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Too much of a good thing: the case of SOCE in cellular apoptosis

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Abstract

Intracellular calcium (Ca^{2+}) is an essential second messenger in eukaryotic cells regulating numerous cellular functions such as contraction, secretion, immunity, growth, and metabolism. Ca^{2+} signaling is also a key signal transducer in the intrinsic apoptosis pathway. The store-operated Ca^{2+} entry pathway (SOCE) is ubiquitously expressed in eukaryotic cells, and is the primary Ca^{2+} influx pathway in non-excitable cells. SOCE is mediated by the endoplasmic reticulum Ca^{2+} sensing STIM proteins, and the plasma membrane Ca^{2+}-selective Orai channels. A growing number of studies have implicated SOCE in regulating cell death primarily *via* the intrinsic apoptotic pathway in a variety of tissues and in response to physiological stressors such as traumatic brain injury, ischemia reperfusion injury, sepsis, and alcohol toxicity. Notably, the literature points to excessive cytosolic Ca^{2+} influx through SOCE in vulnerable cells as a key factor tipping the balance towards cellular apoptosis. While the literature primarily addresses the functions of STIM1 and Orai1, STIM2, Orai2 and Orai3 are also emerging as potential regulators of cell death. Here, we review the functions of STIM and Orai proteins in regulating cell death and the implications of this regulation to human pathologies.

Graphical Abstract

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Sample CRediT author statement

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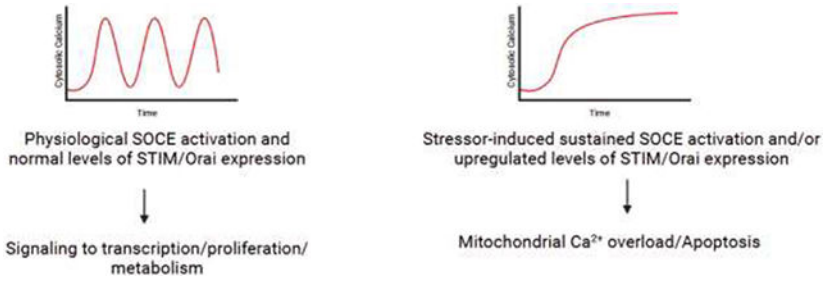
Conflict of Interest

Mohamed Trebak is a paid consultant for Seeker Biologicals Inc. J. Cory Benson has no potential conflict of interest to declare.



Introduction

Intracellular calcium (Ca^{2+}) is a ubiquitous and essential regulator of eukaryotic cell function. As a second messenger employed in a myriad of signaling pathways, intracellular Ca^{2+} regulates diverse functions such as metabolism, transcription, immune function, contraction, proliferation, and apoptosis[1-5]. In order to perform this broad array of functions, intracellular Ca^{2+} homeostasis is tightly controlled spatiotemporally by a variety of ion channels, exchangers, and pumps in the plasma membrane (PM) and subcellular organelles including mitochondria, endolysosomes and the endoplasmic reticulum (ER)[6, 7]. This intricate and tightly regulated network of Ca^{2+} transport ensures checks and balances necessary to maintain a low resting concentration of cytosolic Ca^{2+} (~100 nM) relative to the extracellular matrix (~1-2 mM). As such, this regulation enables Ca^{2+} ions to perform signal transduction while preventing toxic Ca^{2+} overload[1, 6, 8]. Typically, the ER comprises the largest store of intracellular Ca^{2+} in eukaryotic cells (100 μM − 1 mM)[9]. Store-operated calcium entry (SOCE), which is activated by ER Ca^{2+} depletion, is the primary mechanism of regulated Ca^{2+} influx in non-excitable cells[6, 10-12]. SOCE is driven by the intricate interactions of ubiquitously expressed proteins: the two ER membrane-localized Ca^{2+} sensing stromal interaction molecules (STIM1 and STIM2) and the three PM localized Ca^{2+}-selective Orai channel proteins (Orai1, Orai2, and Orai3) [4, 5, 12-14].

In non-excitable cells, ER store depletion is typically initiated by the activation of PM receptors coupled to phosphoinositide-specific phospholipase C (PLC) isoforms which rapidly convert phosphatidylinositol-4,5bisphosphate (PIP_2) into soluble inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG)[15, 16]. The newly mobilized IP_3 subsequently triggers the release of ER Ca^{2+} *via* IP_3 receptors (IP_3RS), resulting in the depletion of the ER Ca^{2+} stores[17-19]. The falling Ca^{2+} levels in the ER lumen activate the Ca^{2+} sensing STIM proteins, causing them to form discrete multimers referred to as puncta at the ER-PM junction and resulting in a conformational change that exposes their C-terminal STIM Orai-activating region/CRAC-activating domain (SOAR/CAD), which physically traps and activates PM Orai channels[1, 5, 12, 13]. Of the SOCE-mediating components, STIM1 and Orai1 have garnered the most dedicated studies, due in large part to their prominent contribution to SOCE and the identification of patients with loss of function (LoF) mutations in the *Orai1* and *STIM1* genes. LoF mutations in *Orai1* and *STIM1* genes result in severe combined immunodeficiency, autoimmunity, ectodermal dysplasia, defective dental enamel development, and myopathies[20-25]. Furthermore, while both STIM1 and

