The role of Ca2+ signalling in the physiology and pathophysiology of exocrine pancreas

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Abstract

The purpose of this paper is to describe recent advances in the studies of Ca2+ signalling and its physiological / pathophysiological roles in the cells of exocrine pancreas. The review is primarily focused on pancreatic acinar cells – this reflects the importance of this cell type for unravelling of Ca2+ signalling mechanisms and downstream functions. Valuable information on the functional relevance of Ca2+ signalling was also recently obtained in studies of pancreatic ductal cells and pancreatic stellate cells; progress in the studies of these cell types is also briefly summarised in this paper.

Keywords

Acute pancreatitis, bioenergetics, Ca2+ signalling, digestive enzymes, endocytosis, exocytosis, pancreatic acinar cells, pancreatic duct cells, pancreatic stellate cells, trypsin, trypsinogen, zymogens.

Abbreviations

CCK, cholecystokinin; ER, endoplasmic reticulum; IP3, inositol trisphosphate; IP3R, inositol trisphosphate receptor; MCU, mitochondrial Ca2+ uniporter; MPT, mitochondrial permeability transition; MICU1/2, mitochondrial calcium uptake 1/2; MPTP, mitochondrial permeability transition pore; NAADP, nicotinic acid adenine dinucleotide phosphate; NAADPR, nicotinic acid adenine dinucleotide phosphate receptor; PMCA, plasma membrane Ca2+ ATPase; ROS, reactive oxygen species; RyR, ryanodine receptors; SARAF, store-operated calcium entry-associated regulatory factor; SERCA, sarcoplasmic/endoplasmic reticulum Ca2+ ATPase; SOCE, store-operated Ca2+ entry; STIM, stromal interaction molecule; TLC-S, taurolithocholic acid 3-sulfate; TRP channels, transient receptor potential channels; TRPC, canonical transient receptor potential channels; TRPM transient receptor potential melastatin channels; TRPV, transient receptor potential vanilloid channels.

Declarations of interest: none.

Introduction

Pancreatic acinar cells and pancreatic ductal cells primarily define the exocrine functions of the organ - secretion of digestive enzymes (many secreted as precursors termed zymogens) and secretion of bicarbonate-rich fluid. A recent study from the S. Muallem group added the secretion of antimicrobial factors that influence gut microbiome to the functions of exocrine pancreas [1]. Pancreatic acinar cells have served as a model for the discovery of important Ca2+ signalling mechanisms. Notably, IP3-mediated Ca2+ release was discovered in pancreatic acinar cells [2]. The effects of other Ca2+ releasing messengers NAADP and cADP-ribose were also observed and characterised in this cell type [3-6]. Acinar cells express three types of IP3 receptors [7-10]. Ryanodine receptors are also expressed in this cell type [11-13] and contribute to the initiation and propagation of Ca2+ signals [12-15]. Pancreatic acinar cells have been utilised to define important Ca2+ signalling concepts, including Ca2+ tunnelling through the lumen of the endoplasmic reticulum (ER) [16] and localised Ca2+ signalling mapped to specific subcellular locations and organellar distributions (e.g. [14, 17-21]). Ca2+ entry into the cell has been primarily attributed to STIM/Orai channels [22-24]; there is also evidence for the involvement of TRPC channels [25]. Pancreatic acinar cells have a well-defined polarised morphology with clearly resolvable and specifically localised cellular organelles: the apical part of the cell contains large secretory granules (also termed zymogen granules), the nucleus is located in the basolateral region, with the bulk of the ER found in the basal and lateral parts of the cell with strands projecting to the apical region [26, 27], and mitochondria are concentrated in perigranular, perinuclear and subplasmalemmal regions [21, 28]. A polarised distribution of mitochondria was also observed in pancreatic ductal cells [29]. IP3Rs are preferentially localised in the proximity to the apical region in both ductal cells [30] and acinar cells (e.g. [8-10]), whilst STIM/Orai complexes (i.e. SOCE channels) are formed in basal and lateral regions [10, 22, 31]. Currently, the principal focus of this research subfield is on the downstream functional implications of Ca^{2+} signalling (summarised in Figure 1) and particularly on cell / tissue pathophysiology associated with aberrant Ca^{2+} responses. This will be the primary focus of our review.

From receptors to Ca2+ signalling.

