure can cause ER stress and induce UPR in pancreas of animals and cultured pancreatic cells (Fig. 1). Depending on the experimental models and the paradigm of alcohol exposure, the three pathways of UPR are differentially impacted. For example, acute alcohol exposure increased UPR components, including GRP78, p-IRE1α, XBP1 and CHOP in human pancreatic acinar cells (hPACs) in a concentration-dependent manner [191]. Prolonged exposure of alcohol increased GRP78 and CHOP expression in AR42J cells [191]. In AR42J cells and mouse primary acini, the co-treatment of cigarette smoke extract and alcohol induced cell death, which was accompanied by PERK activation and increased expression of CHOP [128]. In animal models, it appears that a single episode of alcohol exposure is not sufficient to induce pancreatitis. Therefore, repeated exposure by binge drinking or combined binge and chronic alcohol exposure have been used and shown to cause pancreatitis. For example, repeated alcohol binge exposure (25% ethanol w/v, 5 g/kg/day for 10 days by oral gavage) resulted in pancreatitis-like features in male C57BL6 mice, including inflammation, increased UPR markers (ATF6, GRP78, p-PERK, p-eIF2α and CHOP), elevated expression of amylase and apoptosis [192]. A paradigm of chronic (5% ethanol diet for 2 weeks) plus binge alcohol exposure (5 g/kg, 25% ethanol w/v for 3 days) induced the expression of p-eIF2α, XBP-1, CHOP, ATF-6 and PERK; amylase secretion; pancreatic inflammation and apoptotic cell death in the mouse pancreas [82].

Potential treatment of alcoholic pancreatitis by targeting ER stress and UPR

Based on the aforementioned evidence and our own findings, we hypothesize that ER stress plays an important role in the etiology of alcoholic pancreatitis (Fig. 2). Although alcohol exposure alone may not directly result in pancreatitis, it works together with other pathological conditions, such as genetic alterations and cellular stressors, to initiate the pathogenesis of pancreatitis. Alcohol may promote pancreatitis through the following mechanisms: 1) Since

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alcohol exposure causes ER stress in the pancreas, pre-existing imbalance of ER homeostasis or ER dysfunction may exacerbate alcohol-induced ER stress, which is beyond UPR's ability to restore and results in severe pancreatic damages and pancreatitis; 2) The genetic mutations or protein alterations in key components of UPR or ER-associated degradation (ERAD) pathways may already impair pancreatic cells' ability to alleviate ER stress. Upon alcohol exposure, sustained and severe ER stress results in cell death, inflammation, and other pancreatic damages; 3) Reversely, alcohol exposure, especially chronic and heavy alcohol consumption, may disrupt ER homeostasis or impair UPR or ERAD systems, which sensitizes pancreatic cells to other genetic or environmental stressors. As a result, alcohol abusers are more susceptible to etiological initiators of pancreatitis.

