Chapter 1
Historical Overview of Store-Operated Ca^{2+} Entry

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Abstract Calcium influx is an essential mechanism for the activation of cellular functions both in excitable and non-excitable cells. In non-excitable cells, activation of phospholipase C by occupation of G protein-coupled receptors leads to the generation of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), which, in turn, initiate two Ca^{2+} entry pathways: Ca^{2+} release from intracellular Ca^{2+} stores, signaled by IP_3, leads to the activation of store-operated Ca^{2+} entry (SOCE); on the other hand, DAG activates a distinct second messenger-operated pathway. SOCE is regulated by the filling state of the intracellular calcium stores. The search for the molecular components of SOCE has identified the stromal interaction molecule 1 (STIM1) as the Ca^{2+} sensor in the endoplasmic reticulum and Orai1 as a store-operated channel (SOC) subunit. Furthermore, a number of reports have revealed that several members of the TRPC family of channels also take part of the SOC macromolecular complex. This introductory chapter summarizes the early pieces of evidence that led to the concept of SOCE and the components of the store-operated signaling pathway.

Keywords SOCE • STIM1 • Orai1 • TRPC channels

1.1 The Concept of Store-Operated Ca^{2+}Entry

A number of physiological agonists activate cellular functions by inducing changes in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$). In general, Ca^{2+} mobilization consist of the release of Ca^{2+} from intracellular stores, as well as Ca^{2+} influx from the extracellular medium through Ca^{2+}-permeable channels. Despite the identification of Ca^{2+}as a

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second messenger in the excitation-contraction coupling took place in the mid-twentieth century [1], the relevance of extracellular Ca^{2+}in cellular physiology was already highlighted in the publications of Ringer in the Journal of Physiology in the early 1880s [2, 3]. Throughout the 1960s and 1970s, different laboratories determined Ca^{2+} signals induced by physiological agonists, first using luminescent photoproteins and later on through the use of fluorescent probes, until Ca^{2+} was recognized as a *bona fide* second messenger [4].

After Ringer's findings, the studies concerning the functional role of Ca^{2+} entry were mainly focused on muscle contraction, especially in the heart and the sartorius muscle, where $^{45}Ca^{2+}$ uptake (influx) by the cell was analyzed under different experimental conditions [5, 6]. Among the first analysis of Ca^{2+} entry in non-electrically excitable cells were performed in HeLa cells in culture, where Borle identified two exchangeable pools, assumed as the extracellular Ca^{2+} and Ca^{2+} stored in intracellular compartments, and two unexchangeable Ca^{2+} pools, corresponding to extracellular and intracellular bound Ca^{2+} [7]. A year earlier, the same author reported that the extracellular medium was a major source of Ca^{2+} [8]. Borle defined Ca^{2+} influx in these cells as a facilitated diffusion process that can be affected by increasing the membrane permeability to this ion and not by stimulating an active or metabolically dependent process [7].

Voltage-dependent Ca^{2+}currents independent of metabolic events were described in the early 70s and a mechanism for Ca^{2+} influx operated by the occupation of membrane receptors was also soon reported in electrically excitable and non-excitable cells [9–11]. But, it was in 1986, when a mechanism for receptor-operated Ca^{2+} influx regulated by the filling state of the intracellular Ca^{2+} stores was proposed [12]. The term capacitative Ca^{2+}entry was coined by James Putney to refer to a process whereby the discharge of Ca^{2+} stores within a cell secondarily activates Ca^{2+}entry into the cell across the plasma membrane [12], a mechanism analog to the function of a capacitor in an electrical circuit, since this process is characterized by the fact that charged or full intracellular Ca^{2+} stores prevent Ca^{2+} current through the plasma membrane, while discharge of the intracellular stores is followed by rapid entry of Ca^{2+} into the store and, in the continued presence of inositol (1,4,5) trisphosphate (IP_3), into the cytosol [12–14].

Analysis of the kinetics of the rises in $[Ca^{2+}]_c$ using the intracellular fluorescent probe fura-2 in human platelets revealed that stimulation with the physiological agonist thrombin, which induces active Ca^{2+} release from the stores via generation of IP_3, resulted in Mn^{2+} entry that starts a few tenths of second after discharge of the intracellular Ca^{2+}stores [15]. This finding was consistent with a mechanism controlled by the agonist-sensitive intracellular Ca^{2+} stores. Further studies revealed that cell treatment with thapsigargin, a sesquiterpene lactone obtained from *Thapsia garganica* [16] that inactivates the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) [17] and leads to passive store depletion via Ca^{2+} leak, resulted in Ca^{2+} influx across the plasma membrane independently of IP_3 generation [18]. Soon after this publication, it was found that Ca^{2+} influx evoked either by agonist stimulation or by treatment with thapsigargin was mediated via the same mechanism, thus concluding that the mechanism underlying the activation of capacitative Ca^{2+} entry was