In rodent pancreatic acinar cells the important secretagogues acetylcholine (ACh) and cholecystokinin (CCK) utilise Ca2+ signalling to trigger and regulate secretion; physiological doses of these agonists produce well-defined patterns of oscillatory Ca2+ responses (reviewed in [32-34]). However, the role and the very presence of CCK receptors in human acinar cells has been questioned [35]; this contrasted with studies indicating the functional relevance of CCK receptors in this cell type [36]. The controversy was resolved in an elegant study by T. Liang and colleagues that utilised organotypic slice preparations of the human pancreas and demonstrated cellular effects of CCK stimulation in undissociated human acinar cells [37]. Notably Ca2+ responses to CCK (in conjunction with the recording of exocytosis) were utilised as the primary evidence for the presence and functional role of the CCK receptors in human pancreas [37].

Stimulus-metabolism coupling: interplay between Ca2+ signalling and the bioenergetics of pancreatic acinar cells.

Ca2+ signalling plays an important role in adjusting the bioenergetics of the cell to changing demands imposed by different external stimuli; in other words, stimulus-metabolism coupling. The relationships between the cytosolic Ca2+ signals, mitochondrial Ca2+ signals and NAD(P)H levels, generated by the Krebs cycle, were initially characterised in isolated hepatocytes [38] In pancreatic acinar cells cytosolic Ca2+ oscillations also clearly correlated with the changes of NAD(P)H [39] suggesting importance of this second messenger in the regulation of the Krebs cycle. This notion was further confirmed in a recent study that utilised pancreatic acinar cells isolated from mice with knocked out mitochondrial Ca2+ uniporter (MCU; the main mechanism of Ca2+ entry in this organelle). In such MCU KO cells NAD(P)H responses to CCK stimulation were drastically reduced [40]. The Ca2+-dependent stimulus-metabolism coupling in this cell type is very efficient in preventing ATP loss when ATP usage is strongly increased by hormones or neurotransmitters [41]. Notably, the bioenergetics status of the cell has a powerful effect on Ca2+ signalling - modest ATP depletion has a strong inhibitory effect on Ca2+ leak from internal stores [42] and on Ca2+ oscillations [43]. The mechanism behind the inhibition of Ca2+ oscillations has been recently identified; it involves the sensitivity of IP3 receptors (particularly IP3R2 and IP3R3) to ATP [44, 45]. However, when substantial ATP depletion occurs in pancreatic acinar cells, due to Ca2+ overload triggered by precipitants of acute pancreatitis including bile acids [46, 47] and non-oxidative ethanol metabolites mediated via IP3Rs [48], bioenergetic collapse ensues which shifts cell death patterns towards necrosis [49]. ATP depletion has profound effects on Ca2+ influx [43] and, importantly, Ca2+ extrusion by Ca2+ pumps of the plasma membrane [43, 50, 51]. Insufficiency of Ca2+ extrusion results in Ca2+ toxicity - a ubiquitous mechanism of cell damage. Important studies from J. Bruce group describe the mechanism that is utilised by the acinar cells to retain/restore ATP supply and maintain PMCA activity; this mechanism is insulin-dependent and it is likely to involve non-mitochondrial ATP production [50, 51].

Acute pancreatitis and IP3Rs.

Acute pancreatitis is a frequent disease with considerable morbidity (reviewed in [52, 53]). Ca2+ toxicity is considered as an important factor mediating death /damage of pancreatic acinar cells and the initiation of acute pancreatitis (e.g. [54, 55]). For some inducers of acute pancreatitis, including supramaximal doses of secretagogues, bile acids and non-oxidative ethanol metabolites, aberrant Ca2+ signals form as a result of substantial Ca2+ release from the ER amplified by Ca2+ influx from the extracellular solution (reviewed in [32, 33]). There are recent interesting developments describing relationships of these fundamental Ca2+ transport processes and this disease. In particular, L. Wang and colleagues reported trypsin-induced cleavage of IP3R2 and IP3R3; notably, such cleavage was observed in pancreatic tissue of animals with induced acute pancreatitis [56]. This finding is important because activation of trypsinogen (i.e. formation of trypsin) is an early hallmark of acute pancreatitis [54, 55, 57-59]. All three types of IP3Rs have been

detected in pancreatic acinar cells. IP3R2 and IP3R3 are the main types; genetic knockout of these receptors resulted in almost complete ablation of both secretagogue-induced Ca2+ signals and stimulated exocytosis [7]. Both IP3R2 and IP3R3 are cleaved by trypsin [56]. At the cellular level this results in a reduced frequency and amplitude of cytosolic Ca2+ responses [56]. It is conceivable that trypsin-dependent cleavage represents a negative feedback mechanism, reducing Ca2+ release and consequently Ca2+ toxicity in damaged acinar cells. However, elucidation of both the physiological and pathophysiological roles of this interesting novel phenomenon requires further investigation.

