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TOPIC HIGHLIGHT

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Calcium signaling of pancreatic acinar cells in the pathogenesis of pancreatitis

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Abstract

Pancreatitis is an increasingly common and sometimes severe disease that lacks a specific therapy. The pathogenesis of pancreatitis is still not well understood. Calcium (Ca^{2+}) is a versatile carrier of signals regulating many aspects of cellular activity and plays a central role in controlling digestive enzyme secretion in pancreatic acinar cells. Ca^{2+} overload is a key early event and is crucial in the pathogenesis of many diseases. In pancreatic acinar cells, pathological Ca^{2+} signaling (stimulated by bile, alcohol metabolites and other causes) is a key contributor to the initiation of cell injury due to prolonged and global Ca^{2+} elevation that results in trypsin activation, vacuolization and necrosis, all of which are crucial in the development of pancreatitis. Increased release of Ca^{2+} from stores in the intracellular endoplasmic reticulum and/or increased Ca^{2+} entry through the plasma membrane are causes of such cell damage. Failed mitochondrial adenosine triphosphate (ATP) production reduces re-uptake and extrusion of Ca^{2+} by the sarco/endoplasmic reticulum Ca^{2+}-activated ATPase and plasma membrane Ca^{2+}-ATPase pumps, which contribute to Ca^{2+} overload. Current findings have provided further insight into the roles and mechanisms of abnormal pancreatic acinar Ca^{2+} signals in pancreatitis. The lack of available specific treatments is therefore an objective of ongoing research. Research is currently underway to establish the mechanisms and interactions of Ca^{2+} signals in the pathogenesis of pancreatitis.

Key words: Pancreatitis; Calcium signaling; Pancreatic acinar cells; Overload; Cell injury

Core tip: Calcium (Ca^{2+}) overload is crucial in the pathogenesis of pancreatitis, which results in trypsin activation, vacuolization and necrosis. Such cell injury results from increased Ca^{2+} released from intracellular endoplasmic reticulum Ca^{2+} stores, increased Ca^{2+} entry through the plasma membrane and Ca^{2+} pump defects. Current findings have provided further insight into the roles and mechanisms of Ca^{2+} overload in pancreatitis. The lack of specific treatments is a stimulus for ongoing research. This review summarizes recent advances in our understanding of Ca^{2+} signaling in the pathogenesis of pancreatitis, and discusses how research has guided our search for potential therapeutic targets.

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INTRODUCTION

Pancreatitis remains a disease with significant morbidity and lethality, and is typically caused by alcohol abuse or complications arising from biliary disease[1]. The pathogenesis of pancreatitis is multi-factorial and has not yet been clarified[2-5]. In recent years, several pancreatic mechanisms have been proposed, such as trypsinogen activation[6], pancreatic microcirculation malfunction[7], calcium (Ca^{2+}) overload[8-10] and inflammatory pathways[11-13]. Among these various theories, Ca^{2+} overload is receiving increasing attention and is being extensively investigated in the pathogenesis of pancreatitis[14]. Recent advances in our understanding of Ca^{2+} signaling of pancreatic acinar cells in the pathogenesis of pancreatitis are reviewed in this article, including a discussion on how research has guided our search for potential therapeutic targets.

PHYSIOLOGICAL AND PATHOLOGICAL CA^{2+} SIGNALS IN PANCREATIC ACINAR CELLS

As the most universal carrier of biological signals, intracellular Ca^{2+} is involved in the modulation of virtually all cellular functions, from its origin at fertilization to its end in the apoptotic process[15]. Intracellular Ca^{2+} acts both as a first and a second messenger to control cellular functions *via* regulating free-Ca^{2+} concentrations in the cytoplasm, for example, controlling the contraction and relaxation of muscles, and regulating secretion from exocrine glands[16]. Ca^{2+} signals elicited by physiological stimulation are transient and mostly localized in the granule-containing apical pole, whereas sustained global elevation of cytosolic Ca^{2+} concentrations can be fatal[17-19]. The digestive enzymes produced by pancreatic acinar cells are packaged in zymogen granules in the apical pole[20]. Physiological stimulation elicits proenzyme exocytosis exclusively through the apical membrane[21]. Ca^{2+} overload causes inappropriate intracellular trypsin activation, vacuolization and necrosis[20,22-26], which contribute to subsequent cell injury and are often fatal in human acute pancreatitis[27]. Pretreatment with pharmacological Ca^{2+} chelators or blockers was found to prevent premature digestive enzyme activation, vacuolization, skeletal disruption and acinar cell necrosis induced by Ca^{2+} overload[28].

