Cell Calcium 78 (2019) 48–55

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

# CRAC channels in secretory epithelial cell function and disease

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ARTICLE INFO

*Keywords:*
Secretory cells
Orai1
TRPC channels
$Ca^{2+}$ influx
Toxicity

ABSTRACT

The receptor-evoked $Ca^{2+}$ signal in secretory epithelia mediate many cellular functions essential for cell survival and their most fundamental functions of secretory granules exocytosis and fluid and electrolyte secretion. $Ca^{2+}$ influx is a key component of the receptor-evoked $Ca^{2+}$ signal in secretory cell and is mediated by both TRPC and the STIM1-activated Orai1 channels that mediates the $Ca^{2+}$ release-activated current (CRAC) $I_{crac}$. The core components of the receptor-evoked $Ca^{2+}$ signal are assembled at the ER/PM junctions where exchange of materials between the plasma membrane and internal organelles take place, including transfer of lipids and $Ca^{2+}$. The $Ca^{2+}$ signal generated at the confined space of the ER/PM junctions is necessary for activation of the $Ca^{2+}$-regulated proteins and ion channels that mediate exocytosis with high fidelity and tight control. In this review we discuss the general properties of $Ca^{2+}$ signaling, PI(4,5)$P_2$ and other lipids at the ER/PM junctions with regard to secretory cells function and disease caused by uncontrolled $Ca^{2+}$ influx.

## 1. Introduction

The change in the free cytoplasmic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) encodes information and controls virtually all functions of secretory epithelial cells, including the cardinal functions of secretory granules exocytosis, fluid and electrolyte secretion [1,2]. The tight regulation of $[Ca^{2+}]_i$ occurs in all cellular compartments, from across the plasma membrane (PM) to the cytoplasmic organelles, including endoplasmic reticulum (ER), mitochondria, lysosomes, endosomes, nucleus and secretory granules. The regulation of $[Ca^{2+}]_i$ is done by $Ca^{2+}$ pumps and $Ca^{2+}$ channels that form and dissipate $Ca^{2+}$ gradients on demands.

The $Ca^{2+}$ gradients across the PM and the ER are generated by the PM $Ca^{2+}$ ATPase (PMCA) pump [3] and the sarco-endoplasmic reticulum ATPase (SERCA) pump [4], respectively. The secretory pathway $Ca^{2+}$ ATPase pumps (SPCA) mainly pump $Ca^{2+}$ into the Golgi [5] while mitochondrial $Ca^{2+}$ uptake is mediated by the mitochondrial $Ca^{2+}$ uniporter complex [6–8]. How $Ca^{2+}$ accumulates in lysosomes, endosomes and secretory granules is not well understood, let alone the identity of the proteins mediating the $Ca^{2+}$ accumulation. Known $Ca^{2+}$ channels that regulate $[Ca^{2+}]_i$ include $IP_3$ receptors ($IP_3$Rs) and Ryanodine receptors (RyRs), which mediate the release of $Ca^{2+}$ from the ER [9,10], and store-operated Orai channels [11], the receptor-stimulated TRPC [12,13], and other TRP channels [13] which control $Ca^{2+}$ influx across the PM. In mitochondria, $Ca^{2+}$ is cleared by the mitochondrial $Na^+/Ca^{2+}$ exchanger NCLX (NCX-9) [14] and $Ca^{2+}$ release from lysosomes and endosomes is mediated by TRPML1 [15] and TRPML3 [16], respectively. Two additional channels involved in lysosomal and endosomal $Ca^{2+}$ release are the TPC channels, TPC1 (mainly endosomes) and TPC2 (mainly lysosomes) [17,18]. The TPC channels appears to be $Na^+$ selective and activated by PI(3,5)$P_2$ [19] and NAADP [18,20] to mediate the NAADP-triggered $Ca^{2+}$ release. $IP_3$Rs, Ryanodine receptors (RyRs), and the TPC channels have all been implicated in $Ca^{2+}$ release from secretory granules [21].

The receptor-evoked $Ca^{2+}$ signal makes use of all $Ca^{2+}$ transporting elements to generate specific $Ca^{2+}$ signals for various cellular functions. The signal starts by interaction of ligand with receptors to activate phospholipase C that hydrolyses PI(4,5)$P_2$ at the PM to release $IP_3$ and diacylglycerol (DAG). $IP_3$ binds to the $IP_3$ receptors, which are concentrated at the apical pole of secretory cells [22,23], to trigger $Ca^{2+}$ release at the apical region that initiates a propagated $Ca^{2+}$ wave to the basal pole along the lateral membrane [24,25]. Several receptors, like the cholecystokinin (CCK) receptor in pancreatic acinar cells, also generate NAADP to cause additional $Ca^{2+}$ release from endosome, lysosomes and likely secretory granules at the apical pole [26–28]. $Ca^{2+}$ release from the ER causes clustering of the ER $Ca^{2+}$ sensor STIM1 [29,30], which binds to PI(4,5)$P_2$ at the ER/PM junctions [29,31] where it activates the Orai1 [11,32] and TRPC channels [33] leading to $Ca^{2+}$ influx.