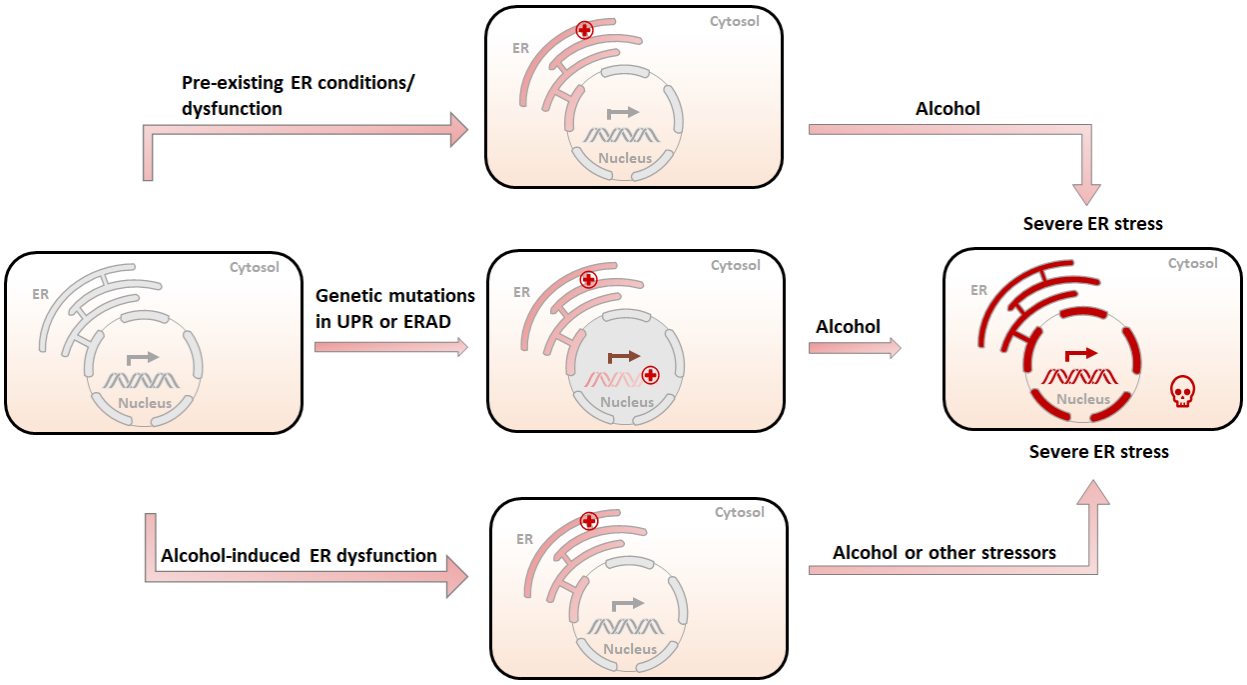

Figure 2: Possible etiology of alcohol-related pancreatitis. 1) A pre-existing ER condition resulting from stressors other than alcohol (tobacco, high-fat diet etc.) is further exacerbated by alcohol exposure, which causes irreversible damage of the ER and subsequent cell death. 2) Genetic mutations in UPR or ERAD compromise the ability of ER to dealing with unfolded/misfolded proteins, and therefore sensitize the ER to alcohol-induced damages, which

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leads to severe ER stress and pancreatic damages. 3) Pre-exposure to alcohol compromises the ability of ER to maintain its homeostasis and makes the ER to be susceptible to subsequent alcohol exposure or other ER stressors, resulting in severe pancreatic damages.

Since ER stress plays an important role in the pathogenesis of alcoholic pancreatitis, pharmacological modulations that target ER stress may be an effective strategy for therapy (Fig. 3). Small molecules that can regulate ER homeostasis and the UPR/ERAD system have drawn great attention for this purpose. In addition, repurposing existing drugs in a new pharmacology class is the safest and cheapest option for disease intervention. Although there are currently no drugs approved by the FDA for alcoholic pancreatitis, a number of FDA-licensed drugs that exert therapeutic effects through controlling ER homeostasis and mitigating ER stress can be repurposed and tested for the disease [193-195].