STIM2 are expressed ubiquitously, STIM1 expression is higher in most tissues compared to STIM2, making its influence more readily discernible[26, 27]. Despite the predominance of STIM1, STIM2 has been documented as a major contributor to SOCE in a variety of tissue types, including neurons, dendrites, NUT 3T3 fibroblasts, and colorectal carcinoma cells[28-31]. Notably, STIM1 requires significant depletion of the ER store to activate and is generally considered the major activator of SOCE during agonist stimulation. STIM2, which is activated with low to moderate levels of store depletion was initially thought to play a homeostatic cellular function by maintaining resting levels of ER Ca^{2+}. However, emerging evidence supports a prominent function of STIM2 in physiological Ca^{2+} signaling to transcription (beyond store refilling) when low physiologically relevant concentrations of agonists cause modest ER Ca^{2+} store depletion [32, 33]. Further, STIM2 contributes to SOCE through enhanced recruitment of STIM1 to the ER-PM junction[32, 34-36]. Similar to the predominance of STIM1 in the literature, Orai1 is the best characterized of the three Orai homologs, and is noted to have a major contribution to SOCE in many tissues[24, 37-49]. By contrast, the functions of the remaining Orai homologs are less well characterized, due in large part to a lack of selective pharmacological agents and antibodies that target them[6]. Despite this, there are an increasing number of studies that have begun to shed light on the function of these homologs. Knockout of Orai2 and Orai3, both independently and in combination, reveal that SOCE is enhanced by their absence, suggesting that Orai2 and/or Orai3 form heteromultimeric channels with Orai1 and act as negative regulators under native conditions[50-53]. Orai3 has been shown to synergize with Orai1 in mediating SOCE, transcriptional activity and metabolic reprogramming in B cells during activation[54]. Additionally, Orai3 has been shown, in conjunction with Orai1, to form the store-independent arachidonic acid-regulated Ca^{2+} (ARC) influx pathway activated by either arachidonic acid or its metabolite, leukotriene C_4 [55-62].

Cellular Ca^{2+} homeostasis must strike a delicate balance to enable a diverse array of signaling outcomes and influence cell fate decisions. In most instances of physiological stimulation, cells respond to low concentrations of receptor agonists originating from surrounding tissue or circulation[63]. These low levels of stimulation give rise to transient and regenerative spikes of cytosolic Ca^{2+} known as oscillations[15, 64-66]. Typically, Ca^{2+} oscillations in most cells are initially driven by the release of Ca^{2+} by IP_3RS, but beyond the first few spikes, they are sustained by SOCE[67, 68]. The frequency of Ca^{2+} oscillations increase with the concentration of agonist until sufficiently high levels of stimulation induce a plateau of high intracellular Ca^{2+} levels[69-72]. Notably, the frequency of cytosolic Ca^{2+} oscillations has been tied to distinct physiological responses in cases such as regulating distinct gene expression in T-lymphocytes or the regulation of calmodulin kinase II activity[73-75]. However, while it is tempting to broadly tie the frequency of cytosolic Ca^{2+} oscillations with distinct physiological responses, it is important to note that oscillation frequency can vary stochastically in response to the same stimulus, and that in many cases the frequency of cytosolic Ca^{2+} oscillations is not directly proportional to the extent of the physiological response[16]. Despite this, it can be broadly stated that the most frequent outcomes induced by transient Ca^{2+} oscillations favor cell survival and proliferation[76-78]. Indeed, oscillatory rises in cytosolic Ca^{2+} levels sustained by SOCE have been known to promote survival by stimulating the calcineurin-dependent activation of nuclear factor

of activated T-cells (NFAT) and NF-κB, transcription factors that regulates numerous cell survival genes[79-81] (Fig. 1A). Similarly, transient Ca^{2+} signals have long been known to activate the Akt pathway to promote survival and regulate metabolism[82-88]. By contrast, however, sustained increases of cytosolic Ca^{2+} over long periods of time initiate apoptosis by increasing Ca^{2+}concentrations at the ER-mitochondrial junctions resulting in mitochondrial Ca^{2+} overload and opening the mitochondrial permeability transition pore (MPTP) [76, 89-91] (Fig. 1B).

Apoptosis is a form of programmed cell death that is necessary for normal tissue homeostasis and cell turnover and is employed to dispose of cells that are either no longer required or detrimental to the health of the surrounding tissue[91, 92]. Apoptosis plays essential roles in virtually all elements of an organism's life, from embryonic development to termination of immune responses, and its dysregulation is intertwined with the pathophysiology of cancer[93-97]. Apoptosis is regulated primarily by two main pathways: the extrinsic pathway in which a death receptor is activated by an extracellular pro-apoptotic agonist resulting in a signaling cascade leading to caspase 3 activation; and the intrinsic pathway, which is activated by severe forms of mitochondrial dysregulation caused by stimuli such as accumulation of unfolded proteins, reactive oxygen species (ROS) or Ca^{2+} overload[91, 98]. Pertinent to this review, the mechanisms through which Ca^{2+} overload is initiated to trigger apoptosis are numerous and varied. One such mechanism is mediated by the excess release of ER Ca^{2+} stores by IP_3R into the ER-mitochondria junctional space and the subsequent propagation of Ca^{2+} into the mitochondria *via* MCU[91]. The activation of IP_3RS have been frequently observed in response to apoptotic stimuli, and it has long been noted that silencing the expression of IP_3RS in lymphocytes imparts a resistance to apoptosis in response to various stimuli[99-102]. Voltage-gated Ca^{2+} channels have also been shown to induce Ca^{2+} overload and thereby mediate apoptosis[91]. In particular, L-type voltage-gated Ca^{2+} channels have been shown to convert depolarization-triggered Ca^{2+} entry into apoptotic signals in chromaffin cells, PC12 cells, and pancreatic beta cells[103-105]. Additionally, various members of transient receptor potential (TRP) channel superfamily were shown to play a significant role in Ca^{2+}-mediated apoptosis in response to a variety of stimuli including oxidative stress[106], high glucose[107], natural compounds such as menthol[108-110], capsaicin[111, 112], and cannabidiol[113, 114] as well as apoptotic signaling mediated by the Fas receptor[115]. Below, we will focus on SOCE and its function in the induction of Ca^{2+} overload and apoptosis.

