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Acute pancreatitis: pathogenesis and emerging therapies

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Abstract

Acute pancreatitis is a severe inflammatory disorder with limited treatment options. Improved understanding of disease mechanisms has led to new and potential therapies. Here we summarize what we view as some of the most promising new therapies for treating acute pancreatitis, emphasizing the rationale of specific treatments based on disease mechanisms. Targeted pharmacologic interventions are highlighted. We explore potential treatment benefits and risks concerning reducing acute injury, minimizing complications, and improving long-term outcomes. Mechanisms associated with acute pancreatitis initiation, perpetuation, and reconstitution are highlighted, along with potential therapeutic targets and how these relate to new treatments.

Keywords: Acinar cell, Acute pancreatitis, Calcium signaling, Transporters, Treatment

Introduction

Acute pancreatitis (AP), a sudden inflammatory disease of the pancreas, can range from mild discomfort to a severe, life-threatening illness. It is one of the most common causes of gastrointestinal disease-related hospitalizations in the United States.[1] Past AP annual expenditures in the United States were estimated to be $2.6 billion.[2] Globally, the pooled incidence of AP is approximately 34 cases per 100,000 general population, making it a significant concern for public health.[3] Moreover, the global incidence of AP is increasing, with an estimated average annual percent increase of approximately 3% between 1961 and 2016.[4]

There is considerable morbidity and mortality as well as medical costs associated with AP. Globally, there were approximately 115,000 AP deaths in 2019.[5] In its most severe form, AP can result in systemic inflammatory response syndrome (SIRS), multiple organ failure (MOF), increased infection rates, and mortality rates of up to 30% in those with severe disease.[6] Though most AP patients survive the disease, they can experience long-term consequences, including recurrent AP, chronic pancreatitis, exocrine and endocrine insufficiency, and an increased risk of pancreatic cancer.[7–9]

Although the risks associated with AP are well known, current treatment strategies for AP are supportive and include fluid resuscitation, pain management, and nutritional support.[10] Current treatment paradigms do not target the underlying pathophysiological mechanisms of this disease. Investigators have anticipated that understanding AP's natural history and mechanisms will lead to new therapeutic strategies to reduce this debilitating disease's short-term and long-term burden; these goals are just being met. This article aims to delve into the most foundational mechanisms underlying AP and explore related new potential treatments that could improve patient outcomes.

Goals of therapy

The primary goals of AP therapy are multifaceted and aim to reduce the severity of the acute injury and its complications, shorten intensive care unit (ICU) and hospital stays, reduce mortality, and decrease the associated medical and quality of life costs. An unresolved question is whether limiting acute and short-term injury will reduce the emerging longer-term complications such as pancreatic exocrine insufficiency, diabetes, and pancreatic cancer. For example, research has highlighted the role of interleukin (IL)-6 as an early predictive marker for severe pancreatitis.[11] Other studies have underscored the importance of IL-6 in driving the progression of preneoplastic pancreatic lesions.[12,13] These findings prompt an intriguing question of whether therapies targeting IL-6 in the short-term could potentially reduce the risk of pancreatic cancer or other long-term complications in patients with AP and prompt the question of the timing and length of therapy needed to do so. The potential negative effects of treatments also need to be considered. For example, what is the risk of reducing acute inflammatory responses to an extent that might increase the risk of infection or change healing responses? Thus, the duration of treatment and balance between managing the acute phase and preventing short-term and long-term complications need to consider potential off-target effects of treatments.

Mechanisms of pancreatitis injury and recovery vary over time

Our mechanistic knowledge of pancreatitis comes largely from in vivo rodent studies and ex vivo studies in rodent and human pancreatic tissue slices and isolated pancreatic cells. Confirmation of mechanisms described in rodents in human tissues has been limited. In brief, the initiating event most often occurs in the pancreatic acinar cell, where multiple forms of injury can lead to abnormal intracellular calcium signaling.[14]

Though less studied, injury responses also occur in the pancreatic duct and endothelial cells early in the disease and contribute

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to disease initiation and perpetuation.[15] Changes in acinar cell calcium signaling can coordinate pathologic responses in mitochondria and autophagic pathways,[16] activate digestive enzymes within the acinar cell, misdirect secretion, and drive the production of inflammatory mediators. A complex-ordered inflammatory cascade follows in the pancreas, likely beginning with platelets, then neutrophils and inflammatory macrophages. The resolution of AP requires suppressing the acute inflammatory cells and activating an anti-inflammatory cascade. Other factors, such as reduced blood flow, vascular injury, vessel occlusion, tissue hypoxia, and neurogenic inflammation, can modulate the injury's severity and recovery effectiveness.

Less is known about the factors regulating the AP recovery phase than those mediating early phases of injury or how the acute therapies discussed below might affect recovery and long-term AP sequelae. However, in addition to the mechanisms previously described, one key aspect of tissue recovery is the clearance of necrotic debris and revascularization.[17] This process is mediated by macrophages, which phagocytize necrotic tissue and facilitate recovery.[18] One group has demonstrated that M1 macrophages dominate during the proinflammatory phase of AP, while M2-like macrophages dominate during pancreas repair and regeneration. Depletion of M2-like macrophages during the recovery phase delayed inflammation resolution.[19]

The precise mechanisms and signaling pathways governing the regenerative processes in the pancreas following AP remain incompletely understood. Furthermore, the long-term consequences of AP, such as the development of new-onset diabetes and pancreatic insufficiency, are areas of growing concern and active research.[20] In a review of 24 prospective clinical studies involving 1102 patients with a first episode of AP, newly diagnosed diabetes mellitus developed in 15% of individuals within 12 months after the first episode of AP.[21] One meta-analysis of 1795 patients from 39 studies demonstrated that 35% of patients studied had exocrine pancreatic insufficiency after AP on follow-up after hospital discharge.[9] It remains unclear how early intervention in AP, particularly strategies aimed at avoiding SIRS, might influence long-term outcomes such as these. This has led to initiatives like the Diabetes RElated to Acute Pancreatitis and its Mechanisms (DREAM) Study, a prospective cohort study designed to investigate and provide the evidence needed to screen for, prevent, and treat DM after AP.[22] There remains a need for continued research into the immediate management of AP and the long-term monitoring and treatment of patients to mitigate these secondary complications.