Ca2+ influx, acinar cell damage and pancreatic pathophysiology.

There has been recent progress in defining the contribution of Ca2+ influx and its specific components/regulators to the Ca2+ toxicity and the initiation of acute pancreatitis. SOCE is mediated by plasma membrane-embedded Orai channels stimulated by STIM proteins (localised in the ER and serving as ER Ca2+ sensors) ([60-63]. STIM1 and Orai1 channels have been characterised in pancreatic acinar cells [10, 22] and the inhibition of these channels reduced the damage in both mouse and human pancreatic acinar cells [23, 24, 64]. Importantly, SOCE inhibitors also reduced the severity of experimental acute pancreatitis in multiple models [64]. These findings were recently confirmed and extended by R. Waldron and colleagues [65]; this study demonstrated differences in the relative expression of Orai in the two species of rodents (Orai1 is dominant in mice, whilst higher expression of Orai 2 was found in rats). Furthermore, the authors reported strong suppression of acute pancreatitis severity in both species by Orai inhibitor CM4620 [65]. Notably, this inhibitor suppressed Ca2+ - dependent responses not only in the acinar cells but also on immune cells participating in the development/progression of this disease [65]. The relevance of SOCE mediated by STIM/Orai to the pathophysiology of acute pancreatitis was recently highlighted by the study from S. Muallem's group demonstrating dynamic changes of SOCE-associated regulatory factor (SARAF, previously known as TMEM66 [66]) and its ability to modify the disease severity [67]. In two models of experimental acute pancreatitis overexpression of SARAF, which is known to inactivate SOCE [66], reduced severity of the disease, whilst the knockout of this protein conversely increased severity. Notably, the protective effects of SARAF were limited to a mild form of caerulein-induced acute pancreatitis, whilst the severe form was unchanged by SARAF [67] indicating the limits of its protective action and suggesting the redundancy of injurious mechanisms

The family of Ca2+ influx channels contributing to the initiation of pancreatitis has been recently expanded in studies of acute pancreatitis induced by mechanical damage and excessive pressure. These studies revealed the importance of mechanoreceptor Piezo1 (stretch-activated cationic channels [68]) for Ca2+ toxicity affecting pancreatic acinar cells [69, 70]. Both sheer stress and Yoda1 (pharmacological activator of Piezo 1) increased cytosolic Ca2+ and triggered Ca2+ toxicity (manifested by mitochondrial damage and trypsinogen activation) in the acinar cell [69]. Furthermore, infusion of Yoda1 into the pancreatic duct induced acute pancreatitis in mice [69]. Surprisingly, another channel TRPV4 is involved in mediating the effects of Piezo1; acinar cells from TRPV4 KO mice were protected

from Yoda1-induced sustained Ca2+ rises and associated damage. Importantly, Yoda-1 did not trigger acute pancreatitis in TRPV4 KO mice [70]. The authors proposed that the interaction of Piezo1 and TRPV4 (mediated by the activation of phospholipase A2) is essential for the development of pressure-induced acute pancreatitis. Pressure-induced pancreatitis can be triggered by gallstones blocking the junction of pancreatic and bile duct, mechanical trauma of the pancreas and endoscopic retrograde cholangiopancreatography; it accounts for a significant proportion of cases of this disease. The finding of the specific Ca2+-dependent mechanisms underlying this condition has therefore significant translational potential.

Another contributor to Ca2+ influx in pancreatic acinar and ductal cells was recently identified by J Fanczal and P Pallagi from J Maleth group. They found that the TRPM2 (transient potential melastatin-like 2) channel mediates ROS-dependent Ca2+ influx in these cell types [71]. This finding has relevance for biliary acute pancreatitis. Bile acids induce Ca2+ responses [46, 72] and trigger Ca2+ influx with properties clearly different from those expected from STIM/Orai channels [43, 72]. Notably bile acids induce significant Ca2+-dependent ROS production in the acinar cells [47, 71, 73]. Importantly, knockout of TRPM2 reduced the severity of experimental biliary pancreatitis in mice [71]; a phenomenon which is likely to be mediated by changes in the ROS-dependent Ca^{2+} influx.

Effector mechanisms linking aberrant Ca2+ signals to the damage of pancreatic acinar cells: progress with the role of calcineurin.