Of the two primary apoptotic pathways, it is the intrinsic pathway that is of note when examining the pathophysiology of SOCE[76]. Fundamentally, the intrinsic apoptotic pathway is driven by changes in mitochondrial membrane permeability by either the opening of the mitochondrial permeability transition pore (mPTP) or through pore-formation via the actions of pro-apoptotic BCL-2 protein family members[98, 116-119]. The permeabilization of mitochondria lead in turn to the collapse of the mitochondrial membrane potential, the arrest of mitochondrial ATP synthesis, and the release of pro-apoptotic factors such as cytochrome c, which in turn leads a signaling cascade that activates the apoptosis initiator caspase 3[98, 119, 120]. Thus, a pathophysiological connection can be drawn between the cytosolic influx of Ca^{2+} through SOCE and the initiation of the apoptotic response. Below,

we will examine the function of each protein component of SOCE in initiating signaling cascades resulting in cell death, primarily through apoptosis.

STIM1 and cell death

As mentioned above, STIM1 is the more highly expressed STIM homolog and is generally regarded as the major regulator of SOCE in many tissues[26, 27]. This prevalence greatly facilitates its examination and as a result, most studies regarding SOCE-induced cell death have focused on STIM1, often in conjunction with Orai1, over other SOCE components. Reports of STIM1 regulation of SOCE-induced cell death cover a much wider variety of tissues than those for STIM2, Orai2, or Orai3.

Several studies have shown that STIM1 plays a significant role in inducing apoptosis in neurons[121-127]. This function of STIM1 appears to have been largely identified due to triggering events such as traumatic brain injury (TBI) and oxidative stress. TBI is known to cause secondary injury *via* the excessive release of the excitatory neurotransmitter glutamate and the influx of Ca^{2+} ions[121, 128-130]. The release of glutamate during TBI has been shown to activate STIM1-mediated SOCE in primary mouse cortical neurons, resulting in cytosolic Ca^{2+} overload and apoptosis[121]. This increased cytosolic Ca^{2+} load and resulting apoptosis are significantly decreased in neurons in which STIM1 was silenced with siRNA. Further, in vitro studies showed that mGluR1-dependent Ca^{2+} release from the ER of injured neurons was attenuated in the absence of STIM1, suggesting that STIM1 and SOCE contribute to ER refilling in neurons. It seems that an immediate early gene product Homer1a serves as neuroprotective in response to glutamate-induced oxidative stress injuries in HT-22 cells. Homer1a appears to cause dissociation of STIM1/Orai1 interactions to prevent STIM1-mediated Ca^{2+} overload[124]. A separate study found that knockdown of STIM1 in an ischemic rat model significantly decreased neuronal intracellular Ca^{2+} and reduced ischemic neuronal cell death[122]. Similarly, knockdown of STIM1 in rat primary neurons reduced cell death and the expression of cytochrome c in response to high glucose[131]. The function of STIM1 as pro-apoptotic in neurons was highlighted by the action of the sedative dexmedetomidine[123]. This study reported that PC12 cells pretreated with dexmedetomidine significantly downregulated STIM1 and Orai1 expression levels and were protected from cell death induced by oxygen-glucose deprivation. Taken together, these studies indicate a prominent role for STIM1 in the induction of cell death specifically in neurons.

STIM1 has also been shown to regulate apoptosis in hepatocytes[132-136]. Because the liver serves as the primary detoxification system, hepatocytes are regularly exposed to environmental stressors. Based on the observation that ethanol-induced hepatic cell death involved perturbations in Ca^{2+} homeostasis, Liu et al. found that the mRNA and protein expression of STIM1 and Orai1 were significantly upregulated in the presence of 200 mM ethanol[132]. To assess whether this upregulation of STIM1 and Orai1 were responsible for the disrupted Ca^{2+} homeostasis, they employed STIM1 and Orai1 siRNA knockdown, which abrogated ethanol-induced Ca^{2+} elevation and alleviated cell death. In a follow-up study, the same authors showed that the knockdown of STIM1/Orai1 protected hepatocytes from ethanol toxicity by preserving mitochondrial membrane potential and preventing the cells

from undergoing the intrinsic apoptotic pathway[133]. Additional examples of STIM1/Orai1 regulation of hepatocyte apoptosis in response to hepatotoxic compounds were found in the cases of the weight loss agent usnic acid[134], and the industrial contaminant hexavalent chromium[135]. In both cases, inhibition of STIM1/Orai1 alleviated cytosolic Ca^{2+} overload and prevented apoptosis. In addition to regulating hepatocyte apoptosis in response to toxic compounds, STIM1 was also found to be upregulated and to induce apoptosis in hepatocytes under liver ischemia/reperfusion conditions[136]. In this study, liver tissue samples from *STIM1*$^{-/-}$ mice subjected to hepatic ischemia/reperfusion exhibited significantly less cell death, release of the inflammatory cytokines TNF-α, IL-6 and IL-1β, and cleaved caspase 3 in comparison to wildtype mice.