The increase in cytoplasmic $Ca^{2+}$ rapidly activates $Ca^{2+}$ clearance mechanisms to prevent $Ca^{2+}$ toxicity. The $Ca^{2+}$-mediated inhibition of

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https://doi.org/10.1016/j.ceca.2018.12.010
Received 7 November 2018; Received in revised form 28 December 2018; Accepted 29 December 2018

0143-4160/ Published by Elsevier Ltd.

the $IP_3$ receptors [34] and of the Orai [11,35] and TRPC channels [36] act to restrict $Ca^{2+}$ flow into the cytosol. In addition, cytoplasmic $Ca^{2+}$ is taken up by mitochondria to activate energy production and regulate other mitochondrial functions [37–39]. However, the bulk of the $Ca^{2+}$ is incorporated back into the ER by the SERCA pumps and part is extruded out of the cells by the PMCA pumps, including the $Ca^{2+}$ that leaves the mitochondria during the $Ca^{2+}$ spikes. The process of $Ca^{2+}$ release and clearance generate a $Ca^{2+}$ transient that is repeated during the period of cell stimulation, resulting in $Ca^{2+}$ oscillations. The amplitude, frequency and duration of the $Ca^{2+}$ oscillations determine the information of the $Ca^{2+}$ signal, and combinations of which can activate specific $Ca^{2+}$-dependent cellular processes.

A nodal point in sustaining the receptor-evoked $Ca^{2+}$ signal is $Ca^{2+}$ influx across the PM through the Orai channels. Orai1-mediated $Ca^{2+}$ influx provides the source of $Ca^{2+}$ to sustain $Ca^{2+}$ loads into the various stores and sustain the $Ca^{2+}$ signal during receptor stimulation. Moreover, aberrant $Ca^{2+}$ signal and $Ca^{2+}$ toxicity is almost invariably caused by excessive $Ca^{2+}$ influx by TRPC [40–43] and Orai1 channels [44–46], but mostly the latter. Therefore, in this short review we discuss $Ca^{2+}$ influx by Orai1 in secretory cells, and the role of Orai1-mediated $Ca^{2+}$ influx in several key cellular functions and toxicity in secretory cells.

## 2. Orai1 and $Ca^{2+}$ signaling at the ER/PM junctions

Secretory cell receptor-evoked $Ca^{2+}$ signal initiates at the apical pole and propagate to the basal pole. Propagation to the basal pole depends on polarized expression of $Ca^{2+}$ signaling proteins and organelles that store $Ca^{2+}$, such as secretory granules, lysosomes [47,48] and mitochondria [37,38]. The $Ca^{2+}$ signaling proteins at the apical pole include GPCRs [49,50], $IP_3Rs$ [22], SERCA [51] and PMCA4 [52] pumps, and the sensitivity of the apical pole to receptor stimulation [53] has been demonstrated. The polarized localization requires targeting and arrangement of the $Ca^{2+}$ signaling proteins into complexes at discreet cellular domain, the ER/PM junctions. How the junctions are formed and organized in exocrine cells or any cell in vivo is not known at this time. However, recent findings in model mammalian cells [12,54,55], that followed previous findings in yeast [56,57], identified several key components required for assembly of the ER/PM junctions.

Briefly, the studies of lipid transport between the ER and plasma membrane (PM) in yeast revealed the role of the tethers (the three tricalbins [57], Ist2 [58], non-vesicular lipid transporters [59] and VAPA/B [60]) as essential components of the ER/PM junctions [56]. The mammalian homologues of the tricalbins are the three Extended synaptotagmins (E-Syt1-3) [61] and the lipid transport proteins expressed at the ER/PM junctions are the Nir proteins [62,63], ORP5 and ORP8 [64] and the Aster proteins [65]. It is likely that other lipid transfer proteins bind to VAPA/B are also targeted to the ER/PM junctions which have yet to be defined. The tether proteins (E-Syt1-3) are required to maintain the ER/PM junctions [56] and control their size and likely location [55]. The role of the lipid transfer proteins in assembly of the ER/PM junctions has not been fully examined, but they may not be essential components of the junction since they appear to be transferred to the junction in response to changes in cellular lipids [59].

What is known about the localization and function of the lipid transfer proteins is illustrated in Fig. 1. The Nir proteins maintain and replenish the level of PM $PI(4,5)P_2$ [62,63]. They localize at the ER/PM junctions by interacting with the ER localized VAPA through two phenylalanines (FF) in an Acidic Tract (FFAT) motif [60]. At the junctions, the Nir proteins interact with lipids through their Phosphatidylinositol-Transfer Domain (PITD) that binds PI and their Lipin/Ndel/Smp2 (LNS2) domain that binds phosphatidic acid (PA) to mediate an exchange between ER PI and PM PA, thus supplying the ER with PA while maintaining PM PI for the synthesis of $PI(4,5)P_2$ [62]. The ORP5 and ORP8 proteins have an ER spanning single C-terminal transmembrane domain and N-terminal PH and polybasic domain that interacts with PM phosphatidylinositol 4-phosphate (PI4P) [64,66] and $PI(4,5)P_2$ [67]. Their ORD lipid transfer domain binds PM PI4P and $PI(4,5)P_2$ or ER phosphatidylserine (PS) to mediate PI4P/PS exchange, which is supported by the PI4P gradient that is maintained by its conversion to $PI(4,5)P_2$ in the PM and to PI in the ER. The Aster proteins have an ER localized N-terminal single transmembrane domain, a lipid transfer ASTER domain that binds cholesterol and a GRAM domain that interacts with PM PS and PA. The Aster proteins are recruited to the ER/PM junctions in response to increased PM cholesterol and transfer it to the ER. In addition, the Aster proteins interact with the E-Syts and ORP5/8 proteins at the junction [65].

