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Review article

Calcium entry channels and their role in the pathogenesis of acute pancreatitis

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ABSTRACT

Acute pancreatitis (AP) is a common gastrointestinal emergency, and dysregulated calcium (Ca^{2+}) homeostasis within pancreatic acinar cells plays a key role in its development via intracellular Ca^{2+} toxicity and mitochondrial collapse. Abnormal activation of plasma membrane Ca^{2+} entry channels—including store-operated calcium entry (SOCE) channels, transient receptor potential (TRP) channels, and the mechanosensitive channel Piezo1—causes sustained cytosolic calcium overload. This imbalance triggers a series of harmful events, including premature zymogen activation and mitochondrial dysfunction, that create a vicious cycle of cellular injury in the pancreas. Growing evidence highlights the vital role of these Ca^{2+} entry channels in the pathophysiology of AP. Our review outlines current understanding of how these channels contribute to AP development and discusses recent advances, therapeutic applications, and future directions for drug strategies targeting these channels.

1. Introduction

Acute pancreatitis (AP) is a common gastrointestinal emergency characterized by the premature activation of digestive enzymes within pancreatic acinar cells (PACs). This process stimulates pancreatic autodigestion and an inflammatory response that can develop into systemic organ failure [1–3]. Globally, the incidence of AP has risen in recent years, with current annual estimates ranging from 30 to 40 cases per 100,000 people [4,5]. Major etiological factors include gallstone disease, alcohol abuse, and hyperlipidemia [6,7]. Although most cases are mild, nearly 20 % progress to moderate or severe AP. Severe acute pancreatitis (SAP) is linked with high mortality rates—between 20 % and 40 %—due to the lack of specific and effective pharmacological treatments [3]. The limited effectiveness of current management strategies highlights the urgent need for novel therapeutic interventions.

Calcium ions (Ca^{2+}) are ubiquitous second messengers that regulate a wide range of cellular processes in the human body [8]. PACs, the central functional units of the exocrine pancreas, are responsible for synthesizing and secreting digestive enzymes. The apical region of PACs contains numerous zymogen granules, and physiological stimulation by acetylcholine (ACh) or cholecystokinin (CCK) induces tightly regulated intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) oscillations that are typically confined to the apical pole. These localized Ca^{2+} signals facilitate exocytosis and fluid secretion, enabling context-dependent release of digestive enzymes and supporting normal digestion [8–10]. However, under pathological conditions triggered by toxic insults such as alcohol or bile acids, this organized oscillatory pattern is disrupted. Instead, sustained, global Ca^{2+} elevations—characterized by a peak-plateau response—propagate throughout the cell, resulting in Ca^{2+} overload in PACs [11,12]. This aberrant Ca^{2+} mobilization and the consequent prolonged elevation of cytosolic Ca^{2+} levels ($[Ca^{2+}]_c$) trigger a series of pathological events, including premature trypsinogen activation, mitochondrial Ca^{2+} overload, acinar cell death, and pancreatic inflammation, all of which are hallmark features of AP [13]. Importantly, dysregulated Ca^{2+} influx through plasma membrane (PM) channels serves as the initial mechanism underlying these toxic Ca^{2+} signals [14–18]. This review summarizes recent advances in understanding the contributions of specific Ca^{2+} influx channels to AP pathogenesis and explores their emerging potential as therapeutic targets.

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2. Store-operated calcium channels

Store-operated calcium channels (SOCs) are widely expressed in both excitatory and non-excitatory cells and constitute a major calcium signaling pathway in virtually all metazoan cells. By mediating store-operated calcium entry (SOCE), they play critical roles in a broad range of physiological processes—including gene expression, cell motility, secretion, tissue and organ development, and immune responses. SOCE represents a ubiquitous mechanism for regulating Ca^{2+} influx, influencing numerous cellular and physiological functions. Initially identified by Putney [19–21], SOCE is typically activated following the stimulation of G protein-coupled receptors (GPCRs), which triggers phospholipase C (PLC) activation and the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol trisphosphate (IP_3). IP_3 binds to IP_3 receptors (IP_3Rs) on the endoplasmic reticulum (ER) membrane, causing Ca^{2+} release from the ER into the cytosol—a process known as "ER Ca^{2+} store depletion" [22,23]. This depletion subsequently triggers SOCE (Fig. 1). Two central molecular components mediate SOCE. The first comprises the highly Ca^{2+}-selective Orai channels located in the plasma membrane, including Orai1, Orai2, and Orai3. Among these, Orai1 (also known as CRACM1) contains four transmembrane domains, all of which have cytoplasmic-facing N- and C-termini [24]. The strict Ca^{2+} selectivity of the Orai1 channel is conferred by coordination through negatively charged glutamate residues at positions E106 (in transmembrane (TM) 1) and E190 (in TM3), which form essential Ca^{2+} binding sites within the ion conduction pore [25,26]. The second essential component includes the calcium-sensing stromal interaction molecules, STIM1 and STIM2 [27–29]. STIM1 is a single-pass transmembrane protein localized to the ER membrane. Its domain architecture consists of an N-terminal luminal segment containing a canonical EF-hand (cEF), a noncanonical EF-hand (nEF), and a sterile alpha motif (SAM) domain; a transmembrane helix; and a cytosolic C-terminal region featuring three coiled-coil domains (CC1, CC2, CC3), an inhibitory domain (ID), and a polybasic (PB) tail [30–33]. This molecular organization enables STIM1 to function as a critical regulator of SOCE activation.

SOCE is mediated by calcium release-activated calcium (CRAC) channels, which are highly selective for Ca^{2+} [34]. The core molecular components of SOCE are STIM1 and Orai1, with Orai1 serving as the pore-forming subunit that conducts the highly Ca^{2+}-selective current termed I_{CRAC}. In unstimulated cells, STIM1 is diffusely localized within the ER membrane and can undergo microtubule-associated trafficking via interaction with EB1, while Orai1 diffuses freely in the plasma membrane [27–29]. Following depletion of ER Ca^{2+} stores, STIM1 senses the reduction in luminal Ca^{2+} and undergoes a conformational change that initiates its activation [35]. Dissociation of Ca^{2+} from the canonical EF-hand domain triggers the destabilization of the EF-SAM domain [36], propagating an activation signal through the transmembrane domain to the cytoplasmic region of STIM1. This rearrangement disrupts the autoinhibitory interaction between CC1 and the CAD/SOAR domain, resulting in the unfolding of the cytoplasmic segment. The C-terminus adopts an extended conformation, exposing the PB domain, which promotes translocation to ER-PM junctions via electrostatic interactions. Concurrently, the exposed SOAR domain binds to and gates Orai1 channels, opening the CRAC channel pore and permitting extracellular Ca^{2+} influx [37–39]. Subsequently, Ca^{2+} is actively transported back into the ER lumen via the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump, replenishing stores for future Ca^{2+} release in response to physiological demands [40] (Fig. 1).