Pathologic responses of the acinar cell that drive AP and therapeutic targeting

Calcium signaling

There is a consensus that acinar cell calcium signaling changes usually initiate AP.[14,23] In acinar cells, physiologic cytosolic calcium signals oscillate, are transient, and are essential for regulated digestive enzyme secretion. However, in the early phase of AP, acinar cell cytosolic calcium levels are elevated above physiologic responses (5–20-fold), prolonged, and physiologic calcium oscillations disappear. These pathological, sustained elevations in cytosolic calcium are an early event in models of AP and are seen in rodent and human acinar cells.[24,25] The changes in cytosolic calcium signaling can drive mitochondrial dysfunction with the opening of the mitochondrial transition pore and subsequent reductions in ATP levels, intracellular trypsinogen activation,[26] disordered autophagy,[27] endoplasmic reticulum (ER) stress,[28] reduced apical and enhanced basolateral zymogen granule exocytosis,[29] and tight-junction disruption.[30] Though the direct targets of this elevated calcium remain unclear and may be manifold, a role for the calcium-activated phosphatase, calcineurin, in the pathogenesis of AP has been confirmed by using calcineurin inhibitors and mice with calcineurin deletions.[31,32] However, the direct cellular targets of calcineurin that transduce signals and ultimately mediate acinar pancreatitis responses have yet to be identified.

Cellular calcium transporters regulate physiologic calcium homeostasis and can contribute to the early disordered acinar cell calcium signaling in pancreatitis (Fig. 1). Many transporters are important for calcium homeostasis in pancreatic acinar and are shared by inflammatory cells. Intracellularly, the ER-associated inositol 1,4,5-tris-phosphate receptors (IP3Rs) and ryanodine receptors (RYRs) enable calcium to move from the ER stores into the cytosol.[14] Mediators of calcium import on the plasma membrane include store-operated calcium entry (SOCE) channels such as the Orai proteins (particularly Orai1) and transient receptor potential cation (TRPC) channels such as transient receptor potential cation channel subfamily V 1 (TRPV1) and TRPV6. The discrete homeostatic mechanisms that regulate calcium entry across the plasma membrane, calcium release from ER stores, and mitochondrial calcium and lysosomal fluxes modulate cytosolic calcium levels under physiologic conditions and during AP (Fig. 1). Lysosomal, mitochondrial, and nuclear calcium fluxes may modify these responses. Following a stimulus, acinar cell cytosolic calcium levels are primarily reduced by extrusion across the plasma membrane and re-uptake into the ER.

Calcium efflux across the acinar cell plasma membrane is critical for lowering cytosolic calcium levels and largely mediated Ca^{2+} ATPases (PMCA) family of transporters.[33] Na^{+}/Ca^{2+} exchange has little to no role in acinar cell calcium homeostasis. The primary calcium-regulatory mechanisms are largely conserved among various cell types, including inflammatory and stellate cells.[23] Knowledge of the regulatory pathways for calcium entry and extrusion has led to new approaches for AP treatment. Agents that inhibit Ca^{2+} entry or enhance Ca^{2+} extrusion are summarized below and, in Figure 2, have shown considerable promise for reducing AP severity.

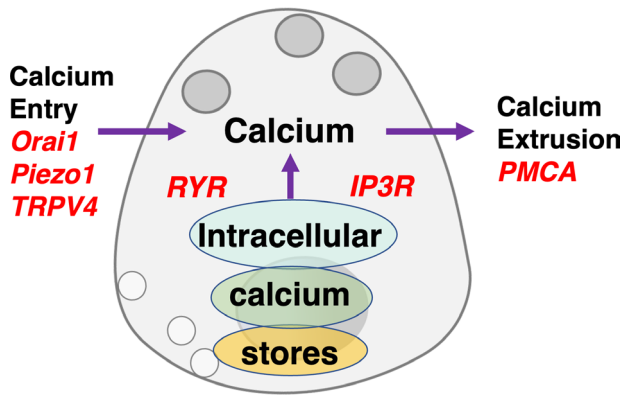

Figure 1. Schematic representation of cellular Ca^{2+} transporters and their role in Ca^{2+} homeostasis. Multiple transporters and proteins regulate acinar cell calcium signaling and are relevant to early acute pancreatitis responses. The schematic illustrates key transporters involved in calcium entry (Orai1, Piezo, TRPV4), intracellular calcium regulation (RYR, IP3R), and calcium extrusion (PMCA). These transporters play a crucial role in maintaining calcium balance in pancreatic acinar cells and inflammatory cells, and their dysregulation can contribute to early disordered signaling in the pathogenesis of acute pancreatitis. IP3R = inositol 1,4,5-tris-phosphate receptor, PMCA = plasma membrane calcium ATPase, RYR = ryanodine receptor, TRPV = transient receptor potential cation channel subfamily V.

Calcium entry (stromal interaction molecule 1, TRPV, Piezo)

SOCE responds to decreases in ER calcium by increasing calcium influx through the calcium release-activated calcium channel Orai1 and its sensor stromal interaction molecule 1 (STIM1), which are located on the plasma membrane and ER, respectively. When ER calcium is depleted, STIM1 oligomerizes and translocates to ER-plasma membrane junctions, where it binds and gates Orai1 to activate SOCE, resulting in calcium entry into the cell.[34] The prominent role of calcium signaling in AP's pathogenesis has focused investigators on regulators of calcium ion flux as potential AP therapeutic targets. For example, CM4620, GSK-7975A, and CM128 are small molecule inhibitors of Orai1, a component of SOCE channels formed by STIM1 and Orai complexes that facilitate Ca^{2+} entry into pancreatic acinar cells. The Orai1 inhibitors CM4620, GSK-7975A, and CM128 can significantly reduce the severity of AP in rodent models by inhibiting SOCE in pancreatic acinar cells, conferring substantial therapeutic benefits in rodent AP models.[35,36] This has moved into human trials for AP therapy. In a phase-2, open-label, dose-response study, 21 patients with AP, SIRS, and hypoxemia were randomized to receive low-dose or high-dose CM4620 plus standard of care (SOC) or SOC alone. CM4620 showed a positive safety profile in this study without increasing serious adverse events compared to SOC. Patients treated with CM4620 displayed improved AP severity, better tolerance to solid foods, reduced persistent SIRS, and decreased hospitalization durations.[37] These are promising preliminary findings.

TRPC channels mediate a significant portion of the receptor-stimulated Ca^{2+} influx. The vanilloid receptor-1 (TRPV1) was the first member of the TRPV subgroup within the TRP family to be discovered, consisting of 6 mammalian members that act as Ca^{2+} entry channels responsive to diverse physical and chemical triggers.[38] Furthermore, mechanical stressors (trauma, gallstones) can initiate AP responses by stimulating calcium influx through these channels. The mechanosensitive ion channel Piezo1 is expressed in pancreatic acinar cells and plays a key role in pressure-induced pancreatitis. Pressure-induced activation of the Piezo1 ion channel can trigger the opening of the TRPV4 channel, resulting in toxic calcium overload and AP.[39] Elevating pressure in the mouse pancreatic duct leads to pancreatitis; this can be prevented by blocking or deleting Piezo1. The Piezo1 antagonist GsMTx4 reduces the severity of AP in murine models.[40] Additionally, inhibiting Piezo1 function is sufficient to prevent pressure-induced AP, while activating Piezo1 can induce pancreatitis in normal mice but not in mice where Piezo1 has been deleted from acinar cells.[40] These findings suggest that blocking Piezo1 could prevent pancreatitis caused by trauma, gallstones, or medical procedures such as endoscopic retrograde cholangiopancreatography (ERCP) that increase pressure in the pancreas. To our knowledge, there are no clinical trials yet that target Piezo1 or TRVP channels.