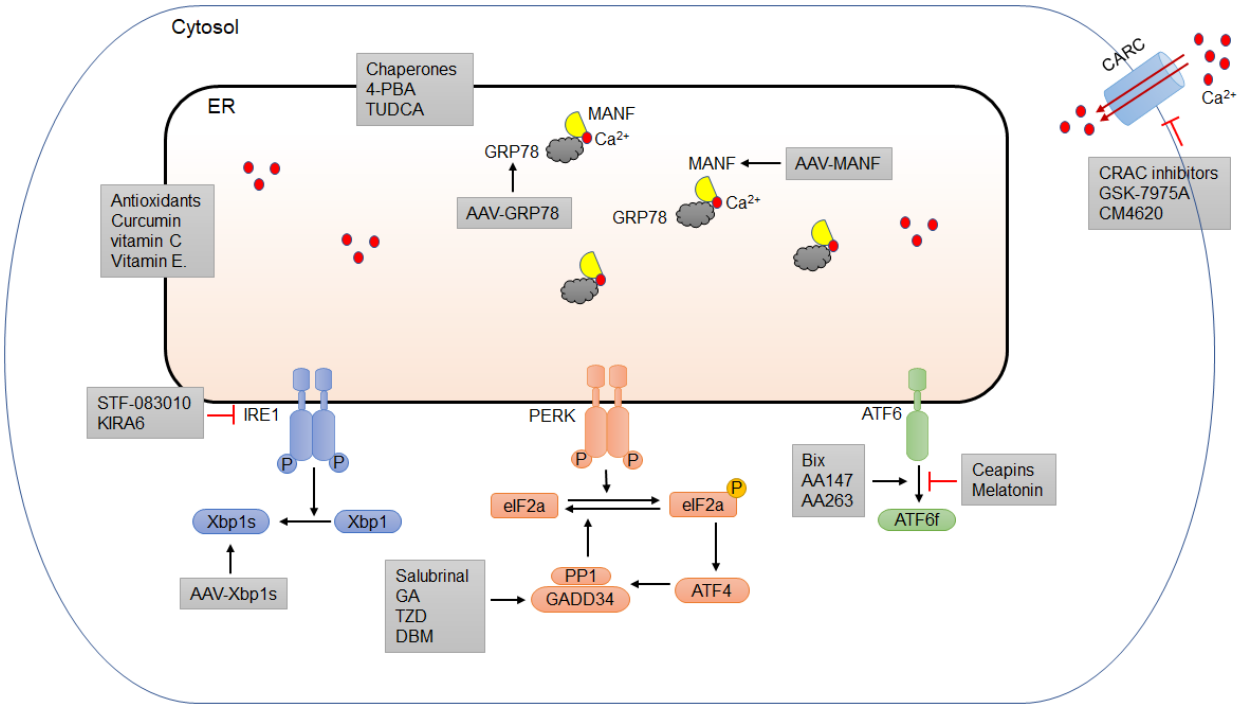

Figure 3: Potential pharmacological intervention for alcoholic pancreatitis targeting ER homeostasis. It is of great potential to identify specific molecules or strategies targeting ER

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stress and different UPR components. One of the most direct pharmacological approaches to alleviate ER stress is to use chemical chaperones, such as 4-PBA and TUDCA to facilitate protein folding and alleviate ER stress. Another effective approach is to use specific small molecule inhibitors or activators to modulate different UPR components. Among the three arms of UPR, PERK/eIF2α is the most important in controlling the protein translation and the transition to apoptotic cell death and has been drawn greater attention. A number of small molecules targeting this pathway have been shown to have protective effects against ER stress-induced damages. Recently, several FDA-approved drugs that can affect some UPR components exhibit potential benefits to alleviate ER stress and reduce pancreatic damages. One of potential mechanisms for alcohol-induced ER stress is the perturbation of ER calcium homeostasis. Small molecules targeting calcium channels have therapeutic potential for ER stress-induced pancreatic damages. Antioxidants, such as vitamin C and vitamin E have been shown to alleviate ER stress and may be useful to treat alcoholic pancreatitis. Gene therapy using recombinant viruses, such as Adeno-associated viruses (AAVs) is becoming an attractive strategy to deliver active UPR components to specific tissues to mitigate ER stress. AAV delivery of several key UPR proteins, such as GRP78 and MANF demonstrates promising benefits to treat ER stress-related tissue damages.