To prevent excessive Ca^{2+} influx, SOCE is tightly regulated by harmful feedback mechanisms involving the store-operated calcium entry-associated regulatory factor (SARAF) [41]. SARAF binds to the STIM1 SOAR domain and attenuates SOAR-induced Orai1 currents [42]. This inhibition is achieved through STIM1-dependent recruitment of SARAF to ER-PM junctions, where it sterically hinders the interaction between the SOAR domain and the C-terminal binding site of Orai1. Furthermore, SARAF facilitates the transition of the STIM1 cytoplasmic domain from an extended, active conformation to a compact, inactive state. This reduces STIM1 accumulation at ER-PM contact sites and diminishes Orai1 activation efficiency,

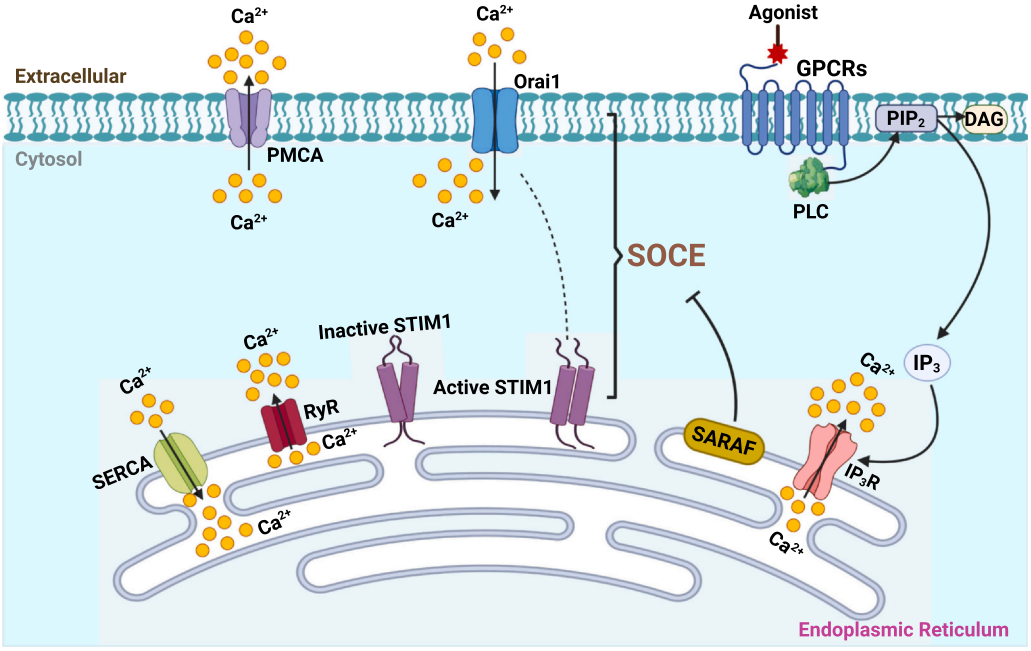

Fig. 1. Stepwise molecular mechanism of store-operated calcium entry (SOCE). The process begins with ER Ca^{2+} store depletion, initiated by PLC-coupled GPCR activation, PIP_2 hydrolysis, and IP_3-mediated Ca^{2+} release via IP_3R. This is followed by STIM1 activation and translocation: the drop in ER Ca^{2+} levels triggers STIM1 conformational change, exposing its C-terminal SOAR/CRAC domain. STIM1 then moves to ER–PM junctions, where it gates Orai1 channels, enabling Ca^{2+} influx. Finally, Ca^{2+} is recycled into the ER via SERCA, while SARAF negatively regulates SOCE to prevent excessive Ca^{2+} entry. Abbreviations: ER, endoplasmic reticulum; Ca^{2+}, calcium; PLC, phospholipase C; GPCR, G protein-coupled receptor; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor; STIM1, Stromal Interaction Molecule 1; SOAR, STIM-Orai activating region; CRAC, calcium-release activated calcium; PM, plasma membrane; PMCA, plasma membrane Ca^{2+}-ATPases; Orai1, Orai calcium release-activated calcium modulator 1; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SARAF, store - operated calcium entry - associated regulatory factor; RyR, ryanodine receptor.