The generation of $PI(4,5)P_2$-rich domain (and perhaps PS-rich domain) and of cholesterol at the ER/PM junctions by lipid transfer proteins has important implications for $Ca^{2+}$ influx and $Ca^{2+}$ signaling [54]. Cholesterol affects many cellular processes by altering membrane fluidity and has a direct effect on many proteins, including ion channels, where Orai1 and TRP channels are no exception [68,69]. Depletion of PM cholesterol impacts TRPC channel localization and thus activation by various stimuli [70]. Opposite effects have been reported for Orai1. Depletion of PM cholesterol resulted in internalization of Orai1 and inhibition of channel activity [71]. In addition, the SOAR domain of STIM1 [72] was reported to possess a cholesterol binding site and cholesterol binding to STIM1 restricts binding of the STIM1 SOAR domain to Orai1 [73]. On the other hand, a cholesterol binding domain was detected in Orai1 and depletion of PM cholesterol and mutation of the cholesterol sensing site in Orai1 increased Orai1 current and $Ca^{2+}$ influx [74]. Although some of the conflicting results may be explained by differential effects of cholesterol on the plasma membrane physical parameters and direct effects on Orai1 and STIM1, this topic needs significant further mechanistic clarification.

The importance of the plasma membrane $PI(4,5)P_2$ is demonstrated by the additional roles it plays in receptor-evoked $Ca^{2+}$ signaling besides providing $IP_3$ to initiate the $Ca^{2+}$ signal. $PI(4,5)P_2$ is a substrate for lipid transfer proteins like ORP5 and ORP8 [67] which control PM lipid composition. $PI(4,5)P_2$ interacts with and directly regulates the function of many channels, including several $K^+$, $Cl^-$ and voltage-gated $Ca^{2+}$ channels, thereby affecting cytosolic ionic composition and the plasma membrane potential [54,75]. $PI(4,5)P_2$ is a prominent PM site for interaction of proteins with Pleckstrin Homology (PH) domains, polybasic domains and other $PI(4,5)P_2$ interacting sites. One of the C2 domains of the E-Syts tethers [61], the PH domain of ORP5 and ORP8 [64,66] and the polybasic domains of Ist2 [58] and the ORP5 and ORP8 [66] anchor the proteins to the PM by binding to $PI(4,5)P_2$.

The polybasic domains are essential for targeting of STIM1 [29,76] and STIM2 [77] to the ER/PM junctions and for stabilization of the puncta. Moreover, presence of the STIM1-Orai1 complex at $PI(4,5)P_2$-poor and $PI(4,5)P_2$-rich domain determines channel function [31]. Orai1 undergoes two forms of $Ca^{2+}$-dependent inactivation, a fast inactivation with a time constant of 10 msec and slow inactivation that is completed in 1–2 min [11,35]. The two forms of inactivation are mediated by a STIM1 sequence [78–80] within the STIM1 CTID domain [20] that guides the SARAF protein [81] to the STIM1 SOAR domain [20]. Interaction of SARAF with STIM1 is dependent on the STIM1-Orai1 complex being in a $PI(4,5)P_2$-rich domain [31]. Depletion of ER $Ca^{2+}$ results in the clustered STIM1 and its interaction with Orai1. In a $PI(4,5)P_2$-poor domain where SARAF does not interact with STIM1, the $Ca^{2+}$ influx through the STIM1-Orai1 complex is maximally active. Subsequently, the STIM1-Orai1 complex translocates to a $PI(4,5)P_2$-rich domain (or $PI(4,5)P_2$ translocates to the STIM1-Orai1 complex) where SARAF interacts with STIM1 to initiate $Ca^{2+}$-dependent inactivation that limits $Ca^{2+}$ influx and protect against $Ca^{2+}$-dependent toxicity [31]. The roll of the $PI(4,5)P_2$ domains in $Ca^{2+}$ influx is illustrated in Fig. 2.

Another protein that regulates STIM1 function is STIMATE [82] that is encoded by TMEM110 [83]. STIMATE is an ER protein that markedly facilitates STIM1 clustering and puncta formation at the ER/PM