RELEASE OF CA^{2+} FROM THE ENDOPLASMIC RETICULUM

There are two types of G protein-coupled receptors localized on the plasma membrane, namely, acetylcholine (ACh) and cholecystokinin (CCK) receptors[8]. ACh is a secretagogue that activates phospholipase C (PLC) through ACh receptor ligand binding, which in turn cleaves phosphatidylinositol 4,5-bisphosphate into the classic Ca^{2+}-releasing messengers inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol to mobilize Ca^{2+} and activate protein kinase C respectively[29]. The other principal secretagogue in acinar cells is the hormone CCK, which exists in multiple molecular forms, such as CCK8 and CCK58. CCK interacts with its receptor and activates adenosine diphosphate-ribosyl cyclase to produce the novel Ca^{2+}-releasing agent nicotinic acid adenine dinucleotide phosphate (NAADP) and cyclic adenosine diphosphate-ribose (cADPR).

There are two types of regulated Ca^{2+}-release channels localized on the endoplasmic reticulum (ER) membrane, namely, the IP_3 receptors (IP_3R) and ryanodine receptors (RyR). IP_3R are concentrated in the apical part of the acinar cell and binding of IP_3 activates gated Ca^{2+} channels to release intracellular stored Ca^{2+} from the ER, which participates in the apical cytosolic Ca^{2+}-spiking response to stimulation with physiological concentrations of ACh[10,19,30,31]. RyR in the basal region of acinar cells are activated by NAADP and cADPR, and oligomers form gated Ca^{2+} channels to release intracellular Ca^{2+} from ER stores[32] in response to stimulation with physiological concentrations of CCK[33-35]. Intriguingly, the Ca^{2+} response mediated by RyR was observed in the apical pole in mouse acinar cells and required functional IP_3R, which could be interpreted as co-localization and coordination of RyR and IP_3R[36].

Hyperstimulation with agents (in contrast to physiological stimulation) can induce acinar cell injury by IP_3R-induced release of Ca^{2+} from the ER. The Ca^{2+} increase spreads from the apical pole to the basolateral part of the acinar cell, and a sustained global Ca^{2+} elevation causes pancreatitis-like cellular changes, such as abnormal intracellular enzyme activation, vacuolization and necrosis[20]. Treatment with IP_3R inhibitors, such as caffeine and 2-aminoethoxydiphenyl borate, can reduce abnormal Ca^{2+} signals and the probability of ethanol-induced pancreatitis, but the low affinity and multiple actions restrict its therapeutic potential[37,38]. Hyperstimulation by CCK8 is specifically dependent on functional RyR, and induces toxic pancreatitis-like changes as a result of sustained global elevation of Ca^{2+} released from the ER. These aberrant Ca^{2+} signals and acinar cell injuries can be blocked *in vitro* and *in vivo* by pretreating with RyR inhibitors[8,39]. Hyperstimulation by CCK also activates PLC, which generates IP_3 and elicits Ca^{2+} overload[20].

Although the ER is a large Ca^{2+} store in the basolateral part of pancreatic acinar cells, there are also extensive acidic Ca^{2+} stores present in the apical part, which similarly release Ca^{2+} into the cytoplasm through IP_3, cADPR and NAADP signaling. Hyperstimulation from bile acids and alcohol metabolites can elicit pathological Ca^{2+} release from both the ER and acidic stores[40,41].