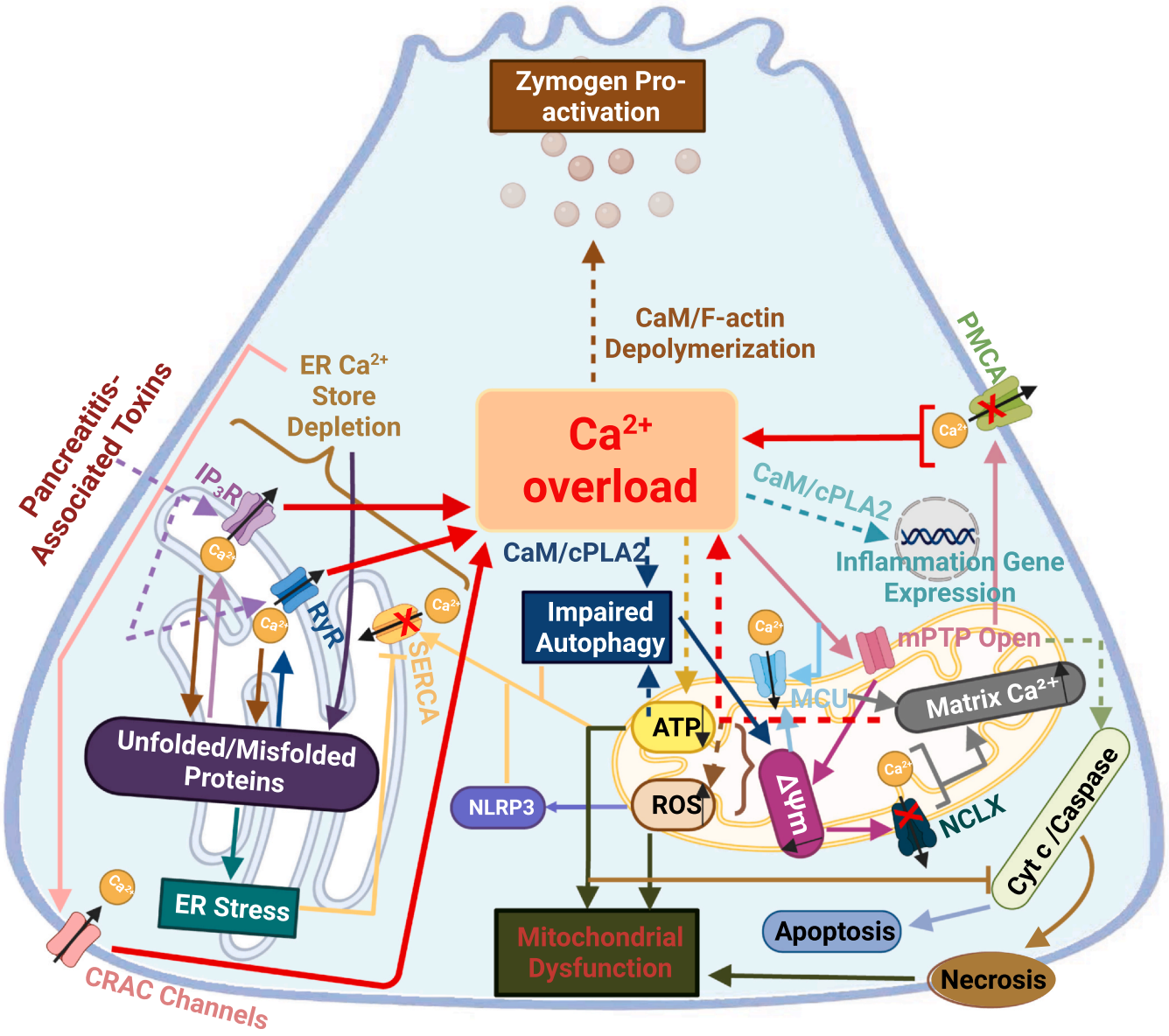

Fig. 2. Pathological cascade in acinar cells during pancreatitis driven by Ca^{2+} overload. Ca^{2+} overload in acinar cells triggers a stepwise pathological cascade during pancreatitis: 1) Toxin-Induced ER Ca^{2+} Release and Store Depletion: Pancreatitis-associated toxins (e.g., supramaximal CCK, bile acids, non-oxidative alcohol metabolites) initiate the cascade by inducing massive Ca^{2+} efflux from the ER through IP_3Rs and RyRs. This leads to ER Ca^{2+} store depletion, which subsequently induces ER stress and activates SOCE, resulting in sustained cytosolic Ca^{2+} overload. 2) Premature Zymogen Activation and Autodigestion: The elevated cytosolic Ca^{2+} activates CaM. CaM activation, coupled with Ca^{2+}-mediated depolymerization of F-actin, disrupts the apical actin network and facilitates the premature intracellular activation of digestive zymogens, ultimately provoking pancreatic autodigestion. 3) Mitochondrial Permeability Transition and Dysfunction: Excess cytosolic Ca^{2+} is taken up into mitochondria via the overactivated MCU. The resultant mitochondrial Ca^{2+} overload prompts the opening of the mPTP, triggering a critical breakdown: the collapse of the $\Delta\Psi_m$, failure of ATP synthesis, and massive generation of ROS. The combination of ATP depletion and oxidative stress disrupts cellular integrity, promoting mitochondrial dysfunction and necrotic cell death. 4) Disruption of Autophagic Flux: Cytosolic Ca^{2+} overload synergizes with CaM to activate $cPLA_2$. The aberrant activation of $cPLA_2$ disrupts autophagosome formation and maturation, thereby impairing autophagic flux, a key cellular clearance pathway. 5) Inflammatory Gene Induction: In parallel, sustained Ca^{2+} signaling activates transcription factors, leading to the upregulation of pro-inflammatory gene expression. A vicious cycle is established where persistent Ca^{2+} overload and the complex crosstalk among ER stress, zymogen hyperactivation, mitochondrial failure, impaired autophagy, and inflammatory signaling mutually reinforce each other, collectively exacerbating acinar cell injury and the systemic inflammatory response in pancreatitis. Abbreviations: ER, endoplasmic reticulum; IP_3Rs, inositol 1,4,5-trisphosphate receptors; RyRs, ryanodine receptors; SOCE, store-operated calcium entry; CaM, Calmodulin; F-actin, filamentous actin; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; $\Delta\Psi_m$, mitochondrial membrane potential; ATP, adenosine triphosphate; ROS, reactive oxygen species; $cPLA_2$, cytosolic phospholipase A2.

contributing to slow calcium-dependent inactivation (SCDI) and ultimately terminating Ca^{2+} influx to protect against cellular Ca^{2+} overload [41,43,44]. SOCE represents a fundamental Ca^{2+} signaling pathway in both excitable and non-excitable cells, playing essential roles in processes such as cell growth, proliferation, exocytosis, enzymatic activation, migration, and immune responses [19,44]. Dysregulation of SOCE has been implicated in multiple pathological conditions, including immunodeficiencies, cancer, neurological diseases, and inflammatory disorders [45–48].

Numerous studies have established that dysregulated CRAC channel activity contributes to pathological Ca^{2+} overload in PACs, promoting premature zymogen activation, the release of inflammatory mediators, and mitochondrial dysfunction, thereby exacerbating AP progression [49–53] (Fig. 2). Lur et al. demonstrated that upon depletion of ER

Ca^{2+} stores using thapsigargin (TG), a SERCA pump inhibitor, STIM1 translocates to basolateral regions of PACs. There, it participates in the formation of ribosome-free terminal structures and ER-PM junctions, serving as a structural platform for interaction with plasma membrane components and enabling localized assembly of SOCE machinery [54]. Hong et al. further reported that Orai1 is predominantly localized to the apical pole of the lateral membrane in PACs. Inhibition of either Orai1 or STIM1 significantly reduced Ca^{2+} influx and oscillation frequency. Upon stimulation, endogenous STIM1 was recruited in a polarized manner to apical and lateral regions, exhibiting approximately 40 % co-localization with Orai1 [55]. Pharmacological studies have highlighted the pathological significance of SOCE in AP. Gerasimenko et al. showed that GSK-7975A, an Orai1 channel blocker, concentration-dependently inhibited SOCE and prevented sustained $[Ca^{2+}]_i$ overload, protease activation, and necrosis in PACs induced by palmitoleic acid ethyl ester (POAEE), a mediator of alcohol-associated pancreatitis. It also attenuated $[Ca^{2+}]_i$ elevations triggered by high-dose acetylcholine [49], and suppressed TG-induced endocytic vesicle formation [50]. Further investigations revealed that GSK-7975A significantly ameliorated histopathological and biochemical markers in multiple experimental AP models, including those induced by taurolithocholic acid sulfate (TLCS-AP), cerulein (CER-AP), and fatty acid ethyl esters (FAEE-AP). Protective effects included reduced edema, inflammation, necrosis, serum amylase, IL-6, trypsin activity, and pancreatic/lung myeloperoxidase (MPO) activity. Similar efficacy was observed with CM_128, another Orai1 inhibitor, in both TLCS-AP and FAEE-AP models. In isolated human and mouse PACs, both inhibitors suppressed SOCE and necrotic cell death induced by TG, TLCS, CCK, and cyclopiazonic acid [51]. These findings collectively indicate that SOCE-mediated $[Ca^{2+}]_i$ overload is a central trigger in AP pathogenesis. The consistency of results across human cells and experimental models highlights the translational potential of SOCE inhibition as a therapeutic strategy for AP.