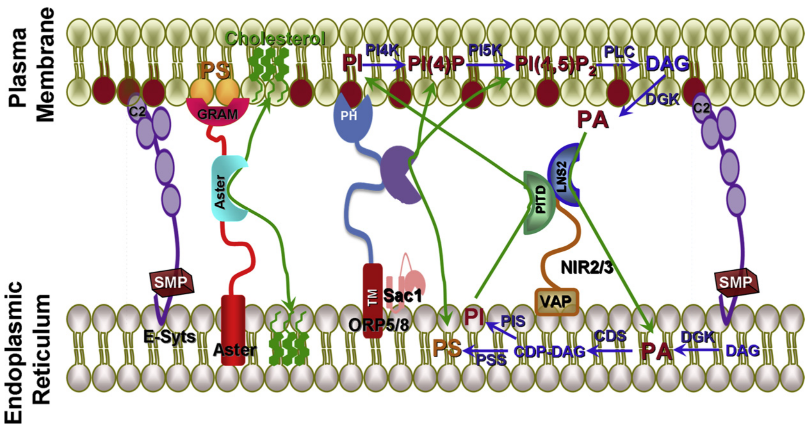

**Fig. 1.** Lipid transfer at the ER/PM junctions.
$PI(4,5)P_2$ is synthesized at the PM by phosphorylation of phosphatidylinositol phosphate (PI) to PI(4)P by PI4 kinase (PI4K) and PI(4)P is phosphorylated to $PI(4,5)P_2$ by PI5K. In response to cell stimulation $PI(4,5)P_2$ is hydrolyzed to diacylglycerol (DAG) and $IP_3$ by phospholipase C (PLC). DAG is converted to phosphatidic acid (PA) by diacylglycerol kinase (DGK). PA is the precursor for PI and phosphatidylserine (PS) in the ER. The ER/PM are tethered by several proteins such as the extended synaptotagmins (E-Syts). Lipid transfer proteins such as ORP5/8, Nir2/3 and Asters A–C and STIM1 contribute to ER/PM tethering once recruited to the junctions. The tether proteins are anchored in the ER by a transmembrane domains and often interact with plasma membrane PI $(4,5)P_2$ and/or PS. Some tethers, like Nir2/3 are anchored to the ER by interaction with VAMP associated protein B (VAP-B) and some like the E-Syts have a hairpin ER interacting domain. Extensive phospholipid transfer takes place between the PM and ER, only part of it is understood at present. ORP5/8 mediate PI(4) P/PS or $PI(4,5)P_2$/PS exchange between the ER/PM, Nir2 mediates PA/PI exchange between the ER/PM and the Aster proteins transfer cholesterol from the PM to the ER.

junctions, by stabilizing the open conformation of STIM1. Whether STIMATE interacts with STIM1 at $PI(4,5)P_2$-poor or $PI(4,5)P_2$-rich domain is not knows at present. However, STIMATE has a polybasic domain [82], which may interacts with acidic lipids, including $PI(4,5)P_2$ and thus aid in translocation of the STIM1-Orai1 complex to the PI(4,5) $P_2$-rich domain. Facilitation of STIM1 clustering by STIMATE to increase $Ca^{2+}$ influx add another level of regulation of the influx and thus excessive $Ca^{2+}$ influx may also result from excessive activation of STIM1 by STIMATE. Additional information is needed on the mechanism by which STIMATE activates STIM1 to better understand a potential role of STIMATE in $Ca^{2+}$ influx pathology

## 3. Orai1 and $Ca^{2+}$ influx in secretory gland functions

$Ca^{2+}$ influx plays a critical role in secretory cell functions. The cardinal functions of secretory gland cells are exocytotic secretion of macromolecules, such as digestive enzymes and mucins, and fluid secretion with defined ionic composition [1]. Both functions are primarily activated by changes in cytoplasmic $Ca^{2+}$ ($[Ca^{2+}]_i$), but $[Ca^{2+}]_i$ synergizes with cAMP to mediates the physiological response ([2,84] and see below]). As shown in Fig. 3, both TRPC channels and Orai1 contribute to receptor- and store-dependent $Ca^{2+}$ influx and physiological $Ca^{2+}$ oscillations [33,85–88]. However, Orai1-mediated influx is essential for all forms of $Ca^{2+}$ influx, likely because it regulates the TRPC channels dependent function and $Ca^{2+}$ influx [89,90].

Exocytosis by secretory gland cells occurs in two phases, a fast phase that is completed within one minute of receptor stimulation and a slow phase that continues for the length of the stimulation period and lasts for many tens of minutes [1,91]. The first phase depends on $Ca^{2+}$ release from internal stores next to the apical pole, consisting of the ready-release granules, while the second phase strictly depends on $Ca^{2+}$ influx [92]. $Ca^{2+}$ influx by Orai1 is essential for the exocytotic secretion function. Exocytosis by lacrimal glands of Orai1 knockout mice is markedly reduced [93] and targeted deletion of Orai1 in pancreatic acini reduced exocytosis of secretory granules, particularly the sustained phase of exocytosis [87]. Several $Ca^{2+}$-regulated and $Ca^{2+}$ binding proteins translate the $Ca^{2+}$ signal to an exocytotic response [94]. The best understood $Ca^{2+}$ binding proteins are the synaptotagmins (Syts), which are found in neuronal and nonneuronal tissues [95]. They sense $Ca^{2+}$ by C2A and C2B domains located in the cytoplasmic C-terminus [96] and several Syts have been identified in various acinar cells [52]. Other $Ca^{2+}$ binding proteins are the exocytosis tethers Munc13/CAPS, which have C2 and PH domains that bind $Ca^{2+}$ and $PI(4,5)P_2$ [97]. In addition there are the Synaptotagmin-like proteins (SLPs) which contain two C2 domains [98] and interact with Syntaxin 2 to control exocytosis in exocrine cells [99]. The specific role