Calcium release from intracellular stores (IP3Rs, RYR)

****RyRs are channel proteins in the ER that facilitate the release of Ca^{2+} from ER calcium reservoirs into the cytosol. Additionally, IP3Rs are channels that regulate the release of Ca^{2+} from the ER into the cytosol.[41] Our group reported that in rats, zymogen activation is driven by Ca^{2+} release regulated by the RYR.[42] Experimental data demonstrated that blocking RYR or depleting its Ca^{2+} pools curtailed zymogen activation without affecting enzyme secretion.[42] Thus, RYR's role in mediating zymogen activation, not enzyme release, underscores its potential involvement in AP. It was later demonstrated that inhibiting RYR reduces early pancreatitis injury. Using the RYR inhibitor dantrolene in mice, it was observed that pretreatment substantially reduced cerulein-induced pancreatitis.[43] Specifically, dantrolene decreased pancreatic trypsin activity and serum amylase levels and improved the overall pancreatic histology and evidence of cellular damage.[43] Though these findings suggest RYR's activation may have a significant role in pancreatitis, to our knowledge, its inhibition has not yet been used prospectively in a clinical setting in the setting of AP. However, dantrolene has been used in human clinical trials in phase Ib/IIa trials of patients with Type 1 Wolfram syndrome, a disorder of ER calcium homeostasis.[44]

Other small molecules, such as caffeine, have been investigated in the setting of calcium signaling in AP. Caffeine and its metabolites inhibit pathological IP3R-mediated calcium signaling in pancreatic acinar cells, a response implicated in AP initiation. Caffeine reduced the severity of experimentally-induced AP by cerulein, taurolithocholate acid, and fatty acid ethyl esters in mice. The protective effects were likely due to inhibition of IP3R calcium signaling rather than other potential mechanisms like phosphodiesterase inhibition. However, high doses of caffeine, up to 25 mg/kg, were required for protective effects in the animal models, which are not practical for clinical use in humans. The findings suggest methylxanthine-based compounds like caffeine might be suitable starting points for

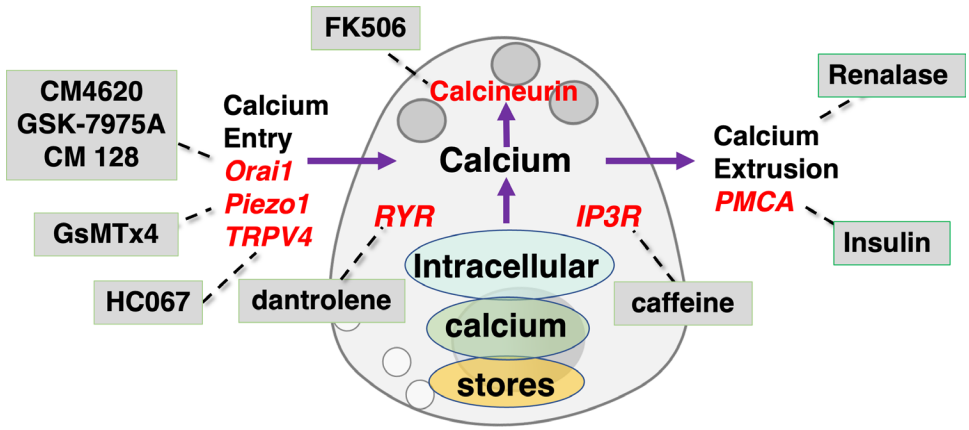

Figure 2. There are multiple potential calcium-regulatory targets for acute pancreatitis therapy. This schematic illustrates the intricate pathways of calcium homeostasis, highlighting the transporters and key signaling molecules involved. In addition, the schematic displays select drugs that target the indicated Ca^{2+} regulators, showcasing potential pancreatitis therapies. Many of these calcium-signaling targeted agents have been shown to attenuate acinar cell responses in acute pancreatitis and reduce AP severity in preclinical rodent models. A few have advanced to clinical trials. AP = acute pancreatitis, IP3R = inositol 1,4,5-tris-phosphate receptor, PMCA = plasma membrane calcium ATPase, TRPV = transient receptor potential cation channel subfamily V.

drug discovery efforts targeting abnormal IP3R calcium signaling as an AP therapy.[45]

Calcium extrusion

Two major mechanisms remove calcium from the cytosol. A calcium ATPase pumps the ion from the cytosol into the ER, and plasma membrane calcium extrusion ATPases of the ATP2B4 family move cytosolic Ca^{2+} into the extracellular space. Stimulation of Ca^{2+} extrusion has strong potential for targeted AP treatment, as summarized below.

Pancreatic acinar cells and duct cells receive high concentrations of islet hormones, most relevantly insulin, through an islet-to-acinar cell portal system. As seen in a T1DM model and an insulin-receptor knockout mouse, insulin signaling deficiency sensitizes to AP development. Insulin protects acinar cells in pancreatitis by providing glycolytically derived ATP to drive the plasma membrane calcium ATPase (PMCA) pumps that lower cytoplasmic calcium. However, it may have additional effects on ER calcium pumps. However, the effective insulin dose for protecting acinar cells against experimental pancreatitis is higher than the insulin doses needed to maximally enhance peripheral glucose uptake in mouse models. Because this would predispose to hypoglycemia and require the use of an insulin clamp if applied therapeutically, its clinical use for AP therapy is not practical.[46,47]

Insulin appears to protect acinar cells indirectly by inducing Akt-mediated phosphorylation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (PFKFB2), which boosts glycolysis and the ATP generation need to drive calcium export by a PMCA. This reveals a potential therapeutic strategy to activate PFKFB2 phosphorylation, eliminating the need for systemic insulin administration.[47] There are several potential agents in early-phase development, though none have entered clinical trials.[47] It may be relevant that a recent publication on insulin therapy for AP suggested that it might reduce the duration of hospitalization and lower ICU-related disease severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE-II]).[48]

Work from Jason Bruce's group has hypothesized that the severity of AP might be linked to the progressive loss of insulin secretion, a consequence of collateral damage to pancreatic β cells.[46] This insulin deficiency could subsequently reduce insulin-driven pancreatic antimicrobial peptide expression (AMP) and secretion into the gut, leading to gut dysbiosis, decreased mucous secretion, inflammation, bacterial translocation, infected pancreatic necrosis, sepsis, and consequently, a more severe progression of AP. Although detailed findings await publication, the group is exploring a correlative study between plasma insulin levels and gut AMPs throughout AP. Such studies aim to discern differences in insulin loss between severe and mild AP cases, potentially highlighting therapeutic opportunities with insulin mimetics or antimicrobial peptides (Jason I. E. Bruce, PhD, unpublished data, 2019–2022, Manchester, UK).