Subsequently, Zhu *et al.* demonstrated—using both Ca^{2+} overload models and experimental mouse models of AP—that caerulein induces SOCE by promoting STIM1-Orai1 interaction. The resulting Ca^{2+} influx activated calcineurin (CaN) in a SOCE-dependent manner, leading to dephosphorylation and nuclear translocation of the transcription factors TFEB and NFAT. This cascade facilitated transcriptional activation of multiple chemokine genes and autophagy-related genes [52]. These findings suggest that targeting CaN may represent a therapeutic strategy to mitigate SOCE-driven pancreatic injury. Moreover, SOCE-mediated modulation of autophagy via CaN-dependent TFEB activation may also contribute to other SOCE-related pathologies. Waldron et al. further reported that CM4620—a selective Orai1 inhibitor developed by CalciMedica—effectively suppressed SOCE, thereby preventing trypsinogen activation, acinar cell death, and the activation of NFAT and NF-κB signaling pathways. This inhibitor also significantly attenuated key pathological features of experimental AP, including pancreatic edema, acinar vacuolization, necrosis, and inflammatory cell infiltration [53]. In a related study, CM5480 was shown to restore expression of the regulatory factor SARAF in PACs, preventing aberrant Ca^{2+} elevation, preserving acinar cell function, and reducing immune cell infiltration [56].

In recent years, the pathological contribution of SOCE has been increasingly recognized not only in pancreatic acinar cells, but also in other cell types involved in AP, including ductal, stellate, and immune cells [53,56–60]. Its role in systemic complications associated with AP has also been further elucidated [53,58,61,62], significantly advancing our understanding of disease mechanisms. Studies have shown that Orai1 inhibitors—including GSK-7975A, CM_128, CM4620, and CM5480—effectively attenuate AP by inhibiting SOCE and preventing sustained Ca^{2+} overload. This leads to reduced pathological trypsin activation, acinar cell necrosis, and inflammatory responses [49–51,53,56–60]. Furthermore, these inhibitors mitigate injury and dysfunction in other pancreatic cell types implicated in AP pathogenesis, thereby limiting progression to severe disease. Among these compounds, CM4620 has a favorable safety profile with limited adverse effects. Recent clinical trials have shown promising outcomes: compared to standard of care (SOC) alone, Auxora (a subcutaneous injectable formulation of CM4620) did not increase the incidence of serious adverse events. Notably, three patients (36.5 %) with moderate AP improved to mild AP following low-dose Auxora treatment. Patients receiving Auxora also exhibited enhanced tolerance to solid food, shorter duration of systemic inflammatory response syndrome (SIRS), and reduced hospitalization rates by the end of the study period [63].

Remarkably, Peng *et al.* proposed that metabolic support via energy supplementation may also ameliorate AP. Mitochondrial production of adenosine triphosphate (ATP) is essential for powering critical cellular processes in PACs, and ATP depletion represents a hallmark of AP. Substituting glucose with galactose prevented or substantially reduced ATP loss and subsequent necrosis; comparable protective effects were observed with pyruvate. In both alcohol- and asparaginase-induced AP models, galactose markedly attenuated ATP depletion, tissue injury, PACs necrosis, and inflammatory storm [64]. These findings suggest that galactose may serve as a novel and effective supplemental therapy for AP. Further studies indicate that a combination of CM4620 and galactose synergistically targets complementary pathological pathways in AP, underscoring its potential as a multifaceted therapeutic strategy for this disease [65].

While inhibition of Orai1 shows therapeutic promise in AP, this channel also plays an essential role in T cell activation [66], raising concerns about potential impairment of immune function and patient recovery. This limitation underscores the need to explore alternative therapeutic targets such as SARAF. Studies in caerulein- and L-arginine-induced AP models have demonstrated that knockdown of SARAF impaired the ability of PACs to regulate SOCE, resulting in exacerbated Ca^{2+} influx, mitochondrial Ca^{2+} accumulation, inflammation, and overall AP severity. In contrast, targeted overexpression of SARAF in PACs attenuated pancreatic damage and inflammation, conferring protection against AP. Significantly, SARAF deficiency did not induce significant behavioral, physiological, or morphological abnormalities in the pancreas or salivary glands, suggesting that its function is primarily relevant under pathophysiological conditions [67]. These findings position SARAF induction or stabilization as a potentially safe and effective medical strategy for AP. Additionally, preliminary evidence supports the *in vivo* efficacy of Pyrtriazoles—a novel class of SOCE modulators—in acute pancreatitis, further expanding the scope of targeted intervention [68].

3. Transient receptor potential channels

The transient receptor potential (TRP) channel family comprises a class of non-selective cation channels initially discovered in Drosophila melanogaster in 1969 and subsequently cloned in 1989 [69,70]. These channels are primarily expressed in the PM of diverse tissues across mammalian species, where they function as key sensors for chemical and physical stimuli, as well as secondary effectors for both metabotropic and ionotropic receptors [71,72].The TRP family encompasses 28 members, classified into seven subfamilies based on structural and functional homology: ankyrin (with only one representative, TRPA1), canonical (TRPC1–6), melastatin (TRPM1–8), mucolipins (TRPML1–3), non-mechanoreceptor potential C (NOMP-like, TRPN1), polycystins (TRPP2–4), and vanilloid (TRPV1–6). Notably, orthologs of TRPN1 were found to be conserved only in Drosophila and zebrafish[72–74]. Molecular topology of TRP channels encompasses six transmembrane (TM1–6) α-helical segments, with a reentrant pore loop between TM5 and TM6, as well as cytoplasmic -NH_2 and -COOH terminal tails. The tetrameric complex assembled by TRP channels forms a central cation conduction pathway through the TM5 and TM6 subunits, with the pore loops interconnected [75]. The primary distinctions among TRP channel subfamilies lie in their N-terminal and C-terminal cytoplasmic domains. For instance, the C-terminal domains of TRPC and TRPV

channels contain binding sites for Ca^{2+} and Ca^{2+}-regulated proteins, rendering them susceptible to modulation by Ca^{2+} concentration changes induced by other cellular receptors and channels [71,76].

In the pancreas, exposure of acinar cells to toxic stimuli activates TRP channels, mediating extracellular Ca^{2+} influx. This leads to a pronounced increase in $[Ca^{2+}]_i$ and initiates extensive cross-talk with multiple cellular organelles. On one hand, accumulated cytosolic Ca^{2+} is taken up by the mitochondrial calcium uniporter (MCU), resulting in excessive Ca^{2+} accumulation within the mitochondrial matrix [77,78]. This disrupts ATP synthesis, promotes the generation of reactive oxygen species (ROS), induces mitochondrial membrane depolarization, and triggers the opening of the mitochondrial permeability transition pore (mPTP). The subsequent release of cytochrome c and apoptosis-inducing factor leads to mitochondrial dysfunction and the activation of apoptotic pathways. Mitochondrial Ca^{2+} overload also impairs mitophagy and inhibits cellular repair mechanisms [79–83].