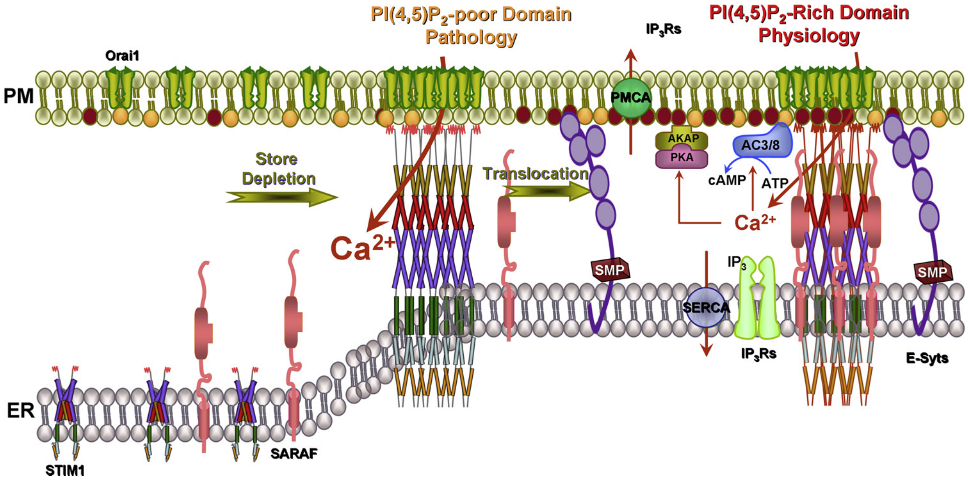

**Fig. 2.** $Ca^{2+}$ signaling and $Ca^{2+}$ influx at the ER/PM junctions.
At the resting state the plasma membrane (PM) and endoplasmic reticulum (ER) components of the receptor-evoked $Ca^{2+}$ signal are not in close contacts and several of them, in particular Orai1, STIM1, and $IP_3$ receptors and the $Ca^{2+}$ pumps are outside the ER/PM junctions. Upon cell stimulation and ER $Ca^{2+}$ release from the ER STIM1 clusters and interact with Orai1 in a $PI(4,5)P_2$-poor domain at which SARAF cannot interact with STIM1 and $Ca^{2+}$ influx is maximally active. Shortly thereafter, within few seconds, the STIM1-Orai1 complex translocates to a $PI(4,5)P_2$-rich ER/PM junctions to where all components of the $Ca^{2+}$ signal clusters, including PMCA in the PM and SERCA and $IP_3Rs$ in the ER. At the junctions STIM1 polybasic domain interacts with PI(4,5) $P_2$ to stabilize the junctions and SARAF interacts with STIM1 to initiate the facilitate the fast and initiate the slow $Ca^{2+}$-dependent Orai1 inactivation and reduce $Ca^{2+}$ influx to a minimum necessary to sustain the physiological $Ca^{2+}$ oscillations. Retention of the STIM1-Orai1 complex at the $PI(4,5)P_2$-poor domain or excess hydrolysis of $PI(4,5)P_2$ by intense receptor stimulation, results in sustained and maximal activation of $Ca^{2+}$ influx and cell pathology.