Amongst the downstream effectors of Ca2+ toxicity are calpains [74], calcineurin [75, 76], mitochondrial Ca2+ overload and consequent mitochondrial damage [77], impaired autophagy [78], disruption of trafficking and vacuolisation [54, 55, 79-81] and intracellular activation of trypsinogen [54, 55] (see Figure 1). The understanding of the connections between the primary Ca2+ sensors and the downstream damage to vital cellular components in the acinar cells is still somewhat patchy. In the case of calpains, which are directly activated by Ca2+, downstream targets are proteins associated with the cellular cytoskeleton (including αII-spectrin, vinculin and E-cadherin) [82]. Interestingly, both high affinity μ-calpain (calpain 1, activated by low μM Ca2+ concentrations) and lower affinity m-calpain (calpain 2, activated by higher Ca2+ concentrations) can be activated by supramaximal concentrations of CCK in pancreatic acinar cells [82]. The consequences of the calpain-mediated cleavage of cytoskeleton-associated proteins in the acinar cells are prominent changes in the F-actin distribution, increased vacuolisation and cell damage (revealed by lactate dehydrogenase release) [82]. It is conceivable that the link between increased vacuolisation and damage / death of the acinar cells is mediated via the recently discovered rupture of vacuoles accompanied by the release of digestive enzymes into the cytosol [83]. For the damaging effects of Ca2+ on the mitochondria the primary Ca2+ sensors are probably proteins regulating Ca2+ entry into the mitochondria via MCU (including MICU1 and MICU2 [84] and enigmatic mitochondrial Ca2+ sensor(s) that trigger opening of mitochondrial permeability transition pore (MPTP) (e.g. [85], reviewed in [86], [87]). Notably, a recent study from G. Biczo, E. Vegh and colleagues [78] suggested that both Ca2+-dependent and Ca2+-independent mitochondrial damage induce impairment of autophagy and that

this impairment of autophagy is vital for further downstream effects including ER stress and disruption of lipid metabolism in the acinar cells, and eventually, development of acute pancreatitis [78]. In this respect somewhat unexpected recent results showing that global MCU knockout did not reduce severity of experimental acute pancreatitis were reported by M. Chvanov and colleagues [40]. A possible explanation of this unexpected finding is the redundancy of damaging mechanisms simultaneously activated in the acinar cells by Ca2+-elevating agonists [40]. In other words, Ca2+-dependent mitochondrial impairment is sufficient to damage the acinar cells and trigger acute pancreatitis, whilst the inhibition of this pathophysiological mechanism is insufficient to prevent the disease, because of the parallel activation of other damaging responses (e.g. intracellular trypsinogen activation). Disruption of trafficking and vacuolisation are prominent features of acute pancreatitis, which could be triggered by excessive Ca2+ rises (e.g. [54, 55, 79, 80, 88]). The primary Ca2+ sensors for these pathophysiological responses are not clear. Synaptotagmin 1 is an important Ca2+ sensor for the initial phase of the apical exocytosis of zymogen granules in pancreatic acinar cells ([89], reviewed in [90]). Physiological secretion of zymogens in the acinar cells involves limited compound exocytosis, which requires both initial fusion of a zymogen granule with the plasma membrane and subsequent fusion between zymogen granules (notably these processes involve different VAMPs) (reviewed in [91]). Pathophysiologically-relevant large endocytic vacuoles form as a result of the aberrant excessive compound exocytosis of numerous zymogen granules followed by membrane retrieval [80]. It is likely that synaptotagmin 1 and/or other synaptogamins, expressed in the acinar cells (3, 6 and 7 [89]), participate in this process. Misdirected basolateral exocytosis of zymogen granules is another cellular response associated with the induction of acute pancreatitis [79, 88, 92]. Notably, the Ca2+-dependent isoform of PKC (PKCa) was reported to initiate this aberrant exocytosis [92].

Perhaps the most impressive recent progress in characterising downstream mechanisms of Ca2+ -induced damage was attained in studies describing the role of Ca2+ and calmodulin-dependent phosphatase calcineurin. This protease has an important role in the regulation of both physiological (e.g. regulation of protein synthesis and adaptive pancreatic growth [93, 94]) and pathophysiological (e.g. [75], [76]) responses in the exocrine pancreas. Activation of zymogens [75] has been reported as a consequence of Ca2+-dependent stimulation of calcineurin. Calcineurin also plays an important role in the activation of NF-κB [76]. This transcription factor is associated with the induction of acute pancreatitis [95] and involved in the synthesis of proinflammatory cytokines in the acinar cells [96]. An elegant study by Li Wen and colleagues demonstrated the prominent role of calcineurin in experimental acute pancreatitis triggered by transient increases of pressure in pancreatic duct [97]. This model is relevant to clinical pancreatitis induced by retrograde endoscopic cholangiopancreatography. Notably, in addition to pharmacological inhibition of calcineurin the study also utilised mice lacking a catalytic subunit of calcineurin. Both pharmacological inhibition and the genetic modification of calcineurin resulted in the strong reduction of the severity of the experimental acute pancreatitis. These results are consistent with the previous studies from the same group highlighting the importance of calcineurin for cellular

and in vivo models of acute pancreatitis (e.g. [75, 76]). These observations are also in line with a recent study that identified the role of calcineurin in mediating the effect of SOCE (determined by STIM1/Orai1 interaction) on induction of autophagy and activation of transcription factors relevant for acute pancreatitis [98].