STIM1 was shown to induce apoptosis in the cardiovascular system[137, 138]. In a case similar to some of those conducted in neurons and hepatocytes, STIM1 and Orai1 regulated apoptosis in cardiomyocytes in response to ischemia/reperfusion injury[137]. As with previous cases in other tissues, STIM1/Orai1 were significantly upregulated in injured conditions, and knockdown of either protein alleviated cytosolic Ca^{2+} overload, decreased ROS production, and attenuated mPTP opening. Interestingly, a follow-up study found that when primary rat ventricular cardiomyocytes subjected *in vitro* to ischemia/reperfusion injury, were pre-treated with the antioxidant and anti-inflammatory compound resveratrol, STIM1 expression was downregulated and apoptosis was alleviated[138]. The ability resveratrol to inhibit STIM1-mediated apoptosis was reported by a separate group who found that pretreatment with resveratrol protected MS-1 microvascular endothelial cells from STIM1/Orai1-mediated apoptosis induced by high glucose levels[139]. A third group proposed a mechanism of how resveratrol inhibited STTM1 function[140]. Resveratrol inhibited ERK1/2 activation—normally triggered by ER Ca^{2+} store depletion—and subsequently prevented the phosphorylation of STIM1 on Ser575, Ser608, and Ser621 thereby preventing STIM1 dissociation from the microtubule-binding protein EB1, STIM1 multimerization and activation of Orai1. Additional studies that point to STIM1 function in regulating apoptosis in the vasculature include the discovery that STIM1/Orai1 proteins induce apoptosis is pulmonary microvascular endothelial cells in response to lipopolysaccharide (LPS) release during acute pancreatitis[141]. Once again, knockdown and pharmacological inhibition of STIM1/Orai1 alleviated SOCE-induced apoptosis initiated by LPS treatment. Interestingly, similar results were reported by two separate groups in human umbilical vein endothelial cells and primary mouse cardiac tissue in LPS models of sepsis[142, 143]. Together, these studies suggest that the inhibition of STIM1/Orai1 may be a tool in preventing cardiovascular cell death in cases of sepsis. Lastly, STIM1 was found to regulate apoptosis in rat endothelial progenitor cells in response to oxidative stress triggered by exposure to excess hydrogen peroxide (H_2O_2)[141]. Knockdown of STIM1 with shRNA decreased the expression of ER apoptosis signaling proteins caspase 9 and caspase 12, decreased ROS levels and rescued mitochondrial membrane potential[141]. It is worth noting that this protection is likely not limited to endothelial progenitor cells, as it has also been previously reported that STIM1 functions as a redox sensor and when under oxidative stress, S-glutathionylation of STIM1 will cause constitutive activation of Orai channels regardless of ER Ca^{2+} store levels [144].

STIM1 plays a key role in regulating immune cell function. Indeed, the activation of T lymphocytes is notably dependent upon Ca^{2+} signaling through SOCE, and existing reviews discuss the role of STIM/Orai-mediated SOCE in T lymphocyte proliferation and apoptosis[1, 3, 145-147]. Given the highly centralized role SOCE plays in healthy T lymphocyte function, it is perhaps fitting that it also represents one of the only documented instances in which the downregulation of SOCE proteins STIM1 and Orai1 were found to facilitate apoptosis *via* the extrinsic pathway initiated by Fas stimulation[148]. The Fas receptor is a key component of immune system regulation by inducing apoptosis in activated lymphocytes and thereby preventing prolonged immune responses that could cause autoimmunity[149]. In an examination of apoptosis in Jurkat T cells mediated by moderate Fas receptor ligation, STIM1 and Orai1 were downregulated and SOCE was reduced by the de-energization of mitochondria and the upregulation of caspase activity[148]. The authors of this study speculated that this decrease in SOCE might serve to protect T cells undergoing apoptosis from shifting into a necrotic cell death pathway by preventing cytosolic Ca^{2+} overload.

Another function for STIM1/Orai1 in regulating apoptosis in immune cells was reported in headkidney macrophages from the species of catfish *Clarias gariepinus*[150, 151]. Infection of these macrophages with *Mycobacterium fortuitum* leads to production of toxic levels of ROS by macrophages and a surge in cytosolic Ca^{2+} to induce apoptosis, thereby destroying the infecting bacteria[152]. Dahiya et al. found that toll-like receptor 2-dependent internalization of *M. fortuitum* by macrophages induced significant ER stress, resulting in the upregulation of STIM1 and Orai1, which in turn activate calpain, causing it to cleave nitric oxide synthase interacting protein and initiate the release of toxic levels of nitric oxide. Knockdown of STIM1 and Orai1 reduced calpain activation, and prevented the accumulation of ROS and macrophage apoptosis, facilitating bacterial survival. A follow-up study by the same group suggested that the accumulation of mitochondrial ROS was dependent upon calcium uptake by the mitochondrial Ca^{2+} uniporter, and that inhibiting mitochondrial ROS with the pharmacological compound YCG063 reciprocally resulted in the downregulation of STIM1 and Orai1[151]. This suggests that SOCE and mitochondrial ROS production create an amplifying positive feedback loop to induce apoptosis in infected macrophages. This is consistent with the previously mentioned reports proposing that STIM1 facilitates apoptosis in response to oxidative stress[126, 141, 144].