The secretory protein renalase, a prosurvival and anti-inflammatory factor, directly activates the PMCA PMCA4b.[49] PMCA4b stimulation by renalase enhances calcium egress from the acinar cell cytosol (Gorelick, MD, Desir, MD, unpublished data, 2013) and also coupled to other cell signals such as AKT and ERK recombinant human renalase (rRNLS) reduces the severity of experimental murine pancreatitis in vivo.[50] It also reduces pancreatitis injury in isolated pancreatic acinar cells in a PMCA4b-dependent manner.[50] These results demonstrate the potential of renalase as a therapeutic agent for pancreatitis by promoting calcium extrusion and reducing cell injury. Additionally, it has been demonstrated that amino acids 220-239 of human renalase1 exhibit the protective effects found in intact renalase in murine models of acute kidney injury.[51] Renalase peptides containing human renalase 1 aa220-239 site are now being investigated for potential therapeutic benefits in preclinical AP models.

Calcium target: calcineurin

In pancreatic acinar cells, increased cytosolic Ca^{2+} activates calcineurin, a phosphatase that is central to the pathogenesis of AP.[52,53] Calcineurin inhibitors, such as tacrolimus (FK506) and cyclosporine A, are often used to manage autoimmune conditions.[54] Past studies have demonstrated that these calcineurin inhibitors, or the genetic deletion of calcineurin, decrease the severity of experimental pancreatitis, including in a post-ERCP model.[55] Targeted deletions of calcineurin suggested distinct cell-specific roles for the enzyme. Specifically, the expression of calcineurin in hematopoietic cells and neutrophils contributes to the development of lung inflammation associated with pancreatitis. In contrast, calcineurin's expression in the pancreas contributes to local inflammation.[32] As such, the beneficial effects observed from blocking or deleting calcineurin in mitigating pancreatitis depend on the site of its expression. This observation led to further murine studies investigating the local effects of calcineurin inhibitors in the pancreatic duct. Introducing calcineurin inhibitors tacrolimus and cyclosporine A with radiocontrast into the pancreatic duct in a post-ERCP AP model dramatically reduced injury without apparent toxicity.[55] Additionally, preclinical intraductal delivery of calcineurin inhibitor formulations was safe and well tolerated in mice.[56] This initial work has led to human clinical trials. One prospective pilot study involved patients who had undergone ERCP; patients were randomized into a control group and a group receiving tacrolimus at 8 PM on the day preceding ERCP and at 8 AM on the day of ERCP. Patients randomized to the tacrolimus group underwent ERCP 2 hours after the morning tacrolimus dose. All patients were monitored for post-ERCP pancreatitis using clinical symptoms of worsening abdominal pain and increased pancreatic enzymes. This trial demonstrated that oral tacrolimus at a cumulative dose of 4 mg significantly decreases the incidence of post-ERCP pancreatitis.[57]

The Rectal INdomethacin, oral TacROlimus, or their combination for the prevention of post-ERCP pancreatitis (INTRO Trial) is an ongoing randomized, controlled, double-blinded trial that will assess the role of tacrolimus in post-ERCP pancreatitis prophylaxis and pharmacologically optimize this therapeutic strategy. The trial plans to randomize 4874 patients undergoing ERCP to receive either 5 mg oral tacrolimus or oral placebo 1 to 2 hours before ERCP. It will follow patient's post-ERCP for 30 days to assess the incidence of post-ERCP pancreatitis.[58] This trial has begun and is planned to end in December 2024.

Organelle dysfunction

The initial changes in cytosolic calcium and other cytoplasmic signaling molecules trigger a coordinated, interrelated series of pathologic responses in acinar cell organelles. The most critical involves mitochondria and the autophagic-lysosomal pathway, each making distinct contributions to acinar cell damage. Relevant to this review, specific agents may be useful in targeting individual organelles.

Mitochondrial dysfunction

Mitochondrial dysfunction drives AP through multiple pathologic mechanisms, including the generation of reactive oxygen species (ROS) and reactive nitrogen species, reduced ATP generation, and release of cytochrome C.[59–61] Oxidative stress damages cell membranes and proteins while activating proinflammatory transcription factors like active protein 1 (AP-1)[62] and nuclear factor kappa-light-chain-enhancer of activated

B cells (NF-kB).[63] Additionally, oxidative stress can damage mitochondrial proteins and DNA, impairing mitochondrial function and ultimately causing ATP depletion, which results in further imbalances in oxidative stress and ion regulation. Oxidative damage and mitochondrial dysfunction contribute significantly to pancreatic acinar cell injury and death in AP.[64] The mitochondrial permeability transition pore (MPTP) plays a critical role in the pathogenesis of AP by inducing mitochondrial dysfunction and necrosis upon its opening. Its opening leads to the loss of mitochondrial membrane potential, swelling of the mitochondria, and necrotic cell death. This process is particularly relevant in AP. Small molecule inhibitors of cyclophilin D, a regulator of the MPTP implicated in AP, have been investigated in preclinical models. One cyclophilin D inhibitor significantly protected mitochondrial membrane potential and reduced necrosis in murine and human pancreatic acinar cells.[65]

Autophagocytic-lysosomal

In addition to mitochondrial dysfunction, the dysfunction of other cellular organelles, such as defective autophagy and lysosomal function, and dysregulation of vesicular transport and trafficking pathways can trigger AP. Autophagy is linked to the activation of pancreatic digestive proteases. Trypsinogen activation to trypsin is an important early event in the pathogenesis of AP and occurs along the secretory pathway and in endolysosomal vacuoles (see "Zymogen activation" section).[66–68] Some have proposed that this generation of active trypsin can cause pancreatic "autodigestion," which is central to pancreatitis development.[69] Others, using murine models, see generation of pancreatic trypsin as less essential to the pathogenesis of AP.