One of the most direct pharmacological approaches to alleviate ER stress is to use small molecules that function as chemical chaperones to facilitate protein folding [196]. There are several chemical chaperones, including FDA-licensed drugs such as sodium phenylbutyrate (4-PBA) and ursodeoxycholic acid (UDCA) that can be readily repurposed for the treatment of alcoholic pancreatitis (Fig. 3). 4-PBA has been approved by the FDA for the treatment of patients with urea cycle disorders by acting as an ammonia scavenger [197, 198]. 4-PBA can also act as an ER stress inhibitor and has been suggested to modulate the restoration of ER homeostasis in many pathological conditions [8, 199-201]. Hong et al. (2018) showed that 4-PBA attenuated tissue injury which was accompanied by reduction of the expression of ER stress markers, inflammatory

response and cell death in sodium taurocholate-induced AP in rats [202]. In addition, the trypsin activation, UPR signaling and apoptosis of rat pancreatic acini induced by the supraphysiological cholecystokinin were suppressed by 4-PBA [203]. UDCA, also known as ursodiol, is a bile acid that has been approved by the FDA as a therapy for gallstone and liver diseases [204-206]. UDCA appears to have beneficial effects in treating idiopathic pancreatitis [207, 208]. However, due to its poor absorption, people have recently shifted their attention to tauroursodeoxycholic acid (TUDCA), a more readily absorbed form that also has the same cytoprotective properties as UDCA. TUDCA is an ER chaperone that has been shown to attenuate ER stress and reduce intracellular trypsin activation, edema formation and the inflammatory reaction of pancreatic tissue in a caerulein-induced AP rat model [209]. Pretreatment of TUDCA suppressed ER stress responses and alleviated ER stress-associated apoptosis in cholecystokinin (CCK-8)-stimulated rat pancreatic acini [210].

Another approach to relieve ER stress is to manipulate the UPR pathways by using small molecule inhibitors or repurposed FDA-licensed drugs (Fig. 3). Among the three arms of UPR, PERK/eIF2α is the most important in controlling the protein translation and the transition to apoptotic cell death [211, 212]. Chemicals that can reduce the protein translation by modulating the PERK/eIF2α pathway are of therapeutic potential. Salubrinal is a selective inhibitor of eIF2α phosphatases that was initially identified in a screen for small molecules that protect the rat pheochromocytoma cell line PC12 from ER stress-induced apoptosis [213]. A recent study showed that salubrinal ameliorated pancreatic injuries by inhibiting the dephosphorylation of eIF2α in caerulein/LPS-induced-AP in mice [214]. However, increased eIF2α phosphorylation by salubrinal was proapoptotic in pancreatic beta cells and exacerbated the toxicity of ER stressors such as the free fatty acids oleate and palmitate, which makes salubrinal an unfavorable drug candidate to treat pancreatic disorders like alcoholic pancreatitis [215]. There are several FDA-approved drugs, including guanabenz acetate (GA), trazodone (TZD) and dibenzoylmethane (DBM), that have been shown to target different components of the PERK/eIF2α pathway and can mitigate ER

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stress. GA is an FDA-approved anti-hypertensive drug. Trazodone is a licensed anti-depressant. DBM is a curcumin analogue that has anti-cancer properties [216]. These drugs have outstanding pharmacokinetics and are considered safe. GA has been shown to attenuate ER stress and play a beneficial role in several models of neurological diseases, including amyotrophic lateral sclerosis (ALS), oculopharyngeal muscular dystrophy (OPMD), hereditary spastic paraplegias (HSPs) and spinal cord injury (SCI) [217-220]. However, It has also been reported that GA sensitizes pancreatic β cells to fatty acid-induced ER stress and apoptosis through PERK/eIF2α signaling [221]. TZD and DBM have been shown to provide neuroprotection and cognitive improvement by reducing protein accumulation in models of prion disease and frontotemporal dementia, with no overall toxicity [193]. In a small-molecule screening for the treatment of diabetes, TZD has been identified as a stimulator for the proliferation of pancreatic β cells [222]. Despite its short-term benefit in alcohol withdrawal syndrome [223, 224], TZD may increase alcohol consumption and worsen the drinking outcomes when stopped [225]. The effects of these drugs in alcoholic pancreatitis, therefore, need to be evaluated in the preclinical models first.