Ca2+ signalling in pancreatic ductal cells

Ca2+ responses to ACh and ATP are important for the normal physiological function of pancreatic ductal cells – secretion of HCO^-_3-reach fluid. Notably, close co-operation between cAMP and Ca2+ signalling cascades in this cell type is required for physiological secretory responses (reviewed in [99]). Similarly to the acinar cells this cell type has a polarised distribution of IP3 receptors, which concentrate in the apical part of the cell [30]. M-H Kim and colleagues characterised the SOCE mechanism in these cells and attributed it primarily to the activity of STIM/Orai channels, preferentially concentrated in the basolateral membrane [100]. Important recent discovery highlighted the role of highly Ca2+ -selective constitutively active epithelial channel TRPV6 in protecting against pancreatitis [101]. This channel is preferentially expressed in ductal cells and its functionally-deficient mutations are associated with early onset chronic pancreatitis in human patients [101]. Notably, mice with functionally-deficient mutation in TRPV6 channel (*TRPV6*$^{mut/mut}$ mice) have more severe cerulein-induced chronic pancreatitis in comparison with control animals, confirming the protective function of this channel. It is conceivable that the primary pancreatic function of TRPV6 is the regulation of Ca2+ concentration in pancreatic fluid and that chronic pancreatitis develops as a result of the insufficiency of such regulation [101].

Recent focus in this subfield was on the Ca2+ signalling induced in ductal cells by the pathophysiologically relevant stimuli. Low/moderate concentrations of ethanol (0.3-30mM) induce Ca2+ signalling and upregulate secretin-induced secretion, this stimulatory effect was abrogated at high concentration (100mM) of ethanol [102]. Similar biphasic effects of ethanol on the transporters responsible for secretion was report by Hegyi and colleagues [103]. The bile acid chenodeoxycholate triggers Ca2+ responses in the ductal cells [104]. Notably a low dose of this bile acid (0.1mM) induced Ca2+ oscillations and stimulated HCO^-_3 secretion. The effect was specific for luminal but not basolateral administration of CDCA. Ca2+ responses were inhibited by xestospongin C and the phospholipase C inhibitor U73122 suggesting involvement of IP3Rs [104]. Notably a higher dose of CDCA(1mM) resulted in the peak-plateau type Ca2+ response and inhibition of secretion. The effect of the high dose was observed for both luminal and basolateral administration of CDCA [104]. In a recent study Katone and colleagues also reported a prolonged Ca^{2+} response to chenodeoxycholic acid (CDCA) [105]. In this case, however, the response was not inhibited by ursodeoxycholic acid, that has been shown to protect the duct cells from CDCA-induced damage and importantly reduce severity of CDCA-induced acute pancreatitis. The protective mechanism of ursodeoxycholic acid is therefore unlikely to be Ca2+-dependent [105]. The specific pathophysiological role of Ca2+ responses in this form of pancreatitis is therefore not clear. Peak-plateau type of Ca2+ responses in ductal cells were recently recorded in pancreatic slice preparations stimulated with CDCA [106]. Notably the responses

were accompanied by cellular movement. The authors discuss the possibility that the movement could be mediated by the activity of myoepithelial cells [106]. This technical development provides a useful avenue for further studies of Ca2+ signalling in undissociated tissue, with potential applications to understanding the interactions of multiple cell types in the exocrine pancreas.