On the other hand, elevated $[Ca^{2+}]_i$ directly activates RyRs and PLCβ on the ER membrane, inducing further Ca^{2+} release from the ER and amplifying store depletion. Additionally, specific TRP channels can stimulate SOCE [55,84,85]. Under these conditions, sustained high $[Ca^{2+}]_i$ inhibits the Ca^{2+}-reuptake function of the SERCA pump, indirectly promoting passive Ca^{2+} leakage from the ER. This results in progressive depletion of ER Ca^{2+} stores and loss of ER Ca^{2+} buffering capacity. Concurrently, reduced luminal ER Ca^{2+} inactivates calcium-dependent chaperones, leading to accumulation of unfolded/misfolded proteins and induction of ER stress [86–88]. The resulting multi-organelle damage synergistically amplifies acinar cell injury. TRPA, TRPC, TRPM, and TRPV channels—which exhibit high Ca^{2+} permeability—thus play a critical role in mediating pathological Ca^{2+} influx and downstream cellular damage [84,89,90] (Fig. 3). Consequently, inhibitors targeting these TRP channels have garnered significant interest as hopeful therapeutic agents for AP.

3.1. Transient receptor potential ankyrin (TRPA) channels

TRPA1, the sole mammalian member of the ankyrin (A) subfamily of TRP ion channels, consists of approximately 1000 amino acids and is characterized by multiple N-terminal ankyrin repeats [91]. It functions as a Ca^{2+}-permeable, non-selective cation channel that is activated by diverse noxious external and internal stimuli, including endogenous signals associated with cellular damage [92]. TRPA1 is highly expressed in nociceptive sensory neurons, where it contributes to pain transduction and promotes sustained inflammatory responses. Consequently, inhibition of TRPA1 represents a potential therapeutic strategy for pain management [93]. Notably, TRPA1 exhibits higher Ca^{2+} permeability compared to most other TRP channels [94], underlining its prominent role in Ca^{2+}-mediated signaling under pathological conditions.

Pancreatic pain and inflammation are hallmark features of pancreatitis, with TRPA1-expressing afferent nerves playing a pivotal role in these processes [95,96]. Studies have shown that TRPA1 agonists—including MO, HNE, and 15d-PGJ_2—elevate $[Ca^{2+}]_i$ in mouse pancreatic dorsal root ganglion (DRG) neurons and specifically activate spinal nociceptive neurons, as indicated by increased c-Fos immunoreactivity, ultimately eliciting pain-related behaviors. These agonists also induced pancreatic inflammation, as reflected by elevated serum amylase, pancreatic MPO activity, and higher histological severity scores; however, these effects were markedly attenuated or abolished in TRPA1-knockout mice [97]. In a cerulein-induced pancreatitis model, early dual inhibition of TRPV1 and TRPA1 (within the first three weeks) completely prevented abnormal Ca^{2+} signaling in DRG neurons, averted Ca^{2+} overload, improved pancreatic morphology, reduced neuronal hypertrophy, suppressed monocyte infiltration, and lowered inflammatory markers, thereby effectively halting progression to chronic pancreatitis (CP) [89]. Additional evidence suggests that pharmacological inhibition or genetic knockdown of TRPA1 reduces ethanol/palmitoleic acid (EtOH/POA)-induced $[Ca^{2+}]_i$ overload and protects quiescent pancreatic stellate cells (PSCs) from cell death. Modulating Ca^{2+} signaling in PSCs via TRPA1 agonists or antagonists may represent a therapeutic approach to promote a quiescent PSC phenotype, thereby attenuating pancreatic fibrosis [98].

3.2. Transient receptor potential canonical (TRPC) channels

The Transient Receptor Potential Canonical (TRPC) family consists of seven members, designated TRPC1 through TRPC7 [99]. These channels are referred to as “canonical” due to their structural and functional homology with the identified initially *Drosophila TRP* channel [100]. TRPCs function as Ca^{2+}-permeable, non-selective cation channels that various signaling molecules, including DAG and IP_3, can activate [101–103]. Upon activation, TRPC channels mediate Ca^{2+} influx into the cytosol, elevating $[Ca^{2+}]_i$ and initiating downstream signaling pathways that modulate the activity of multiple enzymes and transcription factors. TRPC channels are widely expressed in pancreatic tissues, including PACs and PSCs [104–106]. Aberrant TRPC activity has been closely linked to AP and its pathological progression [17,48], positioning these channels as promising therapeutic molecules for AP treatment.

The involvement of TRPC channels in PACs was initially established by Kim et al., who identified the expression of TRPC3 and TRPC6 proteins in mouse pancreatic acini [103]. A recent study confirmed the presence of TRPC3 and TRPC6 in human PACs [104]. Particularly, TRPC channels cooperate with SOCE in the pathogenesis of AP. The spatial proximity of TRPC3 and Orai1 channels facilitates Ca^{2+} influx at ER-PM junctions in PACs [87]. Kim et al. further demonstrated that the genetic deletion of TRPC3 reduced store-operated Ca^{2+} influx, resulting in a decrease of approximately 50 % in both receptor-stimulated and SOC-mediated Ca^{2+} entry. This downregulation attenuated pathologically sustained $[Ca^{2+}]_i$ levels, limited intracellular trypsin activation and actin depolymerization, and ultimately mitigated the severity of pancreatitis [84]. Pharmacological inhibition of TRPC3 with pyrazole 3 (Pyr3) similarly reduced Ca^{2+} influx by about 50 % in experimental AP models [17]. Comparable protective effects were observed following TRPC1 deletion in PACs [55], suggesting that both TRPC3 and TRPC1 contribute to SOCE activity in these cells. These findings identify TRPC3 as a key mediator of Ca^{2+} toxicity, with its inhibition attenuating SOCE-associated pancreatic injury [17]. The role of TRPC3/TRPC6-SOCE in AP has recently been supported by Du et al., who proposed that miR-26a simultaneously targets both channels. This targeting attenuated physiological Ca^{2+} oscillations and pathological $[Ca^{2+}]_i$ elevations in PACs, resulting in attenuated pathological alterations and marked amelioration of experimental acute pancreatitis [48].

TRPC channels are also implicated in the pathophysiology of PSCs. For instance, TRPC6 modulates the response of PSCs to hypoxia, and *Trpc6*$^{-/-}$ deletion suppresses hypoxia-induced Ca^{2+} elevation in these cells [105]. Meanwhile, TRPC3 has been implicated in promoting PSC migration, thereby contributing to tissue fibrosis [106,107]. Storck et al. demonstrated that KCa3.1 channels cooperate with TRPC3 by leveraging TRPC3-mediated Ca^{2+} influx to elevate $[Ca^{2+}]_i$ and upregulate calpain activity, which in turn drives PSC migration and chemotaxis. Genetic knockout of TRPC3 largely abolished the pro-migratory effects of KCa3.1 channels in PSCs [108]. Thus, upregulation of TRPC3 channels may facilitate disease progression in conditions such as pancreatic ductal adenocarcinoma.