IRE1α/XBP1 signaling pathway is another UPR arm that has been implicated in experimental models for alcohol-induced pancreatitis [170, 226]. There are two classes of small molecule inhibitors for IRE1α that have been developed to modulate IRE1α/XBP1 signaling in ER stress-mediated diseases [227]. The first group binds to the RNase domain of IRE1a and inhibits its RNase activity. These inhibitors, including toyocamycin, 3-Ethoxy-5,6-dibromosalicylaldehyde, STF-083010 and 2-Hydroxy-1-naphthaldehyde, have been shown to induce apoptosis in a number of pancreatic tumor cell lines [228]. Of note, STF-083010 has been shown to protect mouse pancreatic 266-6 acinar cells from alcohol-induced cytotoxicity *in vitro* [229] (Fig. 3). Another inhibitor which also belongs to the first group, MKC-3946, was shown to cause cell death in rat pancreatic AR42J acinar cells, primary mouse and human acinar cells *in vitro* [128]. The second class of IRE1α inhibitors targets its kinase domain to exert allosteric control of IRE1α RNase activity. One of the IRE1α kinase inhibitors, kinase-Inhibiting RNase-Attenuator 6 (KIRA6), was

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recently developed and shown to promote the viability and function of the pancreatic beta cells in ER-stress-induced diabetic mice [230] (Fig. 3). Given the opposite effects that IRE1 inhibitors exert on cellular survival and function in different disease models, one should take precautions when repurposing them for alcoholic pancreatitis and examine their effects in experimental models on a case-by-case basis.

The modulators of ATF6 are few due to the unavailability of the crystal structure of the ATF6 protein, which presents challenges for the identification of druggable binding sites [231]. Using a cell-based assay, Gallagher identified ceapins as a class of ATF6- specific inhibitors by preventing the translocation of ATF6 from the ER to the Golgi upon ER stress [232]. The effect of ceapins on the viability or function of pancreatic acinar cells, however, has not been tested in pancreatic inflammatory contexts. Melatonin is another ATF6 selective inhibitor. In a rat model for intracerebral hemorrhage, melatonin has been shown to exert neuroprotective effects via the suppression of the ATF6 pathway [233]. Melatonin was also shown to attenuate inflammation in LPS-induced AP in AR42J cells and in taurocholate-induced AP in rats [234, 235]. Interestingly, pharmacologic ATF6 activation has also been shown to be protective in many diseases, including ischemic heart disease, and diabetes and neurodegenerative disorders [236-240]. Through reporter-based assays, Bix, compound 147 (AA 147) and 263 (AA 263) have been identified and specifically activate the ATF6 arm of the UPR [241-243]. Bix has been shown to exert beneficial effects in experimental models for multiple disease conditions, such as stroke and kidney injury [243, 244]. In a mouse model of ischemic heart disease, AA 147 was shown to exert a protective effect in multiple tissues, including heart, brain, kidney and liver [236]. These selective ATF6-activating compounds are ready to be tested in experimental models for alcoholic pancreatitis.

ER stress can also result from perturbations of calcium level, as ER resident chaperones and folding enzymes have calcium-binding sites and calcium-dependent functions [245]. Alcohol and its metabolites can deplete calcium level in the ER by activating inositol trisphosphate receptors, calcium release channels located in the ER, to induce ER stress and pancreatic acinar

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cell death and inflammation in experimental models for alcohol-related pancreatitis [246, 247]. The release of calcium from the ER would elevate the calcium level in the cytosol, which in turn would activate calcium release-activated calcium (CRAC) channels on the plasma membrane to promote the uptake of extracellular calcium, which would further increase the concentration of intracellular calcium. The pathological elevation of cytosolic calcium and the activated CRAC can further augment cell death and inflammation in the pancreas [133, 248-251]. Small molecules targeting calcium channels have therapeutic potential for ER stress-related disorders like alcoholic pancreatitis. For example, two small molecule inhibitors of CRAC channels (Orai1), GSK-7975A and CM_128 (also known as CM4620), have been shown to inhibit the activation of ORAI1 and prevent cell death and inflammation in thapsigargin-treated human pancreatic acinar cells and mouse models of AP induced by alcohol and palmitoleic acid [249](Fig. 3). In addition to acinar cells, CM4620 has also been shown to target pancreatic stellate cells and immune cells, block calcium entry and reduce pancreatitis features and severity in experimental AP models [252]. In fact, CM4620 has reached Phase I clinical trials for treating AP due to its adequate specificity and low toxicity [253].