Ca2+ signalling in pancreatic stellate cells

Substantial progress was recently attained in characterising Ca2+ signalling in pancreatic stellate cells. These cells are localised in the proximity of the acinar cells. The interest in this cell type was to a considerable extent driven by their remarkable transformation in pathological conditions of chronic pancreatitis and pancreatic cancer, and by the roles played by stellate cells in the pathophysiology of these diseases (reviewed in [107-109]). J. Won and colleagues from D. Yule group systematically characterised Ca2+ signalling in stellate cells and reported that in a quiescent state these cells respond to the application of the muscarinic agonist carbachol (CCh), angiotensin II, bradykinin and ATP [110]. The profile of Ca2+ -releasing agonists drastically changed in the activated stellate cells – they lost responsiveness to carbachol but acquired the ability to respond to PAR agonists thrombin and trypsin [110]. The latter is particularly relevant considering intrapancreatic trypsinogen activation (trypsin formation) in acute pancreatitis [57-59]. Elegant methodological elements of J. Won's study were imaging of Ca2+ responses in the stellate cells located in undissociated pancreatic acini [110] and pathophysiologicaly relevant procedures of stellate cell activation [110]. The findings of this study were confirmed and extended in recent publications by O. Gryshchenko and colleagues from O.H. Petersen group; they reported Ca2+ responses to low, physiologically/pathophysiologically relevant, concentrations of bradykinin and identified receptors responsible for these responses (B2 receptor)[111]. Ca2+ influx in the stellate cells was inhibited by GSK7975A indicating that it is likely to be mediated by STIM/Orai complex [111]. A later work from the same group reported prominent changes of Ca2+ signalling mechanisms following induction of acute pancreatitis – in particular, responsiveness of the cells to bradykinin was reduced and at the same time the cells acquired the ability to generate Ca2+ signals in response to trypsin [112]. Bile acids also trigger Ca2+ responses in the pancreatic stellate cells [113]. Recently, several TRPC channels have been characterised in the stellate cells including TRPC1 that plays a role as pressure sensor [114] and TRPC6 which is involved in response of this cell type to hypoxia [115]. Both channels contributed to Ca2+ responses, activation and migration of stellate cells [114, 115]. Ca2+ responses in stellate cells are likely to be relevant to the prominent functions of this cell type in chronic pancreatitis and pancreatic cancer.

Concluding remarks

The strong focus of this research field is on the pathophysiology of Ca2+ signalling mechanisms in pancreatic cells. This is understandable, considering frequent and severe diseases of exocrine pancreas. The importance of aberrant Ca2+ signalling and Ca2+ toxicity for these diseases has been recognised and several new mechanisms capable of inducing aberrant Ca2+ responses have been identified (and

discussed in this review). It is, however, notable that the physiological role of these mechanisms is frequently less clear. Hopefully, future investigations will identify the contribution of newly identified Ca2+ channels, transporters and sensors to subtle physiological modulation of fluid secretion, exocytotic secretion of zymogens/digestive enzymes and other functions of exocrine pancreas.

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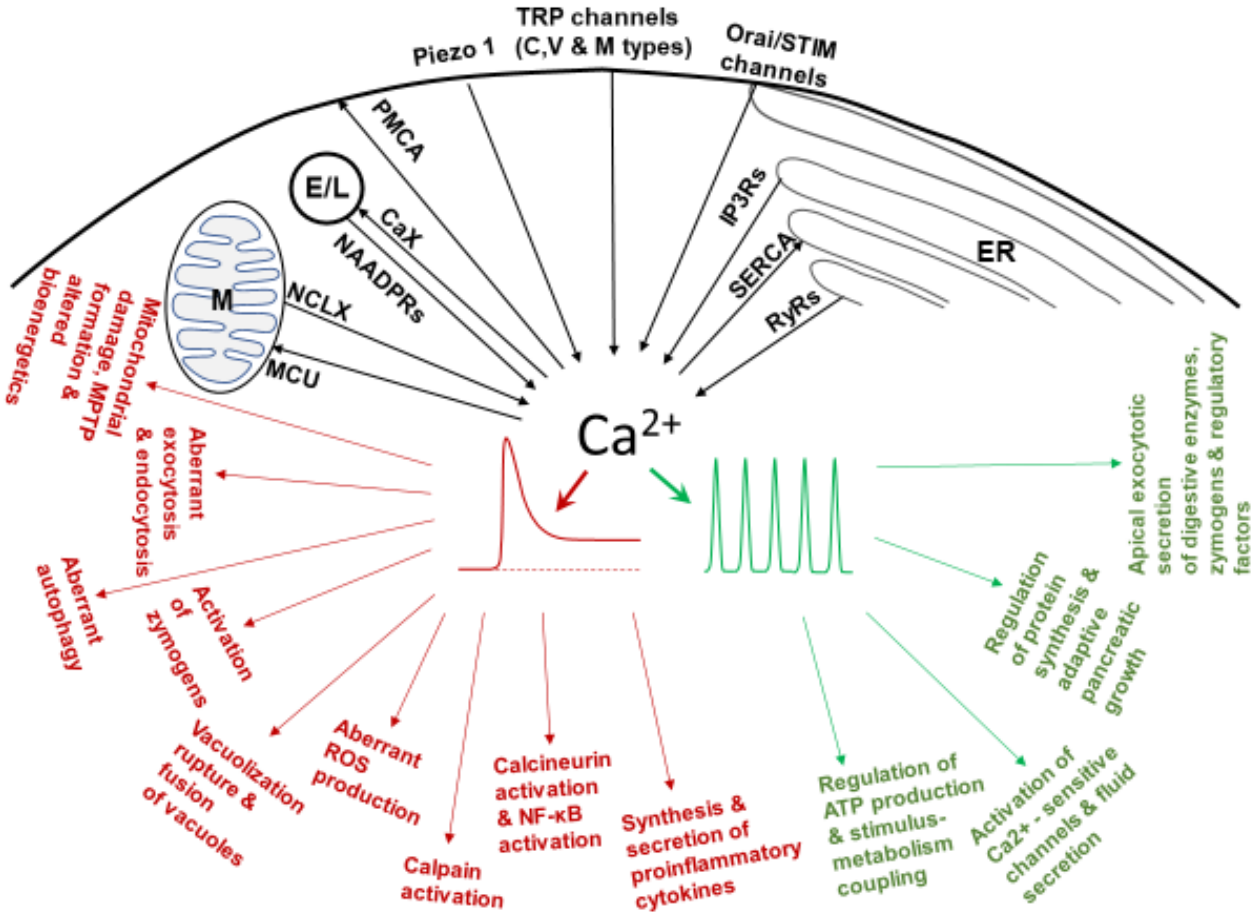