3.3. Transient receptor potential melastatin (TRPM) channels

The TRPM family constitutes the largest and most functionally diverse subfamily of the TRP superfamily [109]. TRPM1, the first member to be identified and cloned, was reported in 1998 [110]. To date, eight members—designated TRPM1 through TRPM8—have been characterized. These channels are broadly expressed and modulate cellular Ca^{2+} signaling by mediating Ca^{2+} influx in response to diverse stimuli,

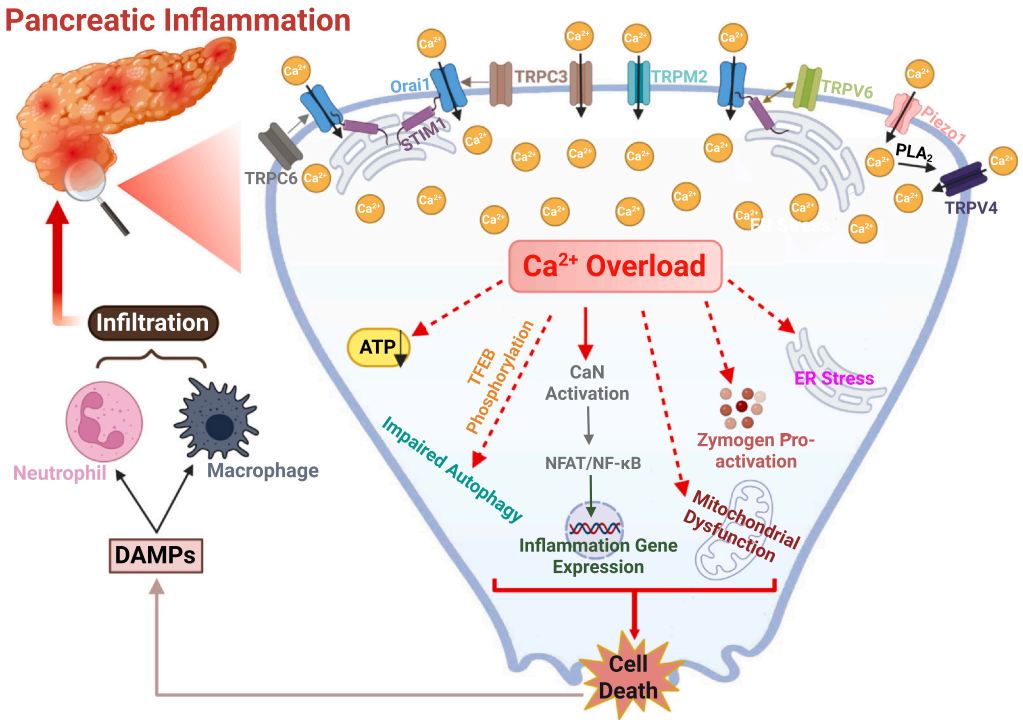

Fig. 3. Dysregulated Ca^{2+} influx channels cooperate to drive pathological Ca^{2+} overload in acute pancreatitis. Dysregulated Ca^{2+} influx through PM channels—and their functional crosstalk—orchestrates pathological Ca^{2+} overload, a critical driver of AP. The process is initiated upon pancreatic toxic injury, where aberrant activation of TRPM2, TRPC3, and Piezo1 channels sequentially mediates the early pathological Ca^{2+} influx into acinar cells. Subsequently, TRPC1, TRPC3, TRPC6, and TRPV6 functionally cooperate with SOCE, amplifying intracellular Ca^{2+} overload. Furthermore, Piezo1 activation recruits the cPLA2–TRPV4 axis, effectively converting mechanical stimuli into sustained pathological Ca^{2+} signaling. The resulting Ca^{2+} elevation activates downstream Ca^{2+}-sensitive signaling nodes such as CaN, which dephosphorylates NFAT to promote inflammatory gene transcription along with NF-κB; concurrently, TFEB is implicated in dysregulated lysosomal and autophagic responses. The propagation of these aberrant Ca^{2+} signals triggers a multi-step pathological cascade within acinar cells, including ER stress, premature zymogen activation, mitochondrial dysfunction, impaired autophagy, and ATP depletion. Widespread cellular injury leads to the release of DAMPs from damaged pancreatic acinar cells (PACs), which in turn activate and recruit immune cells—such as macrophages and neutrophils—into the pancreatic tissue. This immune cell infiltration intensifies local and systemic inflammatory responses, further exacerbating pancreatic injury and establishing a self-amplifying loop of inflammation and damage. Together, these events synergistically exacerbate acinar cell damage and inflammatory responses, underpinning the multidimensional pathology of AP. Abbreviations: PM, plasma membrane; Ca^{2+}, calcium; AP, acute pancreatitis; TRPM2, transient receptor potential melastatin 2; TRPC3, transient receptor potential canonical 3; Piezo1, piezo-type mechanosensitive ion channel component 1; TRPC1, transient receptor potential Canonical 1; TRPC6, transient receptor potential canonical 6; cPLA2, cytosolic phospholipase A2; TRPV4, transient receptor potential vanilloid 4; TRPV6, transient receptor potential vanilloid 6; ER, endoplasmic reticulum; ATP, adenosine triphosphate; CaN, calcineurin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor κB; TFEB, transcription factor EB; DAMPs, damage-associated molecular patterns.

including fluctuations in ion concentrations, small molecules, and lipid mediators [111]. The TRPM family is involved in a wide range of biological processes, such as redox sensing, inflammation, thermosensation, and insulin secretion. As a result, its members have garnered considerable interest as prospective treatments for related diseases [112–115].

Over the past few years, the key role of dysregulated Ca^{2+} influx mediated by TRPM channel activation has been increasingly elucidated in AP. TRPM2 is expressed in the PM of both mouse pancreatic acinar and ductal cells and can be activated by oxidative stress, such as that induced by H_2O_2 treatment. TRPM2 activity contributes to bile acid-induced extracellular Ca^{2+} influx in PACs, promoting acinar cell necrosis *in vitro* independently of mitochondrial damage or fragmentation. Furthermore, experimental bile acid-induced pancreatitis was attenuated in TRPM2-knockout mice, whereas TRPM2 deficiency did not confer protection in cerulein-induced AP, suggesting that TRPM2 inhibition may represent a possible curative method specifically for biliary pancreatitis [116]. Liu et al. reported increased functional expression of Ca^{2+}-dependent TRPM3 in DRG neurons innervating the pancreas in a rat model of AP. Injection of the specific TRPM3 agonist CIM0216 activated pancreatic TRPM3, inducing pain and neurogenic inflammation in AP. Conversely, pharmacological blockade of TRPM3 alleviated these symptoms [117]. These findings indicate that, alongside TRPV1 and TRPA1, TRPM3 serves as a key channel involved in pancreatic nociception, neurogenic inflammation, and AP-associated pain, positioning it as a key target for pain management in AP. An emerging study underlined that TRPM4 mediates Ca^{2+} overload-induced mitochondrial dysfunction and acinar cell death. Both pharmacological inhibition and genetic knockdown of TRPM4 alleviated pancreatic injury and reduced mortality in AP mice, with the protective effect attributed to improved mitochondrial function in PACs [118]. Collectively, these findings highlight the crucial role of TRPM channels and TRPM-mediated Ca^{2+} overload in the pathogenesis of AP.