the discharge of the intracellular Ca^{2+} stores per se and not the cellular levels of inositol phosphates [19]. The concept of a Ca^{2+} entry mechanism regulated by the stores was further confirmed by electrophysiological studies that reported that Ca^{2+} stores discharge activated a Ca^{2+} current in mast cells called Ca^{2+} release-activated Ca^{2+} current, I_{CRAC}, the first store-operated Ca^{2+} current identified [20]. In fact, in addition to the physiological pathway to activate capacitative Ca^{2+} entry via generation of IP_3, this mechanism for Ca^{2+} influx has been reported to be activated by a number of experimental maneuvers leading to a reduction in the amount of free Ca^{2+} in the intracellular stores. These procedures include treatment with thapsigargin, as well as other SERCA inhibitors, such as cyclopiazonic acid or di-*tert*-butylhydroquinone [21, 22] (agents that prevent Ca^{2+} store refilling), loading of Ca^{2+} stores with the metal Ca^{2+} chelator N,N,N,N-tetrakis(2-pyridylmethyl)ethylene diamine (which reduces free intraluminal Ca^{2+} concentration without altering $[Ca^{2+}]_c$ [23, 24]), or dialyzing the cytoplasm with the Ca^{2+} chelators EGTA or BAPTA, which bind Ca^{2+} leaking from the stores, thus preventing store refilling (see [25]). From that point capacitative Ca^{2+}entry was also known as store-operated Ca^{2+} entry (SOCE) [26] or store-mediated Ca^{2+}entry [27]. Since SOCE is the most extended term we will use this denomination throughout the chapter.

The manuscript by Kwan and coworkers [19] also raised a key conceptual feature of SOCE. The initial observations had suggested that the transport of extracellular Ca^{2+} into the cell involved a direct movement of Ca^{2+} into the intracellular stores, since refilling of the Ca^{2+} stores were found to occur with no substantial elevation in $[Ca^{2+}]_c$ [12, 28]. However, this hypothesis somehow limited the role of Ca^{2+} entry to the refilling of the intracellular Ca^{2+} stores. Using the trivalent cation lanthanum, which induces a concentration-dependent inactivation of Ca^{2+} extrusion through the plasma membrane Ca^{2+}-ATPase, and impairs Ca^{2+} entry [29, 30], Kwan and coworkers observed that, in the absence of Ca^{2+} extrusion and entry, Ca^{2+} stores were refilled by Ca^{2+} released into the cytoplasm upon agonist stimulation, providing evidence that store refilling did not involve a direct route into the intracellular Ca^{2+} pools, but rather is the result of a sequential Ca^{2+} entry into the cytoplasm and subsequent reuptake into the Ca^{2+}stores by active SERCA pumping [19, 31].

SOCE has also been described in a number of excitable cells, including neurons [32], cardiomyocytes [33], smooth muscle cells [34] and both endocrine [35–37] and neuroendocrine cells [38, 39]. In these cells, the functional role of SOCE is not limited to store refilling but it plays an important functional role as revealed by a number of disorders observed in the presence of defective SOCE [40–44].

SOCE activation in electrically excitable cells could trigger Ca^{2+} entry through voltage-operated channels by causing membrane depolarization [45, 46], which might result directly from the activation of store-operated Ca^{2+} (SOC) channels, which can be permeable to Ca^{2+}, as well as to other cations, such as Na^+, and have reversal potentials near 0 mV. In addition, indirect mechanisms for membrane depolarization associated to rises in $[Ca^{2+}]_c$ have been reported, such as a Ca^{2+}-dependent inhibition of voltage-dependent K^+ channels [47] reported in pulmonary arterial smooth muscle cells [48]. In contrast to these observations, current evidence supports that the SOCE element STIM1 interacts with the voltage-gated $Ca_v1.2$ chan-

nels and suppresses its activity [49, 50]. Since functional expression of voltage-operated Ca^{2+} channels, including $Ca_v1.2$, has been reported not only in excitable cells but also in non-electrically excitable cells, such as T and B lymphocytes and mast cells [51–54], these findings further confirm the role of STIM1 as an essential element in the modulation of agonist-induced Ca^{2+} signals.

The electrophysiological analysis of store-operated currents has revealed the presence of two types of currents: the Ca^{2+} release-activated Ca^{2+} current (I_{CRAC}) and a heterogeneous set of non-CRAC currents, described in different cell types with diverse biophysical properties grouped under the denomination of store-operated currents (I_{SOC}) [25]. The I_{CRAC} current was the first store-operated Ca^{2+} current identified using combined patch-clamp and fura-2 measurements to monitor membrane currents in mast cells [20]. I_{CRAC} is a non-voltage-operated current, unlike Ca^{2+} currents through the Ca_v family of channels, that exhibits large current amplitude at negative potentials and approaches the zero current level at very positive potentials. In addition, the current-voltage relationship for I_{CRAC} reveals a significant inward rectification at negative voltages [20, 25]. The channels conducting I_{CRAC} (CRAC channels) show a single channel conductance <1pS and are highly selective for Ca^{2+} over monovalent cations. The Ca^{2+}:Na^+ permeability ratio has been estimated around 1,000:1. Removal of extracellular Ca^{2+} in the presence of external Na^+ and Mg^{2+} has been reported to abolish this current [55, 56]. However, CRAC channels lose this selectivity in divalent-free solutions, which allow Na^+ to permeate the channels, leading to whole cell currents that are five to eightfold larger than the Ca^{2+} currents [57, 58].