Scattered reports have also identified instances of STIM1 induction of apoptosis in a variety of other tissues including the pancreas[153], gastric cancer[154], and mammary tissue[155]. In an *in vitro* model of diabetic hyperlipidemia, a mouse pancreatic β-TC3 cell line significantly upregulated STIM1 and Orai1 expression in response to free fatty acids[153]. The resulting increase in SOCE enhanced the expression of the ER stress response protein CHOP and activated caspase 3, initiating apoptosis. In human gastric cancer cell lines BGC-823 and SGC-7901, treatment with 3,3'-diindolylmethane—a natural phytochemical known to induce apoptosis in gastric cancer—was proposed to act *via* the upregulation of STIM1 and subsequent cytosolic Ca^{2+} overload, which was rescued by STIM1 knockdown [154]. STIM1 and Orai1 alike were found to regulate apoptosis in the injured mammary tissue of dairy cows suffering from subacute ruminal acidosis resulting from a carbohydrate-rich diet[155]. Finally, STIM1 was found to regulate apoptosis in

normal cervical epithelial cells but not cervical cancer cells cultured in soft collagen substrates designed to test cellular responses to mechanical stimuli[156]. Together, these studies indicate the widespread influence of STIM1 on SOCE and apoptosis across many tissues and disease states.

STIM2 and cell death

Despite the comparative lack of dedicated research focused on STIM2 relative to STIM1, there have been a small number of studies indicating that STIM2 can play a role in the induction of cell death. The earliest identified role for STIM2 in inducing cell death was described in neurons[28]. In this study, STIM2 was identified as an essential regulator of SOCE in neurons, and responsible for significant cytosolic Ca^{2+} accumulation and cell death under oxygen-glucose deprivation in isolated wildtype mouse neuronal cells. By contrast, neurons isolated from *Stim2*$^{-/-}$ mice were protected from Ca^{2+} accumulation and associated cell death. These results were replicated *in vivo*, where the *Stim2*$^{-/-}$ mice were protected from ischemic stroke. In agreement with these findings, an independent study found that the knockdown of STIM2 in neurons had neuroprotective effects in TBI/traumatic neuron injury models both *in vivo* and *in vitro*[157]. Furthermore, this work demonstrated that knockdown of STIM2 in mouse neurons prevented mitochondrial Ca^{2+} overload, thus drawing the connection between STIM2 activity and the intrinsic apoptosis pathway. More recently, the role of STIM2 in inducing ischemic cell death was also illustrated in the rat cardiomyoblast cell line H9c2[158]. In this study, the release of cytochrome c from the mitochondria was measured after subjecting the H9c2 cells to ischemia/reperfusion, and the authors reported an increase in cytochrome c under ischemic conditions in wildtype cells, while knockdown of STIM2 significantly reduced the release of cytochrome c under the same conditions. Taken together, these studies indicate that STIM2 plays an intriguing role in inducing apoptosis in ischemic conditions that warrants further investigation in other tissues.

STIM2 was proposed to play a role in regulating apoptosis in colorectal cancer[159, 160]. In a comparison of human colon carcinoma cell line HT29 versus the normal human mucosa cell line NCM460, the loss of STIM2 in the HT29 line resulted in partially depleted ER Ca^{2+} stores and resistance to apoptosis[159]. The knockdown of STIM2 in the NCM460 cells is similarly protective from apoptosis. Consistently, a separate study showed that increased expression of STIM2 in colorectal tumors resulted in the suppression of tumor growth[160]. In this study, colorectal tumor xenografts that were identified as exhibiting high STIM2 expression levels displayed significantly less vascular invasion and a heavily reduced proliferation rate compared to tumor xenografts exhibiting low STIM2 expression.

Orai1 and cell death

Orai1 is by far the best characterized of the Orai homologs, with many studies showing virtually equal contributions of STIM1 and Orai1 in mediating apoptosis. Several studies have identified instances in which Orai1 is a major contributor to the induction of apoptosis. The earliest example of Orai1-mediated cell death was in prostate cancer cells[161]. In this study, Orai1 was the primary mediator of apoptosis in response to chemotherapeutics such as cisplatin and oxaliplatin, and its expression was downregulated in steroid-deprived prostate

cancer cells. Consistent with previously reported findings[162], the prostate cancer cells that survive steroid-deprivation *via* the downregulation of Orai1 simultaneously acquire a resistance to cisplatin-induced apoptosis as a result[161]. Orai1 was suggested to regulate apoptosis of pancreatic acinar cells of multiple mouse models of acute pancreatitis[163]. Pancreatic acinar cells were protected from pancreatitis-triggered apoptosis in the presence of various pharmacological inhibitors of SOCE such as GSK-7975A. However, it should be noted that current pharmacological agents, including GSK-7975A, are poorly selective for Orai1, and instead affect all Orai homologs[164]. Thus, it is possible that this observed apoptotic protection is mediated by other Orai homologs, rather than strictly by Orai1. Additional apoptotic roles induced by Orai1 in response to oxidative stress were described in the mouse hippocampal cell line HT22 in an *in vivo* mouse model[165, 166]. Of particular note, molecular docking, thermal shift and plasmon resonance assays suggested that the neuroprotective supplement icaritin prevented apoptosis in response to H_2O_2-induced oxidative stress through direct binding and inhibition of Orai1[166].