3.4. Transient receptor potential vanilloid (TRPV) channels

The TRPV channel family comprises six members (TRPV1–6), named for their responsiveness to vanilloid compounds such as capsaicin [119]. Among these, TRPV1–4 function as thermosensitive non-selective cation channels, while TRPV5 and TRPV6 are highly selective for Ca^{2+} [120]. TRPV channels are widely expressed across diverse cell types and tissues, primarily localized to the plasma membrane. As Ca^{2+}-permeable, mechanosensitive receptors, they have gained attention as encouraging targets in conditions such as cancer, neurodegenerative diseases, and pain disorders [99,121–123]. Specially, TRPV1, TRPV4, and TRPV6 have been implicated in dysregulated Ca^{2+} influx during pancreatitis [89,96,124,125].

Results from the study demonstrated that all measured parameters—resting intracellular $[Ca^{2+}]_i$, peak response, and decay time—were significantly elevated after both 3 and 6 weeks of cerulein treatment.

Compared to the group treated with cerulein for 6 weeks, these parameters were markedly reduced in animals receiving combined cerulein and TRPV1 antagonist treatment for 3 weeks [89]. Beyond its contribution to pancreatic inflammation, TRPV1 also plays a significant role in pain signaling during pancreatitis [89,96,97,126,127].

Evidence indicates that Ca^{2+} influx mediated by TRPV4 and TRPV6 is implicated in both AP and CP. In most PSCs, TRPV4 activation induced sustained, dose-dependent calcium mobilization. Administration of a TRPV4 antagonist suppressed this Ca^{2+} activity even under baseline conditions. Furthermore, TRPV4 antagonism has been shown to attenuate both inflammation and pain-related behaviors in experimental models of AP and CP [124,128,129]. Similarly, the TRPV4 agonist GSK101, as well as arachidonic acid and 5',6'-epoxyeicosatrienoic acid, significantly increased $[Ca^{2+}]_i$ in PACs—an effect abolished by the TRPV4 antagonist HC067. In PACs isolated from TRPV4-knockout mice, neither Yoda1 nor fluid shear stress elicited sustained $[Ca^{2+}]_i$ elevation [130]. Additionally, functional variants in the calcium channel TRPV6 have been linked to early-onset CP. Patients with non-alcoholic early-onset CP were found to carry TRPV6 gene variants that impair channel function, likely through disruption of Ca^{2+} homeostasis in pancreatic cells [125]. The latest study has demonstrated that TRPV6 is functionally expressed in both human and mouse PACs and interacts with STIM1 to promote store-operated Ca^{2+} overload and pancreatic injury during AP. These findings further establish TRPV6 as a novel therapeutic target for mitigating Ca^{2+} overload in the treatment of AP [131].

4. Piezo channels

The mechanosensitive ion channel family Piezo, encoded by the genes Piezo1(FAM38A) and Piezo2(FAM38B), was first identified by Coste et al. in 2010 [132]. Piezo1 functions as a mechanosensitive, cation-selective calcium channel critical for mechanotransduction and mechanodependent responses in both excitable and non-excitable tissues. With a molecular structure exceeding 2500 amino acids and containing 38 transmembrane helices, Piezo1 assembles into a homotrimeric, propeller-shaped channel in the PM. Mechanical activation induces a conformational shift from a curved, closed state to a flattened, open state, permitting the permeation of Ca^{2+} and other physiologically relevant cations (e.g., Na^+, K^+, Mg^{2+}) across the membrane [133,134]. Piezo1 is predominantly expressed in non-sensory tissues, including the vascular and lymphatic systems, lungs, skin, gastrointestinal tract, and pancreas [134–137]. It participates in diverse physiological processes, such as lymphatic development, axon guidance, vascular morphogenesis, and immune regulation [138–141].

While Piezo2 has been reported to be expressed in baroreceptors and to cooperate with Piezo1 in regulating baroreflex and blood pressure [142]. It is more commonly associated with sensory neurons and specialized epithelial cells, where it modulates physiological processes, including touch, pain perception, thermosensation, proprioception, respiration, and digestion [143]. Interestingly, no evidence to date indicates that Piezo2 participates in the formation of functional clusters with any Ca^{2+}-activated ion channels.

Piezo1-mediated Ca^{2+} influx overload disrupts $[Ca^{2+}]_i$ homeostasis, inevitably impacting major Ca^{2+} storage organelles such as mitochondria and the ER. Specific activation of Piezo1 channels using the agonist Yoda1 or its analogue Dooku1 has been shown to elevate Ca^{2+} concentrations in human umbilical vein endothelial cells and mitochondria [144]. This enhancement enhances mitochondrial respiration and glycolysis, thereby stimulating ATP production. Similarly, another study demonstrated that Piezo1 activation induces mitochondrial Ca^{2+} uptake and subsequent oxidative phosphorylation (OXPHOS), with cAMP signaling contributing to the increase in mitochondrial OXPHOS following Piezo1 activation [145]. Additionally, one study found that substrate rigidity stimulates Piezo1 activation, resulting in Ca^{2+} influx. This initiates a signaling cascade involving extracellular signal-regulated kinases 1 and 2 (ERK1/2) activation and phosphorylation of dynamin-related protein 1 (DRP1), ultimately resulting in mitochondrial fragmentation and subsequent apoptosis [146].

Depending on its subcellular localization, Piezo1 activation can induce not only extracellular Ca^{2+} entry but also Ca^{2+} release from intracellular stores [147]. María Velasco-Estevez et al. observed that, in the presence of extracellular Ca^{2+}, the Piezo1 agonist Yoda1 initially elevates $[Ca^{2+}]_i$ levels, likely through Ca^{2+} influx via membrane-localized Piezo1 channels. This subsequently triggers calcium-induced calcium release (CICR) from intracellular stores [148]. Fam38A (Piezo1) also mediates integrin activation by recruiting the small GTPase R-Ras to the ER, stimulating calpain proteases through enhanced Ca^{2+} release from cytosolic stores [149]. The depletion of Ca^{2+} from intracellular stores can activate CRAC channels on the PM, further promoting extracellular Ca^{2+} influx and facilitating the replenishment of intracellular Ca^{2+} stores [150].