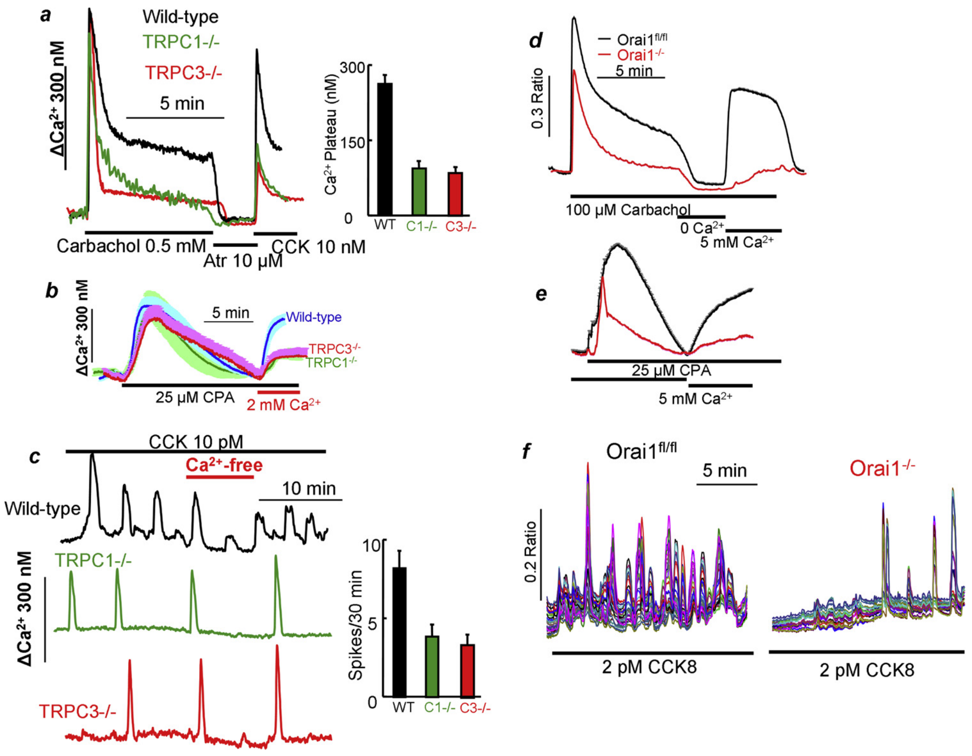

**Fig. 3.** TRPC channels and Orai1 participates in store-operated $Ca^{2+}$ influx in pancreatic acinar cells.

$Ca^{2+}$ was measured in freshly isolated pancreatic acini prepared from wild-type mice (black in a, c–e, blue in b) or TRPC1$^{-/-}$ mice (greed in a–c), TRPC3$^{-/-}$ mice (red in a–c) or Orai1$^{-/-}$ acini (red in d, c). The cells were stimulated with 100 μM carbachol (a, d) or treated with 25 μM CPA (b, e) to depleted ER stored $Ca^{2+}$ and then exposed to $Ca^{2+}$-free solution and solution containing 2 or 5 mM $Ca^{2+}$ to assay store-dependent $Ca^{2+}$ influx. Note that deletion of either TRPC1 or TRPC3, which interacts to mediate the same $Ca^{2+}$ influx pathway, reduced influx by about 50%. Deletion of Orai1 in acinar cells almost completely inhibited the influx. The effect of knockout of TRPC1, TRPC3 and Orai1 o the physiological $Ca^{2+}$ oscillations are shown in (c) and (f), respectively. The results with TRPC channels (a–c) were taken from reference [40] and with Orai1 (d–f) were taken from reference [87].

of $Ca^{2+}$ influx by Orai1 in relation to the function of these proteins remains to be established.

Fluid and electrolyte secretion is a fundamental function of all epithelia and in secretory glands it occurs in two stages. The serous cells secrete plasma-like fluid that flows to a ductal or ductal-like system that determines the final volume and ionic composition of the secreted fluid [1]. Fluid and electrolyte secretion are regulated by synergy between the $Ca^{2+}$ and cAMP/PKA signaling pathways [2]. Many of the ion transporters mediating epithelial fluid and electrolyte secretion are activated by the scaffolding protein IRBIT ($IP_3$ receptors binding protein released with $IP_3$) [100,101]. In the resting state IRBIT is associated with the $IP_3$ receptors. Upon cell stimulation with $Ca^{2+}$ and cAMP mobilizing agonists, the $IP_3Rs$ are phosphorylated by PKA, which increases their affinity for $IP_3$ and reduces their affinity for IRBIT [84]. A small physiological increase in $IP_3$ triggers $Ca^{2+}$ oscillations and at the same time releases IRBIT from the $IP_3Rs$. IRBIT will then interact with and activate ion transporters to promote fluid and electrolyte secretion [84].

In addition to activation by IRBIT, ion channels mediating fluid and electrolyte secretion are directly activated by $[Ca^{2+}]_i$. The key transporters involved in acinar cell fluid and electrolyte secretion are the volume-sensitive basolateral membrane $Na^+/K^+/2Cl^-$ cotransporters NKCC1 and the $Ca^{2+}$-activated $K^+$ channel Kcnma1 and the luminal membrane $Ca^{2+}$-activated $Cl^-$ channel ANO1 and the $Ca^{2+}$-activated $K^+$ channel Kcnn4 [1,102,103] (illustrated in Fig. 4). The receptor stimulated increase in $[Ca^{2+}]_i$ activates the $Ca^{2+}$-activated $K^+$ and $Cl^-$ channels to evoke $K^+$ efflux across the basolateral membrane and $Cl^-$ efflux across the luminal membrane and the obligatory water flow through the luminal aquaporin water channels [1,102]. This results in cell shrinkage that participates in termination of the $Ca^{2+}$ spiking due to inhibition of $Ca^{2+}$ influx channels [104] and perhaps $Ca^{2+}$ release [105]. Cell shrinkage, in turn, activates NKCC1 to replenish the released KCl and restore cell volume [106]. Electroneutrality is maintained by $Na^+$ flow through the tight junctions (Fig. 4).

The fundamental importance of $Ca^{2+}$ influx by Orai1 in epithelial fluid and electrolyte secretion is evident from the anhidrosis observed in patients with non-functional mutations in Orai1 and STIM1 [107,108]. In addition, deletion of Orai1 in mice impaired lacrimal glands tear secretion [93] and lactation [109] and targeted deletion of Orai1 and STIM1 and STIM2 in sweat glands resulted in anhidrosis in mice [107]. The critical role of Orai1 mediated $Ca^{2+}$ influx in many fluid and electrolyte secretory epithelia is due to the direct and specific activation of ANO1 and likely $K^+$ channels by the Orai1 mediated $Ca^{2+}$ influx. The importance of $Ca^{2+}$ influx for sustained activation of the $Ca^{2+}$-activated $Cl^-$ current in epithelia was established long before the identification of Orai1 and ANO1 [110]. However, the relationship between them was well documented in sweat glands, in which activation of Orai1 by receptor-stimulated or passive store depletion resulted in sustained activation of ANO1. By contrast, in the absence of Orai1, activation of ANO1 was transient and lasted only until the $Ca^{2+}$ stored in the ER was exhausted [107]. It is likely that Orai1 and ANO1 are present at the same ER/PM junctions at the luminal membrane, because activation of ANO1 is mediated by $Ca^{2+}$ in the same microdomain [111]. In addition, SOC-mediated $Ca^{2+}$ influx activates the native and expressed KCa3.1 in HEK cells [112]. Moreover, in mast cells the non-functional Orai1 mutants that inhibited $Ca^{2+}$ influx also inhibited activation of KCa3.1 [113].