Figure 1. Simplified diagram of Ca2+ signalling mechanisms in pancreatic acinar cell and downstream consequences of normal and aberrant Ca2+ signalling. Green arrows indicate physiological functions. Red arrows indicate pathophysiological / damaging responses. Relationships between the downstream responses are complex and omitted in this figure. Abbreviations utilised in the figure: CAX, Ca2+/H+ exchanger; E/L, endosome/lysosome; ER, endoplasmic reticulum; IP3R, inositol trisphosphate receptor; M, mitochondrion; MCU, mitochondrial Ca2+ uniporter; MPTP, mitochondrial permeability transition pore; NAADPR, nicotinic acid adenine

dinucleotide phosphate receptor; NCLX, Na+/Ca2+/Li+ exchanger; PMCA, plasma membrane Ca2+ ATPase; ROS, reactive oxygen species; RyR, ryanodine receptors; SERCA, sarcoplasmic/endoplasmic reticulum Ca2+ ATPase; STIM, stromal interaction molecule; TRP channels, transient receptor potential channels; TRPC, canonical transient receptor potential channels; TRPM transient receptor potential melastatin channels; TRPV, transient receptor potential vanilloid channels.

Highlighted papers

Ahuja, M.; Schwartz, D.M.; Tandon, M.; Son, A.; Zeng, M.; Swaim, W.; Eckhaus, M.; Hoffman, V.; Cui, Y.; Xiao, B., et al. Orai1-Mediated Antimicrobial Secretion from Pancreatic Acini Shapes the Gut Microbiome and Regulates Gut Innate Immunity. Cell Metab 2017, 25, 635-646, doi:10.1016/j.cmet.2017.02.007.

This study describes a novel function of exocrine pancreas – maintenance/regulation of gut microbiota.

Wang, L.; Wagner, L.E., 2nd; Alzayady, K.J.; Yule, D.I. Region-specific proteolysis differentially modulates type 2 and type 3 inositol 1,4,5-trisphosphate receptor activity in models of acute pancreatitis. J Biol Chem 2018, 293, 13112-13124, doi:10.1074/jbc.RA118.003421.

The paper describes cleavage of IP3R2 and IP3R3 by trypsin and functional implication of such cleavage. This could be conceptually important for Ca2+ signalling during acute pancreatitis.

Romac, J.M.; Shahid, R.A.; Swain, S.M.; Vigna, S.R.; Liddle, R.A. Piezo1 is a mechanically activated ion channel and mediates pressure induced pancreatitis. Nat Commun 2018, 9, 1715, doi:10.1038/s41467-018-04194-9.

The study describes a novel mechanism that can contribute to Ca2+ toxicity, damage of pancreatic acinar cells and initiation of pressure-induced pancreatitis.