Experimental and genetic models demonstrate that impaired autophagy and lysosomal function in pancreatic acinar cells play a foundational role in the initiation and development of AP. While mechanistically complex, disruptions at multiple steps, including defective cathepsin processing, reduced lysosomal enzyme activities, altered vacuolar H^+-ATPase localization, decreased levels of the lysosomal membrane lysosome-associated membrane protein (LAMP) proteins, impaired autophagosome clearance, and blocked lysosomal enzyme targeting, contribute to dysfunction in this pathway. Regardless of whether dysfunction occurs during autophagosome formation or completion of autophagy, the resultant inhibition of autophagic flux leads to the accumulation of active trypsin in the acinar cell, cytoplasmic vacuolization, metabolic changes including reduced ATP production, and pancreatitis.[70,71]

One group investigated the interaction between premature intracellular activation of digestive proteases within pancreatic acini and the systemic inflammatory response during severe pancreatitis in mice. They found that not only acinar cells but also infiltrating macrophages can activate digestive proteases during endocytosis of zymogen-containing vesicles, a process dependent on pH and cathepsin B (CTSB), leading to macrophage activation through NF-κB, ultimately contributing to systemic inflammation and pancreatitis severity.[72] It is possible that trypsinogen in macrophages may account for the generation of pancreatic trypsin long after disease onset, with the acinar cell being its initial source.

Dysfunction in one organelle impacts others through their metabolic interdependence and signaling crosstalk, ultimately leading to key features of pancreatitis like intrapancreatic trypsinogen activation, inflammation, and cell death. Targeted genetic disruption of organelle components like the lysosomal protein LAMP2 can cause spontaneous pancreatitis in mice,[73] further demonstrating organelle dysfunction's key role in disease pathogenesis.[16] As such, therapeutics to broadly restore organelle homeostasis might effectively treat pancreatitis.

Inflammatory mediators

Changes in circulating and tissue levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], IL-1β, IL-6, IL-8)[74] and anti-inflammatory cytokines (eg, IL-10)[75] during AP have been well-documented in rodents and shown in human disease. One such report characterized the trajectories of key proinflammatory (angiopoietin-2, IL-6, IL-8, monocyte chemoattractant protein [MCP]-1, resistin) and anti-inflammatory (hepatocyte growth factor [HGF], soluble tumor necrosis factor-alpha receptor 1 [sTNF-αR1]) cytokines over the first 5 days after onset in a prospective cohort of AP patients. The study found that proinflammatory cytokines were significantly elevated early in severe acute pancreatitis (SAP) compared to mild forms but exhibited a downward trajectory after day 1 in SAP versus milder forms with flat or upward trajectories.[76] Anti-inflammatory cytokines increased over time in mild and severe disease. The findings indicate that proinflammatory cytokine responses occur rapidly and are time-dependent in SAP. This highlights the need to enroll SAP subjects early in the disease when investigating immune mechanisms or designing trials targeting cytokines.

Resistin is a small adipokine implicated in obesity. A meta-analysis of 11 studies involving 892 AP patients found that circulating resistin levels were significantly higher in patients with SAP than those with mild AP, suggesting that elevated resistin levels may predict AP.[77]

Activin A, a member of the TGF-β superfamily, has recently emerged as a significant potential mediator of inflammation in AP. Activin A is released into the bloodstream during inflammatory events and modulates inflammatory responses.[78] In the setting of AP, serum activin A levels correlate with disease severity in murine models and patient cohorts,[79] suggesting its potential as a predictive clinical marker and therapeutic target for severe cases. Moreover, activin A predictive capability of AP severity occurs independently of other risk factors such as body mass index.[80] Follistatin is a protein that specifically binds to and inhibits the actions of activin A.[81] One recent study in murine models demonstrated that following bacterial lipopolysaccharide administration, activin A rapidly increases in circulation, predominantly sourced from bone marrow–derived cells, especially neutrophils, while circulating Follistatin shows a delayed increase.[82] Additionally, inhibiting activin A with a neutralizing antibody in mice with AP decreased disease severity.[80] These results raise the question of whether activin inhibition could be a viable treatment strategy for AP; to our knowledge, no clinical studies in human subjects have been done to test the effectiveness of activin inhibition for AP treatment.

The role of proinflammatory cytokines in the pathogenesis of AP raises the question of whether anti-inflammatory molecules that suppress oxidative stress or inflammation reduce AP severity and its complications.[83] One study found that by suppressing NF-κB proinflammatory signaling, resveratrol pretreatment could attenuate pancreas injury, inflammation, and oxidative stress in a mouse model of hyperlipidemia-induced AP. Whether this translates to human AP remains to be seen.[84]

As the understanding of cytokine involvement in AP continues to evolve, the mixed lineage kinase domain-like protein (MLKL) function emerges as a research focus. MLKL and its activated form, p-MLKL, were upregulated in the pancreas in a mouse model of AP, independent of RIPK3, the canonical upstream activator of MLKL. Knockout of MLKL, but not Ripk3, reduced the severity of pancreatitis in mice by promoting M2 "healing" macrophage polarization in the pancreas.[85] This suggests a protective role for M2 macrophages in AP. This effect was mediated in part by reducing the release of the chemokine (C-X-C) ligand (CXCL10) from injured pancreatic acinar cells, which normally act to polarize macrophages toward the proinflammatory M1 phenotype. Neutralization of CXCL10 reduced macrophage M1 polarization and pancreatitis severity in mice.[85] This suggests inhibition of the MLKL-CXCL10-macrophage axis as

a potential therapeutic approach in AP and highlights a non-canonical inflammation-related role for MLKL separate from its canonical necroptotic function.

TNF-α inhibition has been demonstrated to reduce injury in experimental AP. Antibody inhibition of TNF-α reduced disease severity and improved survival in mouse and rat models of AP.[86,87] Importantly, delaying TNF-α inhibition until after pancreatitis onset was more protective than early prophylactic treatment, suggesting that its role may be time-dependent.[87] Later studies demonstrated that the TNF-α inhibitor, infliximab, enhanced the therapeutic effectiveness of octreotide by reducing biochemical markers of injury, improving organ function, and reducing pathology scores in a rat model.[88] The results support the potential of anti–TNF-α therapy as an AP therapy and the Randomised treatment of Acute Pancreatitis with Infliximab: Double-blind multi-centre trial (RAPID-I trial), a phase IIb, randomized, double-blind, placebo-controlled, multicenter trial of infliximab in patients with AP. The RAPID-I is one of the first clinical trials in AP that involves a degree of precision medicine. The trial plans to use transcriptomics to elucidate any genetic factors in patients that may be linked to improved response to infliximab.[89]

Recently, lactate has been identified as an inflammatory modulator in acute inflammatory pancreatic and liver injury. Hoque et al[90] demonstrated that lactate, through the lactate receptor Gi-protein–coupled receptor 81 (GPR81), counteracts the activation of the NLRP3 inflammasome by negatively regulating Toll-like receptors, leading to reduced inflammation and organ damage. Given its protective effects in mouse models, lactate and its receptor GPR81 are potential targets of immunomodulatory therapy for patients with AP and other acute organ injuries. This information has provided a mechanistic rationale for clinical studies comparing post-ERCP pancreatitis and AP outcomes in patients given intravenous lactated Ringer or normal saline for treating AP. In post-ERCP AP, a clear benefit for aggressive hydration with lactated Ringer during ERCP and post-procedure has been shown.[91] Though small preliminary studies suggest a therapeutic advantage of intravenous lactated Ringer over normal saline in hospitalized patients with AP, large prospective clinical studies are planned.