It is important to note that in cells where TRPC channels participate or influence store-dependent $Ca^{2+}$ influx, $Ca^{2+}$ influx through TRPC channels is essential for fluid secretion and activation of the channels. For example, deletion of TRPC1 in mice reduced store-dependent $Ca^{2+}$ influx and salivation in response to muscarinic stimulation, which was attributed to inhibition of the $Ca^{2+}$-activated $K^+$ channel in salivary glands acinar cells [88]. A recent study examined the role of $Ca^{2+}$ influx in the activation of endogenous ANO1 in salivary gland cells and reported that $Ca^{2+}$ influx by TRPC1 increased plasma membrane expression of ANO1 and was required for activation of ANO1 [114]. In smooth muscle cells, ANO1 colocalized and immunoprecipitated with TRPC6 and $Ca^{2+}$ influx by TRPC6 specifically activated ANO1 [115]. A potential explanation for activation of ANO1 by $Ca^{2+}$ influx from both Orai1 and TRPC channels can be due to cell specific coupling of ANO1 to the two types of $Ca^{2+}$ influx channels. Another alternative is an interdependence of $Ca^{2+}$ influx by the two channels. TRPC1 was suggested to regulate the level of plasma membrane Orai1 [116], and the

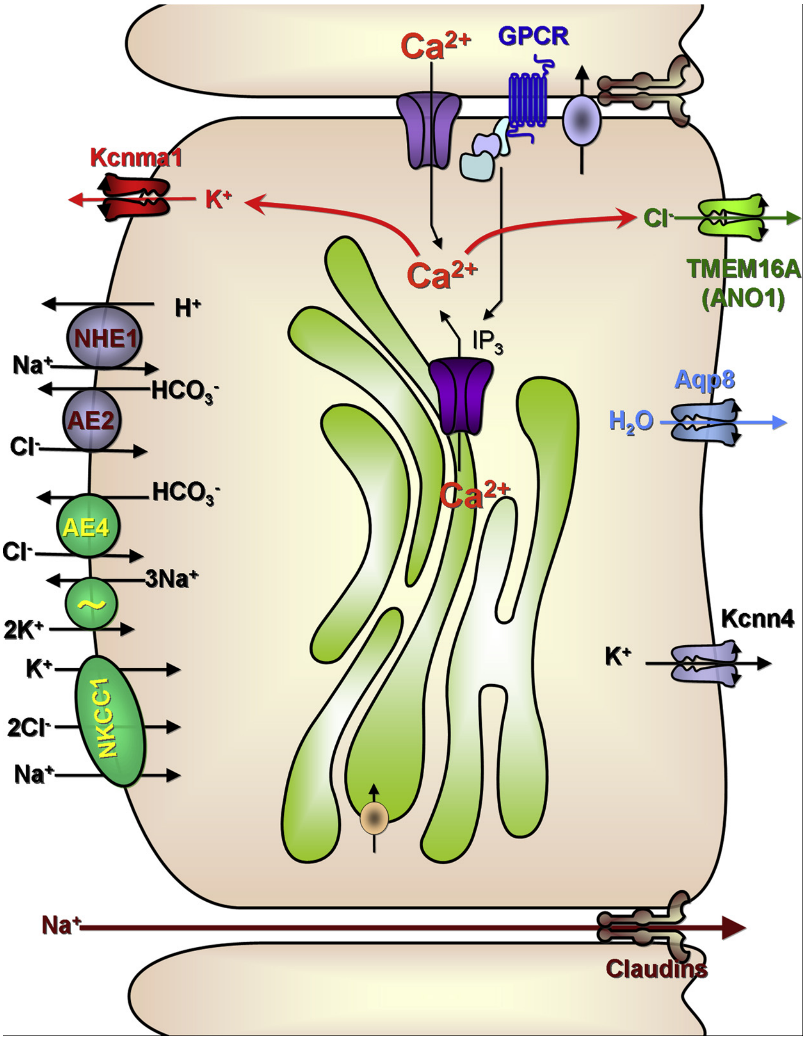

**Fig. 4.** Mechanism of fluid and electrolyte secretion by secretory glands acinar cells.
The key transporters mediating acinar cells fluid and electrolyte secretion are the basolateral $Na^+/K^+/2Cl^-$ cotransporters NKCC1 and the $Ca^{2+}$-activated $K^+$ Kcnma1 and the luminal $Ca^{2+}$-activated $Cl^-$ channel ANO1 and the water channel Aqp5. The basolateral membrane $Na^+/H^+$ exchanger NHE1 and $Cl^-/HCO_3{}^-$ exchanger AE2 control $pH_{in}$ and cell volume and the $Cl^-/HCO_3{}^-$ exchange AE4 participates in $Cl^-$ secretion. Cell stimulation that increases $[Ca^{2+}]_i$ results in activation of Kcnma1 and ANO1 and $K^+$-$Cl^-$ efflux, the obligatory water efflux through Aqp5 and cell shrinkage to halt the $Ca^{2+}$ oscillations. Cell shrinkage phosphorylates and activates NKCC1 that restores cell $K^+$ and $Cl^-$ and cell volume to allow the next $Ca^{2+}$ spike a fluid and electrolyte secretory event.