STORE-OPERATED Ca^{2+} (SOC) INFLUX

Another abnormal Ca^{2+} signal in the pathogenesis of pancreatitis is extracellular Ca^{2+} entry, which is regulated at the plasma membrane of acinar cells by SOC channels[42]. Under physiological conditions, CCK and ACh induce the release of Ca^{2+} from the ER, followed by Ca^{2+} extrusion from the cell, suggesting that SOC entry is required to elevate intracellular Ca^{2+}. The molecular mechanism underlying these pancreatic Ca^{2+}-entry channels is ill-defined. Current research suggests that Ca^{2+}-entry channels belong to the transient receptor potential family, including Ca^{2+} release-activated Ca^{2+} channel protein 1 (Orai1), transient receptor potential channel 1, and stromal interaction molecule (STIM) 1[43,44]. Recent studies indicate that STIM proteins serve as sensors, are concentrated in the ER membrane, and monitor the Ca^{2+} concentration in the ER lumen. When the luminal concentration is reduced in response to secretagogue stimulation, STIM proteins sense the changes, accumulate and translocate to the plasma membrane where they co-localize with and activate Orai1 channels[45-48].

Orai1 channels are localized not only in the apical part of acinar cells, but also in the basal and lateral membranes, which cover about 95% of the pancreatic acinar cell surface[43]. Following ER Ca^{2+} store depletion, Orail1 interacts with STIM and activates SOC channels. The wide distribution of Orai1 channels enables sustained Ca^{2+} entry under physiological conditions, without the need for local Ca^{2+} concentrations, and refilling of the ER Ca^{2+} stores after agonist-elicited depletion[8]. However, Orai1 activity can result in an abnormal sustained global Ca^{2+} elevation following pathological stimulation, such as by high, toxic concentrations of CCK8, alcohol and bile acid, which all elicit intracellular Ca^{2+} overload that is mostly dependent on external Ca^{2+} influx[20,23,25]. Therefore, SOC entry may be crucial for the development of acute pancreatitis. Without external sustained global Ca^{2+} entry, cellular injury does not occur[20,22-25,49]. Removal of external Ca^{2+} or abrogation of elevated Ca^{2+} with a Ca^{2+} chelator can protect acinar cells against abnormal changes, such as trypsinogen activation and vacuolization[20,25,49]. SOC channel blockers might therefore be a possible therapeutic approach for the treatment of acute pancreatitis[7].

Ca^{2+} PUMP DEFECTS

Sarco/endoplasmic reticulum Ca^{2+}-activated adenosine triphosphate (ATP)ase (SERCA) is an ER Ca^{2+} pump which actively re-uptakes Ca^{2+} into the ER lumen to compensate for resting leakage into the cytosol[8,50]. Under normal physiological conditions, the elevation of intracellular Ca^{2+} can activate the SERCA pump[19,27,51], and Ca^{2+} release elicited by stimulation is followed by Ca^{2+} re-uptake. The rate of uptake decreases as luminal Ca^{2+} concentration increases until the uptake rate equals the resting leak rate[8]. Pathological stimulation by bile acids or fatty acids can elicit Ca^{2+} overload by inhibiting the SERCA pump and depolarizing the inner mitochondrial membrane, resulting in reduced ATP production, which in turn lessens the ability of the SERCA pump to restore ER Ca^{2+} stores[25]. Prolonged and uncompensated Ca^{2+} overload released from ER stores can cause thapsigargin activation and vacuolization in pancreatic acinar cells, which can be visualized directly[20].

All eukaryotic cells export Ca^{2+} through two pathways, the plasma membrane Ca^{2+}-ATPase (PMCA; commonly called the Ca^{2+} pump) and the Na^{+}-Ca^{2+} exchanger (NCE), to prevent Ca^{2+} overload and for the maintenance of intracellular Ca^{2+} at the appropriately low level[52,53]. The PMCA has high Ca^{2+} affinity but low transport capacity and is ATP-dependent. Any elevation of cytosolic Ca^{2+} can activate the PMCA to rapidly extrude Ca^{2+} in physiological conditions. Whereas ER-released Ca^{2+} is localized in the apical part and Ca^{2+} entry occurs across the basolateral surface, PMCA Ca^{2+} extrusion is confined to a small apical region only, which restricts the PMCA function as a fine-tuner of cell cytosolic Ca^{2+}. Pathological stimulation can depolarize mitochondria and cause a deficiency in ATP production, which inhibits Ca^{2+} extrusion and aggravates the cytosolic Ca^{2+} overload[24,54].