Zymogen activation

A characteristic early AP response is the activation of protease zymogens, particularly trypsinogen, in the pancreatic acinar cell. Trypsinogen can also be activated outside the acinar cell after entering the interstitial space through acinar cell death, basolateral exocytosis, or back diffusion from the pancreatic duct lumen through disrupted tight junctions, which can become endocytosed and activated in macrophages. This activation enhances their inflammatory state.[72] Trypsinogen activation in the acinar cell likely occurs in a non-zymogen granule compartment along the secretory pathway[67,92] and within endocytic vesicles.[93] Chvanov et al[94] have demonstrated that large endocytic vacuoles containing trypsin are formed in experimental models of AP. These endocytic vacuoles are predicted to rupture and release trypsin into acinar cell cytosol or exocytosis of trypsinogen into the extracellular space.[94] The result is predicted to lead to inappropriate intracellular protease activity, and trypsin activation of other digestive proenzymes such as chymotrypsinogen, proelastase, procarboxypeptidase, and prophospholipase A2 could contribute to AP injury.

There is a consensus that lysosomal hydrolases are central to trypsinogen activation. The "co-localization hypothesis" posits that in the initial phases of AP, acinar cell digestive zymogens, such as trypsinogen, actively mix with lysosomal hydrolases within vesicular compartments in the acinar cell. This merging is proposed to facilitate trypsinogen activation by the lysosomal hydrolase CTSB, which can activate trypsinogen in an acidic environment.[95] Research involving AP mice with a targeted deletion in the CTSB (gene supports its role). When subjected to experimental secretagogue-induced pancreatitis, the CTSB-deficient mice exhibited a significant reduction in trypsin activity—over 80% less than their wild-type counterparts. Correspondingly, the manifestation of pancreatic damage, measured by serum amylase and lipase activities, as well as the degree of acinar tissue necrosis, was halved in the CTSB-deficient mice.[96] This evidence underpins the role of CTSB in activating intrapancreatic trypsinogen, thereby supporting the co-localization hypothesis. However, selective compartmental acidification may also be important.

Notably, pancreatic protease zymogen activation has not proven a useful therapeutic target. Whether this reflects challenges to appropriately time the therapy, inability to inhibit relevant proteases, or lack of importance of intrapancreatic zymogen activation in mediating AP severity remains unclear.

Pathologic responses of the non-acinar cell that drive AP and therapeutic targeting

Fat cells and triglycerides

Fat cells and their triglyceride content can modulate AP severity. Specifically, hypertriglyceridemia can cause severe pancreatitis. Blood levels of triglycerides directly relate to the risk of developing AP.[97] Lipases hydrolyze triglycerides to generate free fatty acids, which can vary in their ability to damage the pancreas. Unsaturated fatty acids are particularly harmful and can cause mitochondrial dysfunction, calcium overload, and the generation of inflammatory mediators in pancreatic acinar cells.[98–100] Additionally, hypertriglyceridemia worsens outcomes in AP, regardless of the initial cause.[101] This effect appears to be increased in obese patients and mice, likely due to lipolysis of intrapancreatic fat.[98] One group found that during AP, pancreatic triglyceride lipase (PNLIP) leaks into visceral adipose tissue, causing excessive lipolysis independent of adipocyte-autonomous adipose triglyceride lipase, leading to increased non-esterified fatty acids, more severe organ failure, and reduced survival. In contrast, this mechanism does not occur in acute diverticulitis, indicating a specific role of PNLIP-induced lipolysis in the pathogenesis of organ failure during pancreatitis.[99] These results suggest that treatments that lower triglycerides or inhibit relevant lipases could potentially reduce the severity of AP.

Insights into the mechanisms of lipid toxicity are appearing. In human patients and mouse models, increased free unbound fatty acids, especially unsaturated fatty acids like linoleic and oleic acid, can enter and damage immune cells by interacting with cell membrane phospholipids and mitochondrial membranes. This impairs immune cell functions like phagocytosis, reduces bacterial clearance, and increases susceptibility to infections during pancreatitis.[102] Additionally, some work has suggested lipotoxicity from peri-pancreatic fat necrosis is a key factor in converting mild to severe AP in obesity.[103] These studies suggest that preventing an increase in unbound fatty acids or promoting their binding to albumin could reduce infections in and severity of AP. Inhibition of lipolysis using the lipase inhibitor orlistat in an obese mouse model of pancreatitis reduced pancreatic necrosis, systemic inflammation, lung and kidney injury, hypocalcemia, and mortality.[98] These findings suggest that lipotoxicity mediated by UFAs contributes to the severe outcomes in obese patients with pancreatitis and that treatment modalities that reduce lipolysis could reduce AP severity.

Pancreatic triacylglycerol lipase and pancreatic lipase-related protein 2 (PNLIPRP2) may be suitable targets for drug development. These 2 proteins are present in fat necrosis in human and experimental pancreatitis and can efficiently hydrolyze triglycerides to toxic unsaturated free fatty acids that cause injury. In cell models, pancreatic triacylglycerol lipase and PNLIPRP2

caused lipotoxic injury.[104] In mouse models, PNLIP activity increased during AP, generating excess non-esterified fatty acids.[99] These findings suggest pancreatic triacylglycerol lipase and PNLIPRP2 contribute to local and systemic lipotoxic injury in severe AP. This further supports pancreatic lipase inhibition as a potential therapeutic approach in AP and that pancreatic triacylglycerol lipase and PNLIPRP2 may be suitable drug targets for this strategy.

Previous studies have examined the potential effects of dietary factors on AP. Obese individuals who consume more saturated fat have more saturated visceral fat triglycerides that are resistant to hydrolysis by pancreatic lipase. This reduces the generation of free fatty acids that can cause lipotoxic injury. In contrast, in leaner individuals who consume more unsaturated fat, the more unsaturated visceral triglycerides are readily hydrolyzed by lipase. This generates high lipotoxic-free fatty acid levels that worsen inflammation and organ failure.[100] The findings provide a potential explanation for the "obesity paradox" in AP, where obesity sometimes seems protective. The results suggest dietary fat saturation, not just the amount of body fat, contributes to pancreatitis severity through effects on lipotoxicity.