Alcohol can also cause ER stress and pancreatic acinar cell injury by altering the redox state of the ER. Many experimental models of alcohol-related pancreatitis have shown that alcohol exposure leads to oxidative stress in the ER through its oxidative metabolites/by-products or the generation of ROS [82, 128, 192, 254]. Curcumin is a natural antioxidant extracted from turmeric that has been shown to protect the pancreas by lowering the severity and inflammatory response in a rat pancreatitis model induced by alcohol and a low-dose of CCK [255] and non-alcoholic pancreatitis models [255-257]. Because of its safeness, tolerability and low toxicity, curcumin has been tested in clinical trials for numerous diseases [258], both alone or in combination with other reagents, and it has been shown to be protective against alcohol intoxication [259] and pancreatic cancer [260-262]. Therefore, curcumin is a promising candidate for the treatment of alcoholic pancreatitis. Other therapeutical antioxidant candidates are vitamins that have antioxidant

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properties, such as vitamin C and E. Both vitamins are significantly low in the dietary intakes of patients with idiopathic CP [263] or low in the blood of patients with alcoholic AP [264] or CP [265]. Supplementation of vitamin C or vitamin E have been shown to exert anti-inflammatory and other beneficial effects in AP patients [266] and in a rat model of alcoholic CP [267].

Gene therapy using recombinant viruses is becoming an attractive strategy to deliver active UPR components to specific tissues. This method avoids the pleiotropic effects of systemic and chronic administration of ER stress-targeting compounds. Adeno-associated viruses (AAVs) are the current choice to deliver therapeutic genes because of their safety profile demonstrated in pilot clinical trials [268]. GRP78 is an important ER chaperone and participates in the regulation of all three arms of UPR signaling [269]. Enhanced GRP78 expression can alleviate ER stress in experimental models for a variety of disorders [270]. For example, AAV-mediated gene transfer of GRP78 ameliorated retinal cellular injury by mitigating ER stress in mice [271], rats [272] and human retinal epithelium cells [273]. In a rat model of Parkinson's disease, overexpression of GRP78 by recombinant AAV attenuated ER stress, promoted the survival of nigral dopamine (DA) neurons and restored behavioral deficits [274]. Over-production of GRP78 driven by a rat insulin promoter in pancreatic beta cells provided protection against high-fat-induced ER stress and diabetes in mice [275]. In a caerulein-induced AP model, *Grp78*$^{+/-}$ mice displayed greater pathological alterations, including morphological change, cell necrosis, edema and inflammation, when compared to wild-type mice, suggesting a protective role of GRP78 in AP [276]. Therefore, one may take GRP78 into consideration as a potential therapeutic target in alcoholic pancreatitis, and AAV-mediated delivery of GRP78 may be readily tested in experimental models.

The downstream transcription programs of the three UPR signaling pathways are mediated by transcription factors XBP1 (IRE1 pathway), ATF4 (PERK pathway) and ATF6 (ATF6 pathway), either individually or co-operatively. Gene delivery of those transcription factors may also be a potential strategy to optimize the beneficial effects of certain pathways in different diseases. Overexpression of XBP1 in the nervous system of adult animals by viral-based delivery