channel function of Orai1 and TRPC channels was required for physiological-receptor-mediated $Ca^{2+}$ influx [89]. Further studies on the relationships between Orai1, STIM1, TRPC channels and ANO1 and $K^+$ channel, in particular within specialized microdomain of the ER/PM junctions, are required to better understand these important regulatory functions that are critical for epithelial fluid and electrolyte secretion.

## 4. $Ca^{2+}$ influx in secretory glands pathology

It is well established that both, reduced and excessive $Ca^{2+}$ influx are associated with cell dysfunction and pathology in various cell types, including secretory glands [12,45,108,117,118]. As mentioned above, non-functional mutations in Orai1 and STIM1 in humans and their deletion in mice resulted in anhidrosis [108]. In addition, targeted deletion of Orai1 in pancreatic acinar cells of adult mice revealed a critical role in the pancreas with the control of the gut microbiome [87]. Deletion of Orai1 in pancreatic acinar cells inhibited receptor-stimulated $Ca^{2+}$ influx and secretion of antimicrobials by acinar cells to the jejunum. This resulted in dysbiosis, damaged intestinal barrier, sepsis and death, despite the full activation of the intestinal innate response [87]. In this respect, germline deletion of Orai1 resulted in lacrimal glands inflammation [93]. These findings argue for an important function of acinar cells in epithelial innate response that depends on $Ca^{2+}$ influx mediated by Orai1. These findings may have important clinical implications because acute and chronic pancreatitis influence the human gut microbiome [119,120].

Excessive activity of Orai1 and TRPC channels is the initiator of $Ca^{2+}$ overload and cell toxicity [40,46,85,86,121,122]. Excessive $Ca^{2+}$ influx results in accumulation of $Ca^{2+}$ in the mitochondria of salivary gland cells [123], enterocytes [124], hepatocytes [125] and pancreatic acinar [46] and stellate cells [126]. The $Ca^{2+}$ overload causes excessive mitochondrial ROS generation, cell damage and cell death [127–129]. Chronic excessive ROS has several deleterious effects. ROS activates TRPC [130,131] and TRPM2 channels [132], modulates STIM1-Orai1 interaction and function [133] and is a potent inhibitor of PMCA pumps in epithelial cells [134,135]. This results in a feedforward effect that further increases $Ca^{2+}$ influx and cell toxicity. This scenario has been worked out in great details in the pancreas in relation to acute pancreatitis [136]. The two types of $Ca^{2+}$ influx channels shown to mediate the excessive pathological $Ca^{2+}$ were the TRPC [40,85] and Orai1 channels [86,87,121].

There is no effective treatment to either chronic or acute pancreatitis. The importance of $Ca^{2+}$ influx channels in the pathology of pancreatitis suggested $Ca^{2+}$ influx channels as potential targets for treatment. Several studies attempted to evaluate this option. The first was genetic [40] and pharmacological inhibition of TRPC3 [85], which reduced receptor stimulated and store-operated $Ca^{2+}$ influx by about 50%. Inhibition of TRPC channel $Ca^{2+}$ influx was quite effective in reducing the pathology of acute pancreatitis, but only when the channels were inhibited prior to induction of pancreatitis, while inhibition of the channels after induction of acute pancreatitis was not effective in reducing disease symptoms [85]. Greater success was observed by inhibition of Orai1 [121], in which inhibition of Orai1 prior to induction of acute pancreatitis prevented the disease, and ameliorated the symptoms of the disease when applied after induction of the pancreatitis in several mouse models [121].

As promising is the use of Orai1 inhibitors to treat Ca$^{2+}$ overload in epithelia and inflammatory diseases in other tissues [45,118], it is important to note the plethora of crucial roles of Orai1 in cellular and tissue physiology and their intricate regulation by Ca$^{2+}$. A significant change in the Ca$^{2+}$ signal due to inhibition of Orai1 can be as toxic as excessive Ca$^{2+}$ influx. Good examples are the many aberrant functions of the immune system caused by deletion of Orai1 and the STIM proteins [118] and the dysbiosis caused by deletion of pancreatic acinar cells Orai1 [87]. Perhaps a better approach will be to use a combination of partial inhibitors of TRPC and Orai1 channels that may prevent undesired effects due to prominent inhibition of the channels. Another option might be modulation of proteins that regulate the Ca$^{2+}$ influx channels. One such protein is SARAF [31,81], an inhibitor of Ca$^{2+}$ influx channel and the other is STIMATE [82], which controls STIM1 clustering. Increasing SARAF activity and reducing STIMATE activity can be an alternative, perhaps safer approach to reducing pathological Ca$^{2+}$ influx and its associated toxicity.

## Acknowledgments

We thank Dr. Beth McNally for careful reading of the manuscript and suggestions. The authors are supported by intramural NIH grant DE000735-7.

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