Orai1 has also been found to play diverse roles including the induction of apoptosis in immune cells[145]. In addition to the previously mentioned study that identified STIM1 and Orai1 as regulators of apoptosis in T lymphocytes[148], an additional study found that Orai1 alone was equally capable of mediating T lymphocyte death[167]. In this study, the $CD4^+$ T cells of *Orai1*$^{-/-}$ mice were found to be resistant to T cell receptor stimulation-induced cell death as a result in changes to Fas receptor expression and reduced mitochondrial Ca^{2+} uptake. Additionally, upon challenge with an activating anti-CD3 antibody *in vivo*, the $CD4^+$ T cells of *Orai1*$^{-/-}$ mice survived at significantly higher rates than the $CD4^+$ T cells of *Orai1*$^{+/+}$ mice, reinforcing the proapoptotic function of Orai1 in T lymphocytes. Lastly, Orai1 regulated apoptosis in foam cells in a mouse model of atherosclerosis[168]. In this system, Orai1-dependent Ca^{2+} influx occurred in response to acute administration of oxidized low-density lipoprotein, and resulted in the activation of apoptosis signal-regulating kinase 1. This effect was mitigated by siRNA knockdown of Orai1, and by inhibition of SOCE with another poorly selective pharmacological agent, SKF96365[168].

Orai2 and cell death

The potential function of Orai2 in cell death has gone nearly unexamined since its discovery, and largely remains a mystery. However, a pair of studies conducted in 2019 by separate groups have revealed that similar to STIM2, Orai2 appears to play a role in regulating apoptosis in the brain[169, 170]. Using a bioinformatics approach, and analyzing gathered RNA-seq data from the *The Cancer Genome Atlas and the French, Sun and Gene Expression Omnibus*, Yuan et al. identified significant upregulation of Orai2 in glioblastoma samples[169]. Furthermore, they found a strong positive correlation between expression of Orai2 in glioblastoma with the expression of cytochrome c, caspase 3, and caspase 9. While this study lacks *in vitro* and *in vivo* experiments to draw a direct mechanistic connection between Orai2 expression and apoptosis, the results suggest a relationship between the two. The second study, by contrast, examined the role of Orai2 in regulating neuronal cell death in response to ischemic stroke both in a mouse model and *in vitro*[170]. In this study, Orai2 was found to be a major contributor to SOCE and to strongly promote the accumulation of Ca^{2+} and expression of caspase-3 in the cortical neurons of wildtype mice in ischemic

conditions. By comparison, the cortical neurons of *Orai2*$^{-/-}$ showed significantly less SOCE, Ca^{2+} accumulation, and expression of caspase 3. As a result, these findings indicate that Orai2 plays a similar role in the regulation of SOCE-mediated apoptosis in neurons as STIM2.

Orai3 and cell death

As with STIM2 and Orai2, there is currently a deficiency in the number of studies examining the function of Orai3 in cell death. Indeed, most studies of Orai3 and cell death suggest that Orai3 plays a vastly more prominent role in apoptosis resistance, growth and invasion of cancer cells than in inducing apoptosis[76, 171-176]. For instance, knockdown of Orai3 in pancreatic ductal adenocarcinoma (PDAC) cell lines caused enhanced SOCE [177], which is consistent with the function of Orai3 as a negative regulator of SOCE [14, 53, 177]. In this study, the authors showed that knockdown of Orai3 inhibited PDAC cells growth and promoted apoptosis, suggesting that in these cells Orai3 offers a survival advantage by negatively regulating SOCE activity and preventing Ca^{2+} overload-mediated apoptosis. Interestingly, Orai3 knockdown in normal pancreatic cells inhibited SOCE [177], cautioning against extrapolating findings in malignant cell lines to the physiology of primary cells and systems. Curiously, one of the few examples of Orai3 inducing apoptosis was identified in a human lens epithelial cell line (HLEpiC) resulting from an observation that Orai3 expression is dramatically increased in the cataracts of diabetic patients[178]. In this study, HLEpiCs cultured in high glucose (25.6 mM) exhibited significant upregulation of Orai3 and STIM1 expression compared to HLEpiCs cultured in normal glucose (5.5 mM). Interestingly, Orai1 protein expression was reduced in the high glucose condition. SOCE measurements in cells with either Orai3 or STIM1 knockdown seemed to indicate that SOCE was significantly reduced in HLEpiCs cultured in high glucose, although some of these recordings showed atypically transient Ca^{2+} entry signals. These results were compounded by the observation of increased apoptotic markers in the controls compared to cells with Orai3 knockdown. Primary cultured lens epithelial cells from *Orai3*$^{-/-}$ diabetic rats showed that SOCE was virtually abolished compared to cells from diabetic wildtype rats. Finally, the lens turbidity levels were significantly lower in *Orai3*$^{-/-}$ diabetic rats compared to their diabetic wildtype counterparts. These results suggest that Orai3 might be involved in apoptosis of lens epithelial cells, and contributes to the development of diabetic cataracts[178].