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has been shown to exert protective effects in a mouse model for Huntington's disease (HD) [277], spinal cord injury [278] and PD [279, 280]. More recently, co-expression of XBP1 and ATF6 in a fusion protein by AAV-based delivery showed a more potent effect in neuroprotection and anti-aggregation of mis-folded proteins than XBP1 or ATF6 alone in preclinical models for PD and HD, suggesting a cooperative action of XBP1 and ATF6 in enhancing the folding capacity of the ER and promoting cell survival under disease settings [281]. Overexpression of XBP1 by AAV-mediated delivery may be a promising therapeutic strategy readily tested in alcoholic pancreatitis because XBP1 has been implicated to have a beneficial role in alcohol-induced pancreatic damages in an experimental model for alcohol-related pancreatitis [80]. However, ATF6 has been shown to play a detrimental role in a mouse model for severe AP [282] and CP [188]. Therefore, one should remain cautious when testing the effects of its overexpression in alcoholic pancreatitis. In contrast to the beneficial effects of overexpression of ATF6 and XBP1 in neurodegenerative disorders, AAV-mediated overexpression of ATF4 has been shown to have deleterious effects in the brain of animal models for PD and caused behavioral deficits when compared to the control [283]. Excessive expression of ATF4 by AAV-mediated delivery resulted in cell death associated with ER stress in mouse models for progressive retinal degeneration [284]. A more recent study showed that ATF4 contributed to the pathogenesis of AP in caerulein-induced AP mouse models [285]. Therefore, AAV-mediated delivery of ATF4 seems to be unlikely to exert therapeutic benefits to the alcohol-induced pathology in the pancreas.

Another molecular target of interest in the treatment of alcoholic pancreatitis is mesencephalic astrocyte-derived neurotrophic factor (MANF). MANF is an ER stress-inducible secretory protein expressed in many human and mouse tissues, with a particularly high expression level in secretory tissues such as the pancreas [286, 287]. MANF is activated by alcohol exposure and plays a protective role by alleviating alcohol-induced ER stress in the brain and in cultured acinar cells [199, 229, 288] (Fig. 3). The cytoprotective role of MANF in the pancreas has been demonstrated by increased apoptosis and reduced proliferation of pancreatic beta cells and an

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insulin-deficient phenotype in pancreatic MANF knockout mice [289, 290]. In humans, MANF has also been shown to be essential for ER function and proper pancreatic beta cell function [291, 292]. In fact, MANF has been proposed to serve as a diagnostic biomarker for children with type I diabetes, given the elevated level of MANF found in the serum of type I diabetic children [293]. In contrast to the role of MANF in the endocrine function of the pancreas which has been well characterized, the role of MANF in the exocrine compartment of pancreas has not drawn much attention until very recently. Using an *in vitro* model, we showed an siRNA knockdown of MANF exacerbated alcohol-induced damages in mouse pancreatic 266-6 acinar cells; whereas addition of recombinant human MANF or overexpression of MANF by adenovirus ameliorated alcohol-induced ER stress and cellular injury [229]. While this finding may imply a beneficial role for MANF in alcoholic pancreatitis, further studies of measuring the effect of gain- or loss-of-function of MANF on pancreatitis features in animal alcoholic pancreatitis are necessary. Delivery of the MANF gene to the brain using AAV protected neurons against ischemic injury in animal models [294-298]. Therefore, it is of interest to determine whether AAV delivery of the MANF gene to the pancreas can exert protective effects against alcohol-induced damages. In addition, the serum level of MANF in patients with alcoholic pancreatitis is also worth investigating to determine if MANF can be a biomarker for alcoholic pancreatitis.

Conclusions

Alcoholic pancreatitis is a serious medical concern worldwide and remains to be one of the common causes of pancreatic disease. However, there are no FDA-approved drugs or treatments available for the disease. ER stress has been shown to play a critical role in the pathogenesis and progression of alcoholic pancreatitis. Approaches targeting ER stress may open a new avenue for therapeutic strategies for the disorder. Small molecules and FDA-approved chemicals that aim at UPR and ER homeostasis may be beneficial and promising. Gene therapy for delivering key ER chaperones or UPR proteins to the pancreas may also provide protection (Fig. 3). Further investigation on the precise mechanisms and contribution of each

individual UPR pathway/molecule in response to ER stress in alcoholic pancreatitis could provide insight for novel therapeutic strategies for the disease.

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Conflicts of Interest

The authors declare no conflict of interest.

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