Liang, T.; Dolai, S.; Xie, L.; Winter, E.; Orabi, A.I.; Karimian, N.; Cosen-Binker, L.I.; Huang, Y.C.; Thorn, P.; Cattral, M.S., et al. Ex vivo human pancreatic slice preparations offer a valuable model for studying pancreatic exocrine biology. J Biol Chem 2017, 292, 5957-5969, doi:10.1074/jbc.M117.777433.

This elegant study reports an important methodological development (functional ex-vivo pancreatic slices) and a conceptually important finding (CCK-mediated Ca2+ signalling and exocytotic secretion in human pancreatic acinar cells).

Waldron, R.T.; Chen, Y.; Pham, H.; Go, A.; Su, H.Y.; Hu, C.; Wen, L.; Husain, S.Z.; Sugar, C.A.; Roos, J., et al. The Orai Ca(2+) channel inhibitor CM4620 targets both parenchymal and immune cells to reduce inflammation in experimental acute pancreatitis. J Physiol 2019, 597, 3085-3105, doi:10.1113/JP277856.

This paper describes two mechanisms underlying the effect of Orai inhibitor on the severity of experimental acute pancreatitis: inhibition of Ca2+ influx in the acinar cells and inhibition of responses of the immune cells. The study has considerable translational potential.

Fanczal, J.; Pallagi, P.; Gorog, M.; Diszhazi, G.; Almassy, J.; Madacsy, T.; Varga, A.; Csernay-Biro, P.; Katona, X.; Toth, E., et al. TRPM2-mediated extracellular Ca(2+) entry promotes acinar cell necrosis in biliary acute pancreatitis. J Physiol 2020, 598, 1253-1270, doi:10.1113/JP279047.

This recent paper describes interplay between ROS and Ca2+-signalling cascades with relevance to biliary acute pancreatitis.

Won, J.H.; Zhang, Y.; Ji, B.; Logsdon, C.D.; Yule, D.I. Phenotypic changes in mouse pancreatic stellate cell Ca2+ signaling events following activation in culture and in a disease model of pancreatitis. Mol Biol Cell 2011, 22, 421-436, doi:10.1091/mbc.E10-10-0807.

This study characterises hormones and neurotransmitters that trigger Ca2+ signalling events in quiescent and activated stellate cells. The study highlights remarkable changes in the receptors associated with Ca2+ responses that occurred during the activation process.

Gryshchenko, O.; Gerasimenko, J.V.; Gerasimenko, O.V.; Petersen, O.H. Ca(2+) signals mediated by bradykinin type 2 receptors in normal pancreatic stellate cells can be inhibited by specific Ca(2+) channel blockade. J Physiol 2016, 594, 281-293, doi:10.1113/JP271468.

This paper reports that physiologically relevant concentrations of bradykinin can trigger Ca2+ responses in stellate cells and specifies the receptor type responsible for the bradykinin – induced responses.

Wen, L.; Javed, T.A.; Yimlamai, D.; Mukherjee, A.; Xiao, X.; Husain, S.Z. Transient High Pressure in Pancreatic Ducts Promotes Inflammation and Alters Tight Junctions via Calcineurin Signaling in Mice. Gastroenterology 2018, 155, 1250-1263 e1255, doi:10.1053/j.gastro.2018.06.036.

This study characterised downstream processes linking aberrant Ca2+ signalling and a clinically relevant form of acute pancreatitis.

A. Masamune, H. Kotani, F.L. Sorgel, J.M. Chen, S. Hamada, R. Sakaguchi, E. Masson, E. Nakano, Y. Kakuta, T. Niihori, R. Funayama, M. Shirota, T. Hirano, T. Kawamoto, A. Hosokoshi, K. Kume, L. Unger, M. Ewers, H. Laumen, P. Bugert, M.X. Mori, V. Tsvilovskyy, P. Weissgerber, U. Kriebs, C. Fecher-Trost, M. Freichel, K.N. Diakopoulos, A. Berninger, M. Lesina, K. Ishii, T. Itoi, T. Ikeura, K. Okazaki, T. Kaune, J. Rosendahl, M. Nagasaki, Y. Uezono, H. Algul, K. Nakayama, Y. Matsubara, Y. Aoki, C. Ferec, Y. Mori, H. Witt, T. Shimosegawa, Variants That Affect Function of Calcium Channel TRPV6 Are Associated With Early-Onset Chronic Pancreatitis, Gastroenterology 158(6) (2020) 1626-1641 e8.

This is a conceptually important study reporting association between functionally-deficient mutations of Ca2+ selective TRPV6 channel and chronic pancreatitis in human patients. The study suggests that TRPV6 could play important role in the regulation of Ca2+ concentration in pancreatic fluid and that this role is associated with its protection against pancreatitis.

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