Although the role of triglycerides in AP pathogenesis is well established, the impact of the removal of circulating triglycerides in treating AP remains unclear. In a recent multicenter cohort study of patients with hypertriglyceridemia-associated AP (HTG-AP), plasmapheresis, while effective in lowering plasma triglycerides, was not linked to reduced incidence or duration of AP-associated organ failure but was associated with increased ICU admissions.[105] Other studies have highlighted the lack of advantages of apheresis compared to insulin infusion. In a study comparing continuous insulin infusion and apheresis in 48 patients, apheresis resulted in a rapid 78.5% reduction in triglyceride levels after the first session. In contrast, insulin infusion led to a 44.4% reduction in the first 24 hours. However, despite the effectiveness of apheresis treatments, they did not offer a distinct advantage over insulin infusion in terms of prognosis and associated complications for HTG-associated pancreatitis.[106]

As such, the optimal treatment for lowering triglyceride levels in patients with HTG-AP is undetermined. There may be negative consequences, such as ICU admissions, associated with apheresis and systemic issues, including the lack of widespread availability of apheresis. Larger clinical trials are currently being conducted to help resolve these questions. The EarLy Elimination of Fatty Acids iN hypertriglyceridemia-induced acuTe pancreatitis (ELEFANT) trial is an open-label, multicenter, adaptive randomized clinical trial that is investigating early elimination of triglycerides and free fatty acids in hypertriglyceridemia-induced AP in a minimum of 495 patients. The ELEFANT trial will randomize patients to plasmapheresis, insulin-heparin treatment, or standard fluid therapy within 48 hours of symptom onset. The primary endpoint is a composite of severe AP or mortality.[107] The results will provide high-quality evidence on whether early removal of triglycerides and free fatty acids improves outcomes in hypertriglyceridemia-induced pancreatitis. This could establish a new treatment approach targeting the inciting factors in this subset of patients.

Other potential targets

Store-Operated Calcium Entry Associated Regulatory Factor (SARAF) regulates calcium signaling in pancreatic acinar cells. In mouse models of AP, SARAF levels initially increase but then decrease over time, leading to excessive calcium influx into acinar cells and worsening pancreatitis. SARAF knockout mouse models had more severe pancreatitis, while mice overexpressing SARAF were protected.[108] This suggests that strategies to stabilize or restore SARAF levels in acinar cells could be a potential new therapeutic approach for treating AP.

MicroRNAs may serve as a critical target in the treatment of AP. The microRNA miR-26a is crucial in regulating calcium signaling and overload in pancreatic acinar cells. MiR-26a levels are reduced in experimental mouse models and human samples of AP. Mechanistically, miR-26a directly targets and inhibits the calcium channels TRPC3 and TRPC6, thereby restricting pathological calcium elevations and protecting against pancreatitis. miR-26a deficiency in mice worsened pancreatitis, while miR-26a overexpression, globally or in acinar cells, markedly reduced pancreatitis severity. Additionally, administering a miR-26a mimic mitigated cerulein-induced pancreatitis.[109] This work highlights miR-26a as an intrinsic checkpoint on acinar cell calcium overload. It demonstrates its therapeutic potential to alleviate AP by normalizing pathological calcium signaling, suggesting the need to investigate further other miRNAs that may be involved in calcium signaling or other mechanisms underlying AP development.

Anticoagulants

Heparin and its non-anticoagulant derivatives can protect against SAP in mouse models. The drugs reduced pancreatic necrosis, inflammation, and macrophage infiltration in SAP, independent of anticoagulant function.[110] Release of high mobility group box 1 (HMGB-1) from pancreas macrophages, which can drive inflammation and multi-organ damage in SAP, is inhibited by this drug class and independent of their anticoagulant function. Reduced HMGB-1 release is associated with reduced intestinal barrier dysfunction and, lung injury and decreased mortality.[110] With regard to non-heparin anticoagulants, one group found that orally administered dabigatran etexilate (with anticoagulant and trypsin-inhibiting activities) could reduce trypsin activity and had therapeutic efficacy in a cerulein pancreatitis mouse model (T7K24R), but not in a more aggressive AP model.[111] This work demonstrates that benzamidine derivatives like dabigatran can be potent trypsin inhibitors. However, their efficacy may be limited by the severity of the pathology and drug concentrations in the pancreas.[111] Clinically, a retrospective study of 190,474 AP patients found that those on anticoagulation therapy before onset had lower risks of ICU admission, acute kidney injury, organ failure, and inpatient mortality, suggesting a therapeutic role in AP.[112] These results suggest that heparin, non-heparin anticoagulants, and non-anticoagulant heparin derivatives may be future options for AP treatment.

Hormones

Hormonal regulation plays a critical role in the body's response to various forms of stress, including AP. In this context, hormones like ghrelin, leptin, and melatonin are metabolic regulators and are found to be protective roles in AP. By interacting with immune factors, these hormones may support innate defense mechanisms that reduce the severity of pancreatitis.

Ghrelin has been shown to exert a protective effect in AP models by modulating inflammatory pathways.[113,114] Specifically, ghrelin decreases the expression of nuclear factor kappa B (NFκB) and the inflammatory signal transduction pathway,[115] leading to lower levels of inflammatory cytokines such as IL-1β and tumor necrosis factor-α (TNFα).[116] Furthermore, ghrelin's protective influence extends to reducing pancreatitis-associated lung injury and neutrophil sequestration, showcasing its systemic anti-inflammatory potential.[116,117]

When given intraperitoneal or intracerebroventricular, leptin, another hormone modulating immune response, can reduce experimental AP severity.[116] The underlying mechanism involves the engagement of sensory nerves and the neuropeptide calcitonin gene–related peptide (CGRP), essential for leptin's protective action.[118] Leptin enhances pancreatic tissue repair and decreases lung injuries, similar to ghrelin.[119] Its therapeutic

effects include the activation of the nitric oxide (NO) system, improvement in pancreatic microcirculation, and the potential release of glucocorticoids that attenuate inflammation.[120,121]

Melatonin, commonly known for regulating circadian rhythms, also confers protection against acute pancreatic inflammation.[114,122] Its administration to animal models before inducing pancreatitis results in a marked reduction of inflammation markers, such as edema and leukocyte infiltration. It decreases proinflammatory cytokines while increasing anti-inflammatory IL-10 levels.[114,123] It also diminishes apoptosis and necrosis in pancreatic tissues and improves pancreatic blood flow, which aids in the clearance of inflammatory mediators.[113,124,125]

These findings support that ghrelin, leptin, and melatonin could be integral components of the natural defense system against pancreatic inflammation. Their increased blood levels during the initial phase of pancreatic inflammation represent a physiological response to suppress or mitigate the inflammatory process within the pancreas, offering a promising avenue for therapeutic intervention in AP.