The pancreas is highly susceptible to mechanical injury, which can directly initiate pancreatitis. For example, gallstones—the most common cause of AP—often induce pancreatic damage through elevated intra-pancreatic pressure [151]. Similarly, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is strongly associated with increased pancreatic duct pressure during the procedure. Romac et al. developed a clinically relevant mouse model to examine the effects of elevated intraductal pressure on the pancreas. Their results showed that increased pressure significantly raised pancreatic weight, serum amylase levels, and MPO activity, confirming that elevated intraductal pressure can induce AP. Using qRT-PCR and confocal microscopy, the authors further demonstrated that Piezo1 mRNA was the most abundant among mechanosensitive ion channels tested, with prominent localization on the surface of PACs, indicating that Piezo1 is the primary mechanosensitive channel in the pancreas. The study also highlighted a strong link between pressure-induced pancreatitis and Ca^{2+} signaling. Mechanical disruption during PAC isolation activated calcium-sensitive 5-lipoxygenase[135]. Moreover, applying localized mechanical force via micropipettes to dye-loaded acinar cells induced a rapid increase in $[Ca^{2+}]_i$, followed by sequential propagation of the Ca^{2+} signal to neighboring cells, consistent with functional coupling among acinar units [152].

In parallel, the study by Romac et al. investigated the modulation of Ca^{2+} signaling by the Piezo1 activator Yoda1 and mechanosensitive channel inhibitors. They reported that Yoda1 increased $[Ca^{2+}]_i$ in PACs, whereas GsMTx4—a peptide inhibitor of mechanosensitive cation channels—suppressed this Yoda1-induced Ca^{2+} rise. To further validate the specificity of these responses *in vivo*, the researchers generated a mouse model with a Piezo1-Specific knockout of PAC. Acinar cells from these mice did not respond to Yoda1 stimulation and maintained normal $[Ca^{2+}]_i$ upon CCK challenge. Additional experiments demonstrated that Yoda1 treatment significantly increased pancreatitis-associated parameters, including pancreatic oedema, serum amylase, and MPO activity, in wild-type mice; however, it failed to induce pancreatitis in Piezo1 acinar-specific knockout mice. Together, these findings indicate that mechanical stress-induced activation of Piezo1 causes sustained elevation of $[Ca^{2+}]_i$ in PACs, thereby promoting the development of pancreatitis [135] (Fig. 3).

TRP channels are recognized as amplifiers of Piezo1-mediated signaling, and functional interactions between Piezo1 and TRP channels have been documented across multiple cell types [153–155]. In freshly isolated pancreatic acini, Piezo1 activation stimulates cytosolic phospholipase A_2 ($cPLA_2$), leading to subsequent opening of TRPV4 channels [130]. Researchers observed that TRPV4-knockout mice were protected against pancreatitis induced by the Piezo1 agonist Yoda1, indicating that TRPV4 mediates the translation of Piezo1-dependent mechanosensation into pathological progression. Based on these findings, a model has been proposed wherein membrane deformation and Ca^{2+} signaling cascades activate a functional Piezo1/TRPV4 channel complex [156] (Fig. 3).

TRPV4 also contributes to Piezo1-mediated alterations in free cytosolic Ca^{2+} level in PSCs. While the specific Piezo1 agonist Yoda1 or prolonged high shear stress typically induced sustained $[Ca^{2+}]_i$ elevation in wild-type PSCs, both stimuli elicited only transient Ca^{2+} increases in PSCs isolated from TRPV4-knockout mice. Combined application of two phospholipase A_2 (PLA_2) inhibitors significantly suppressed the Yoda1-mediated sustained $[Ca^{2+}]_i$ increase in wild-type PSCs. Furthermore, the mechanosensitive channel inhibitor GsMTx4 abolished the transient $[Ca^{2+}]_i$ elevation induced by high shear stress in TRPV4-deficient PSCs. These results confirm that Piezo1 mediates the initial transient Ca^{2+} influx, whereas subsequent TRPV4 channel opening is essential for achieving sustained $[Ca^{2+}]_i$ elevation [157]. The study on PSC durotaxis further revealed synergistic activation of Piezo1 and TRP channels driving Ca^{2+} influx. Durotaxis in PSCs was shown to depend on Piezo1 activity, and inhibition of TRPV4 in PSCs derived from TRPC1-knockout mice significantly impaired durotactic responses. This suggests that Piezo1 alone is insufficient to regulate durotaxis and requires functional cooperation with TRPV4 and/or TRPC1. Consistent with this, Ca^{2+} influx rates were reduced in the presence of a TRPV4 inhibitor compared to controls [158].

5. Conclusions and future directions

Dysregulated Ca^{2+} influx through plasma membrane ion channels, culminating in intracellular Ca^{2+} overload, has been firmly established as a central driver in the pathogenesis of AP. This review has systematically delineated the activation mechanisms and pathological contributions of key Ca^{2+} entry pathways—namely SOCE, TRP channels, and the mechanosensitive channel Piezo1—in the initiation and progression of AP. A critical emerging concept is that these channels do not operate in isolation; rather, they engage in complex cross-talk, amplifying aberrant Ca^{2+} signals within PACs and other cell types in the pancreas, thereby exacerbating cellular injury and the inflammatory response. The intricate synergy between these channels and multiple intracellular organelles underpins the multi-faceted pathology of AP, providing a more holistic framework for understanding the disease.

The therapeutic potential of targeting these Ca^{2+} entry pathways is substantial. Pharmacological inhibition of Orai1, a core component of SOCE, has shown promising results in preclinical models and early clinical trials, effectively reducing Ca^{2+} overload, pancreatic damage, and systemic inflammation. Similarly, modulating specific TRP subfamilies (TRPA, TRPC, TRPM, TRPV) and the mechanosensor Piezo1 presents viable strategies to alleviate specific aspects of AP, including pain, necrosis, and pressure-induced injury. The discovery of functional complexes, such as Piezo1/TRPV4, highlights the potential for targeting channel interactions as a novel therapeutic approach. Furthermore, strategies aimed at enhancing endogenous regulatory mechanisms, such as boosting SARAF expression to fine-tune SOCE, offer avenues for intervention with potentially fewer side effects.

Despite these advances, several challenges and opportunities lie ahead. Future research must prioritize the development of highly selective inhibitors with optimized pharmacokinetic and safety profiles to minimize off-target effects, particularly given the physiological roles of these channels in immune function and other tissues. A deeper understanding of the spatiotemporal regulation and cell-type-specific contributions of these channels in the heterogeneous pancreatic microenvironment is crucial. Combining Ca^{2+} channel inhibitors with agents targeting complementary pathways—such as metabolic support (e.g., galactose) or anti-inflammatory drugs—may yield synergistic efficacy. Translating these mechanistic insights into clinical practice will require robust biomarkers for patient stratification and the development of effective targeted delivery systems to enhance therapeutic precision. Addressing these fronts will pave the way for transforming the management of AP from supportive care to mechanism-driven, targeted therapy.

CRediT authorship contribution statement

Shuang Peng: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Die Liao:** Writing – original draft, Investigation. **Zhuoya Li:** Writing – review & editing, Writing – original draft. **Zelin Sun:** Writing – review & editing, Writing – original draft. **Yao Jia:** Writing – original draft. **Xuebiao He:** Writing – original draft. **Xiaolin Yang:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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