Another interesting instance in which Orai3 was found to induce apoptosis was identified in kidney proximal tubular cells[179]. In this study, the internalization of accumulated calcium oxalate monohydrate and calcium phosphate crystals by the proximal tubular cells altered their primary Ca^{2+} influx pathway from receptor-operated calcium influx to SOCE *via* the induction of ER stress and the upregulation of STIM1, STIM2, and Orai3. The upregulation of ER stress-related to Nucleus signaling 1 (ERN1) and claudin 1 (CLDN1) were observed in proximal tubular cells with internalized crystals, and were indicative of increased apoptotic signaling. As with previous examples, knockdown of either STIM protein, or Orai3 significantly reduced SOCE and alleviated the expression of ER stress signaling molecules. Notably, while either knockdown of STIM1 or STIM2 reduced the expression of ERN1, only the knockdown of Orai3 reduced the expression of ERN1 and

CLDN1, suggesting that Orai3 plays a more prominent role than that of STIM1/2 in crystal-induced apoptosis.

Conclusions

The majority of studies examining SOCE clearly indicate that its prevailing role is to drive normal cell function and encourage proliferative gene expression (Fig. 1A)[77, 78, 180, 181]. Indeed, this has resulted in very few groups exploring the roles that the SOCE proteins play in inducing cell death. However, when the existing studies are examined as a whole, the current message communicated by the literature as it pertains to the role of SOCE in mediating cell death is that it is fundamentally a process driven by excess in circumstances where the cells are otherwise already vulnerable (Fig. 1B). Many of the studies reviewed herein demonstrate this concept in cases of Traumatic brain injury and/or in ischemia/reperfusion injury[28, 121, 122, 136, 157, 158, 170]. Others demonstrate this concept in the presence of other toxic excesses such as H_2O_2, ethanol, glutamate, glucose, and Ca^{2+}crystals[124, 126, 131, 132, 141, 165, 178, 179]. Notably—albeit unsurprisingly—SOCE appears to almost exclusively drive apoptosis *via* the intrinsic pathway, rather than broadly contributing to the extrinsic pathway. Regardless, the majority of reported instances of SOCE-induced cell death demonstrate that it is seldom the key initiator of apoptosis, but that it instead tips the balance in favor of apoptosis in already stressed cells or systems.

SOCE has been found to induce apoptosis in a growing number of tissues, with STIM1 and Orai1 contributing the majority of cases in the widest variety of tissues. This is not surprising as STIM1 and Orai1 are robust mediators of SOCE with the notable exception of STIM2 and Orai2 in the brain, where they appear to be highly expressed and contribute a sizeable portion of SOCE. In particular, STIM1 has been noted to regulate apoptosis in the nervous system[121-127], the cardiovascular system[137, 138], the immune system[148], as well as in the liver[132-136] and pancreas[153] among other tissues. In many regards, the contributions of STIM1 and Orai1 to the induction of apoptosis can be seen as a reflection of their prevalence in most tissues relative to the lesser-studied homologs STIM2, Orai2, and Orai3. However, it should be noted that many of the studies that identified STIM1 and Orai1 as regulators of apoptosis relied upon knockdown of these homologs specifically, and they did not report on attempts to knockdown the remaining homologs.

Because SOCE primarily plays a role in inducing cell death in systems with pre-existing stressors an intriguing number of potential therapeutic interventions become worthy of consideration. Normally, the disruption of SOCE by pharmacological inhibitors would be associated with unfavorable outcomes in many tissues due to its wide-reaching regulation of healthy cell function and proliferation, especially in the treatment of chronic disease where the effects of SOCE inhibition would be amplified. Indeed, while a recent study has shown that chronic reduction of SOCE in a mouse model with a STIM1 loss of function (LoF) mutation could be therapeutically beneficial, these mice with STIM1 LoF mutation were hypertensive and exhibited tachycardia as a result of catecholamine accumulation in the circulatory system[182], underscoring the ubiquitous involvement of SOCE in human physiological systems. However, the use of pharmacological SOCE inhibitors administered over a confined period of time in cases of ischemia/reperfusion or traumatic brain injury, for

example, would offer a potentially viable and effective treatment option. Ironically, this is particularly true of potential inhibitors for the lesser-studied components of SOCE: STIM2, Orai2, and Orai3. As discussed above, STIM1 and Orai1 represent the primary mediators of SOCE in most tissue types, and most identified instances of pathophysiology involving the dysregulation of SOCE are derived from *STIM1* and *Orai1* LoF mutations[20-27]. Accordingly, one would expect the highest probability of a negative outcome by the pharmacological inhibition of STIM1 and Orai1. By contrast, STIM2, Orai2, and Orai3 play more subtle regulatory roles in most tissues, while also exhibiting significant upregulation in expression and contribution to pathophysiological activity in instances such as ischemia/reperfusion or TBI. Thus, a window of opportunity is created to both efficiently target the pathophysiology while also minimizing potential off-target effects. This would work only if Orai2 and Orai3 are indeed forming channels on their own. One important caveat to consider within this context is that Orai2 and Orai3 might be forming heteromeric channels with Orai1, thus inhibiting Orai1 activity and SOCE. In this case, any therapeutic drug should be targeted to this heteromeric channel. Unfortunately, the currently available pharmacological tools do not possess sufficient selectivity to achieve this goal, as the oligomeric state and Orai isoform composition of SOCE channels in any given cell type remains unclear and most available agents target multiple Orai homologs[164]. Thus, future research efforts should be dedicated to the elucidation of the molecular make-up of native SOCE channels in different cell types and on the discovery of pharmacological agents that selectively target individual Orai homologs as well as various heteromeric Orai compositions that exist under native conditions.