An emerging interest in examining the utility of corticosteroids for severe AP treatment is reflected by a favorable meta-analysis.[126] The benefits of corticosteroids when used in selective coronavirus disease 2019 (COVID-19) patients may also be a factor. A 5-year prospective clinical trial based on the Beth Israel Deaconess Medical Center on corticosteroid use in severe AP is underway (completion date: 2027; gov ID: NCT05160506) in the United States.

Gut microbiome

Recent research has underscored the gut microbiome's influence on AP using experimental models.[127] Antibiotic therapy can improve the course of AP in rodents by reducing innate immune system activation.[128,129] However, we are unaware of findings that show similar benefits of antibiotics in clinical AP.

A recent study has also shown how microbial imbalances may relate to the severity of necrotizing pancreatitis. In a study comparing the gut bacteria of healthy individuals with AP patients, marked differences were found in microbial diversity and composition. Specifically, patients with necrotizing pancreatitis demonstrated microbial species with altered ketone body and benzoate metabolism.[130] Enterococcus faecium and Finegoldia magna were identified as potential biomarkers for necrotizing pancreatitis and infected necrotizing pancreatitis, respectively.[130] These findings suggest that gut microbiota profiles could inform early necrotizing pancreatitis diagnosis and treatment, highlighting the microbiome's potential as a target for AP management and intervention. However, probiotics' role in treating AP remains controversial. A meta-analysis of 13 randomized controlled trials with 950 patients reveals that supplementing pre-, pro-, and synbiotics to standard enteral nutrition may reduce hospital stays for severe AP in Chinese cohorts. However, other clinical outcomes showed no significant improvement.[131] The Probiotics in Pancreatitis Trial (PROPATRIA), a multicenter, randomized, double-blind, placebo-controlled trial of 298 patients with severe AP, demonstrated that enteral probiotic prophylaxis did not decrease infectious complications in patients with severe AP and was linked to significantly increased mortality and gut ischemia in the probiotic arm of the trial. This has caused broad caution about their use in this patient population, though this may change with time and more information.[132–134] Notably, the authors cautioned against considering probiotics universally harmless, especially in critically ill patients.[135] The contrasting results from the prior studies and debate regarding the results of the PROPATRIA trial advocate for further large-scale, rigorously designed, and controlled studies to confirm the efficacy and safety of probiotic supplementation in AP treatment and whether any specific species of bacteria may have specific benefits in AP patients.

Conclusions

AP remains a disease with significant morbidity and mortality despite improvements in supportive care. Pathologic calcium signaling, mitochondrial dysfunction, organelle stress, zymogen activation, lipotoxicity, and uncontrolled inflammation are key mechanisms that drive acinar cell injury and systemic AP complications. This review summarizes promising pharmacologic approaches that target these underlying disease processes, including inhibitors of calcium influx, boosters of calcium efflux, anti-inflammatory therapies, antioxidants, and strategies to lower circulating lipotoxic factors (Table 1).

Table 1

Summary of potential therapeutic targets and agents for AP based on current preclinical studies and early clinical trials

General target	Specific target	Inhibitor or agonist	References
Calcium	Orai1 (SOCE)	CM4620, GSK-7975A, CM_128	[35, 36]
Calcium	TRPV1, TRPV4		[38, 39]
Calcium	Piezo1	GsMTx4	[40]
Calcium	IP3R	Caffeine	[45]
Calcium	RYR	Dantrolene	[43, 44]
Calcium	PMCA (calcium efflux)	Insulin, renalase	[47, 49–51]
Calcium	Calcineurin	Tacrolimus, cyclosporine A	[48, 52, 53, 55]
Mitochondria	MPTP	Cyclophilin D inhibitors	[65]
Inflammation	TNF-α	Anti–TNF-α antibodies, infliximab	[86–89]
Inflammation	MLKL	CXCL10 neutralizing antibody	[85]
Inflammation	NLRP3 inflammasome	Lactate	[90, 91]
Triglyceride hydrolysis	PNLIP	Orlistat	[98]
Triglyceride hydrolysis	PNLIPRP2		[99]
Triglycerides	Circulating Triglycerides	Plasmapheresis, insulin	[105–107]
SARAF	SARAF	SARAF stabilizers	[108]
MicroRNAs	miR-26a	miR-26a mimic	[109]
HMGB-1	HMGB-1	Heparin derivatives	[110]
Trypsin	Trypsin	Dabigatran	[111]

The table lists general target categories, specific molecular targets or pathways within each category, and examples of pharmacological inhibitors, agonists, or other interventions that have shown potential benefits in experimental models or early human studies of AP.

AP = acute pancreatitis, CXCL = chemokine (C-X-C) ligand, HMGB-1 = high mobility group box 1, IP3R = inositol 1,4,5-tris-phosphate receptor, MLKL = mixed lineage kinase domain-like protein, MPTP = mitochondrial permeability transition pore, NLRP3 = PMCA = plasma membrane calcium ATPase, PNLIP = pancreatic triacylglycerol lipase, PNLIPRP2 = pancreatic triacylglycerol lipase and pancreatic lipase-related protein 2, RYR = ryanodine receptor, SARAF = Store-Operated Calcium Entry Associated Regulatory Factor, SOCE = store-operated calcium entry, TNF = tumor necrosis factor, TRPV = transient receptor potential cation channel subfamily V.

Early clinical trials demonstrate the safety and potential efficacy of interventions like TNF-α inhibition, reducing calcium entry with Orai1-inhibition, and tacrolimus in reducing the incidence and severity of pancreatitis. Further studies are needed to show definitively improved clinical outcomes. While additional basic research is still required to elucidate mechanisms fully, the translation of novel treatments from preclinical studies to human trials appears to be accelerating.

Multifunctional therapies that simultaneously address several pathologic mechanisms may provide the greatest benefit. Further characterization of pathologic pathways and crosstalk between organelles and cell types will aid in developing combinatorial treatments. Improved early diagnosis and risk stratification will enable therapies to be administered quickly and targeted to patients most likely to benefit. With continued progress in understanding disease mechanisms and applying this knowledge to human trials, the management of AP is poised for major advances in the coming years. Ultimately, the goal is to move beyond supportive care toward therapeutic interventions interrupting the underlying disease process and improving short- and long-term patient outcomes.

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SZ: Project administration; writing - review & editing. FG: Project administration; resources; supervision; writing - review & editing.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Our review did not involve any clinical or animal experiments and was analyzed only using published open-source studies, therefore did not involve the approval of the Institutional Review Board.

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