The NCE has a low Ca^{2+} affinity and is a high-capacity transmembrane protein of the plasma membrane involved in Ca^{2+} homeostasis, and is especially important in excitable cells. Because of its high capacity, the NCE can extrude Ca^{2+} at a much higher rate than the PMCA, serving as the fast Ca^{2+} transporting system. For example, activation of the NCE prevents Ca^{2+} overload induced by pathological stimulation and cell death in neurons. Inactivation of the NCE can cause neuronal death, which can be visualized directly[55]. In pancreatic acinar cells, the NCE is of little quantitative importance, which explains why Ca^{2+} overloading is particularly dangerous in pancreatic acinar cells[19,27].

As another Ca^{2+} store, mitochondria also participate in maintaining cytosolic Ca^{2+} homeostasis in pancreatic acinar cells. Mitochondria surround the apical pole in a perigranular belt, separating zymogen granules from the basolateral part of the acinar cell, and are also positioned just beneath the plasma membrane and surrounding the nucleus[19,27,55-58]. The membrane potential across the inner mitochondrial membrane is the driving force behind mitochondrial uptake of Ca^{2+} into the matrix through the Ca^{2+} uniporter, a Ca^{2+}-selective ion channel[59,60]. Mitochondria in pancreatic acinar cells play an important role in maintaining cytosolic Ca^{2+} homeostasis[56-58]. When cytosolic Ca^{2+} is elevated by physiological stimulation, mitochondria sense the Ca^{2+} in the environment and take up Ca^{2+} *via* the Ca^{2+} uniporter[60]. Ca^{2+} spikes released from the ER occurring in the apical region can cause immediate Ca^{2+} uptake into the mitochondrial matrix, preventing further spread of the Ca^{2+} signal into the basolateral part of the acinar cell, which contains the nucleus. Perigranular mitochondria function as a Ca^{2+} buffer barrier[8], causing Ca^{2+} uptake termination and Ca^{2+}