In conclusion, the role of SOCE in inducing cell death remains a largely understudied area. Future research efforts will be necessary to understand the breadth and nuances of SOCE-mediated cell death more fully, but existing trends suggest that it plays a pronounced role in tissues already experiencing significant environmental stressors, with ischemia being the most prominent example. Furthermore, it must be emphasized that despite a general lack of studies focused on STIM2, Orai2, and Orai3, they appear to play vital roles in SOCE-mediated cell death that offer highly exploitable opportunities to develop effective treatments where agents targeting the more prominent STIM1 and Orai1 may fail. Regardless of therapeutic potential, the development of selective pharmacological compounds against each Orai homolog and potential native Orai heteromers will greatly facilitate the identification and discovery of novel functions that SOCE might have in cell death, cell function and human disease.

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Abbreviations

Ca^{2+}	Calcium
PM	plasma membrane
ER	endoplasmic reticulum

SOCE	store-operated calcium entry
STIM	stromal interaction molecule
PLC	Phospholipase C
PIP_2	phosphatidylinositol 4,5-bisphosphate
IP_3	inositol 1,4,5-triphosphate
DAG	diacylglycerol
IP_3R	IP_3 receptors
SOAR/CAD	STIM Orai-activating region/CRAC-activating domain
LoF	loss of function
ARC	arachidonic acid/leukotriene C_4-regulated channels
NFAT	nuclear factor of activated T-cells
MPTP	mitochondrial permeability transition pore
ROS	reactive oxygen species
TRP	transient receptor potential
TBI	traumatic brain injury
LPS	lipopolysaccharide
H_2O_2	hydrogen peroxide
ERN1	ER stress-related to nucleus signaling 1
CLDN1	claudin 1

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Highlights

- Store-Operated Ca^{2+} entry is mediated by two STIM and three Orai proteins
- STIM1 and Orai1 are most studied and little is known about STIM2, Orai2 and Orai3
- STIM/Orai mediate intrinsic cellular apoptosis through mitochondrial Ca^{2+} overload

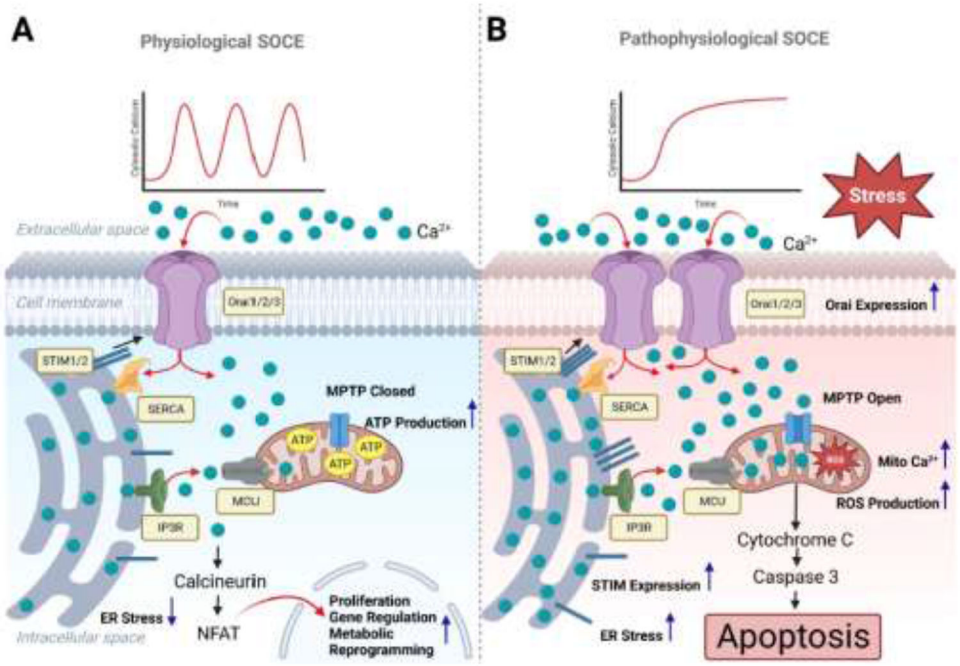

Figure 1.

(A) In healthy tissues, the ER Ca^{2+}-sensing STIM proteins activate the plasma membrane Orai channels to mediate cytosolic Ca^{2+} influx in a physiological moderate and regulated oscillatory pattern. The rise in cytosolic Ca^{2+} under physiological levels of stimulation enhances mitochondrial bioenergetics, and activates the phosphatase calcineurin, which induces the nuclear translocation of transcription factors such as NFAT and initiates the transcription of proliferative and metabolic genes. Under physiological conditions, this Ca^{2+} signal will cease when the agonist is absent. **(B)** In stressed cells and systems, upregulated expression/activation of STIM and Orai induces sustained Ca^{2+} influx over extended periods causing mitochondrial Ca^{2+} overload, increased mitochondrial ROS production, mPTP opening, the collapse of mitochondrial membrane potential, and the release of cytochrome c. The released cytochrome c leads to the activation of caspase 3, and ultimately results in cellular apoptosis.