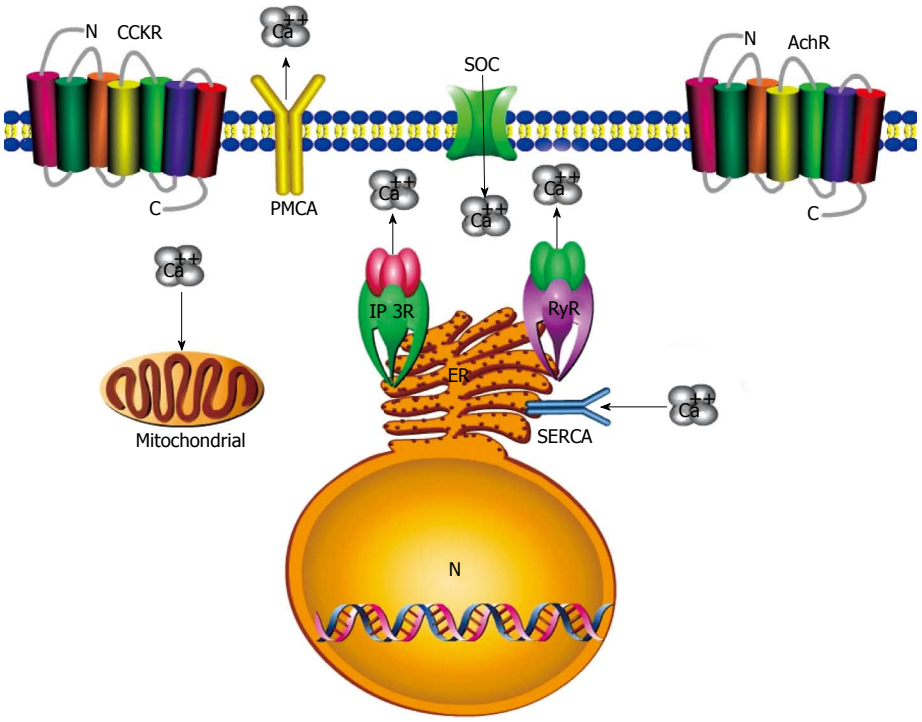

Figure 1 Diagram showing possible interventions for therapeutic targets of pancreatitis. Blockage of Ca^{2+} entry will probably depend on inhibition of the store-operated Ca^{2+} (SOC) channel in the pancreatic acinar cell. Activation of plasma membrane Ca^{2+}-adenosine triphosphate (ATP)ase (PMCA) and sarco/endoplasmic reticulum Ca^{2+}-activated ATPase (SERCA) would enhance Ca^{2+} extrusion from the cell and endoplasmic reticulum (ER). Intracellular Ca^{2+} release from the ER can be prevented through inhibition of the inositol 1,4,5-trisphosphate receptor (IP_3R) and ryanodine receptor (RyR). Preconditioning strategies could protect mitochondrial function to ensure adequate ATP production extrusion by Ca^{2+} pumps and for pancreatic acinar cells to survive intact.

Table 1 Potential therapeutic targets

Potential therapeutic targets
Store-operated Ca^{2+} channel
IP_3 receptor
Ryanodine receptor
SERCA
PMCA
Mitochondria

IP_3: 1,4,5-trisphosphate; PMCA: Plasma membrane Ca^{2+}-adenosine triphosphate (ATP)ase; SERCA: Sarco/endoplasmic reticulum Ca^{2+}-activated ATPase.

removal *via* the mitochondrial NCE[61,62]. Mitochondrial Ca^{2+} uptake activates Krebs cycle enzymes and drives ATP production, supplying ATP for SERCA-mediated Ca^{2+} re-uptake into the ER and PMCA-mediated Ca^{2+} extrusion[27,63]. Pathological stimulation that can induce experimental pancreatitis, such as with bile salts, fatty acids and CCK or its analog, can depolarize the inner mitochondrial membrane, inducing further collapse of the mitochondrial membrane potential and impairment of ATP production[64]. This situation prevents perigranular mitochondrial Ca^{2+} re-uptake and mitochondria cannot buffer the apical Ca^{2+} elevation, causing the local Ca^{2+} signal to spread to the whole of the acinar cell[30]. Failure of ATP production reduces the ability of the SERCA and PMCA pumps to take Ca^{2+} back into the ER and for extrusion, which contributes to Ca^{2+} overload. This is the most likely explanation for why pretreatment with Ca^{2+} chelators can limit the global and sustained elevation of Ca^{2+}.

TARGETS FOR POTENTIAL THERAPY

To date, there is no specific treatment for either acute or chronic pancreatitis[39,65-67]. The current therapy for pancreatitis is limited to the inhibition of proteolytic enzymes. Protease inhibitors have a modest preventative role in experimental animal models, however, they fail to show therapeutic value in clinical treatment[68,69]. An aberrant increase in cytosolic Ca^{2+} is a key molecular event in the pathogenesis of pancreatitis. Intracellular Ca^{2+} overload is a major reason for pancreatic acinar cell injury from toxin stimulation that induces pancreatitis[7,20,22-25,49]. Abnormal, prolonged, global Ca^{2+} signals lead to premature enzyme activation, vacuole formation and acinar cell damage. Thus, it is clinically relevant to identify the targets of the aberrant Ca^{2+} signals[70]. New avenues are required based on current findings in our understanding of Ca^{2+} signaling in the pathogenesis of pancreatitis (Figure 1). Possible interventions include: (1) inhibition of Ca^{2+} entry pathways; (2) enhancement of Ca^{2+} extrusion; and (3) inhibition of the primary Ca^{2+} release from the ER; and iv) protection of mitochondrial function, which can serve as potential therapeutic targets (Table 1). Recent progress in our understanding of Ca^{2+} signals of pancreatic acinar cells in the pathogenesis of

pancreatitis now provides opportunities for the developments of better therapeutic approaches.

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