The I_{SOC} currents are mediated by poorly selective cation channels that exhibit a significantly greater conductance than CRAC channels and show different biophysical properties. I_{SOC} currents have been described in different cell types, including vascular endothelial cells [59, 60], pancreatic acinar cells [61], human A431 carcinoma cells [62, 63], smooth muscle cells [64, 65], submandibular and parotid gland cells [66], liver cells [67], skeletal muscle cells [68], neurons [69] and adrenal chromaffin cells [70]. The Ca^{2+}:Na^+ permeability ratio of the channels conducting this currents is very heterogeneous, ranging from 1:0.07 to 50:1.

SOCE has been reported to play a number of important roles in cell physiology, including, among others, Ca^{2+} store refilling upon agonist stimulation, support for the sustained elevations in $[Ca^{2+}]_c$ required for a number of cellular functions and maintenance of the amplitude of Ca^{2+} oscillations [71, 72]. In addition, a variety of functions have been reported to be regulated by SOCE in a number of cell types, including endothelial cell permeability [73], vascular smooth muscle cell proliferation and contractility [34, 74], platelet function [75, 76], immunological response [77] or exocytosis [70, 78, 79], among many others.

1.2 Activation Mechanisms: Initial Studies

Since the discovery of SOCE, the mechanism underlying the regulation of SOC channels in the plasma membrane by distantly located intracellular Ca^{2+} stores has been intensely investigated and debated. The description that STIM1 is the Ca^{2+}

sensor of the intracellular Ca^{2+} stores in 2005 [80, 81] was a milestone in the identification of the events that regulate SOC channels following a reduction of the intraluminal Ca^{2+} concentration and marked an inflection point between the initial models and the current one. The initial studies can be grouped into those supporting the indirect coupling between the stores and SOC channels, those that propose a direct or conformational coupling between SOC channels and elements in the stores, and those reporting the insertion of preformed channels in the plasma membrane [25, 82].

The indirect coupling hypothesis assumes that Ca^{2+} store depletion results in the generation or activation of diffusible molecules that participate in SOC channel gating. This model includes roles for cGMP [83, 84], a product of cytochrome P450 [85], probably the metabolite 5,6-epoxyeicosatrienoic acid [86], tyrosine kinases [87–89], monomeric GTP-binding proteins [90–92], calmodulin [93] and a still uncharacterized Ca^{2+}-influx factor (CIF) [94, 95].

The conformational coupling hypothesis proposes a physical and constitutive interaction between elements in the membrane of the Ca^{2+} stores and SOC channels in the plasma membrane. This model was originally proposed by Irvine as a mechanism for the activation of SOCE involving IP_3 receptors in the endoplasmic reticulum (ER) and inositol 1,3,4,5-tetrakisphosphate (IP_4) receptors in the plasma membrane [96, 97]. Later on, Birnbaumer and colleagues demonstrated that the association of the IP_3 receptor with transiently expressed TRPC1, TRPC3, and TRPC6 plays a relevant role in the activation of SOCE [98]. This hypothesis received support from studies providing evidence for a role in the activation of SOCE of the protein junctate, an ER Ca^{2+}-binding protein that induces and/or stabilize the interaction between the ER and the plasma membrane [99]. Junctate has been proposed to play an important role in the association of the IP_3 receptors and TRPC3 [99]. Consistent with the conformational coupling are a number of studies reporting that TRPC3 channels present in excised patches can be activated by IP_3 [100]. Furthermore, the N-terminus of IP_3 receptors, containing the IP_3-binding domain, is essential for the activation of plasma membrane TRPC3 channels [101].

In addition to the indirect and conformational coupling hypotheses, a number of studies also supported the activation of SOCE by the translocation and insertion of preformed channels, initially located in intracellular vesicles, into the plasma membrane. This model, that was proposed by Penner and colleagues [90], requires the participation of the synaptosome associated protein SNAP-25 [102]. In hippocampal neurons, HEK 293 cells stably expressing TRPC6 and neuronal and epithelial cells expressing TRPC3 depletion of the intracellular Ca^{2+} stores results in the expression of TRPC channels in the plasma membrane [103–105].

The conformational coupling model assumed that the IP_3 receptor in the stores and SOC channels are permanently associated, so that a decrease in the intraluminal Ca^{2+} concentration is communicated to the SOC channels via a conformational change in the IP_3 receptor. Analyzing the role of the actin cytoskeleton in the activation of SOCE in different cell types, including smooth muscle cell lines, human platelets and other non-excitable cells, such as pancreatic acinar cells and the human hepatocellular carcinoma cell line HepG2, an alternative to the constitutive conformational coupling model called secretion-like coupling or de novo conforma-

tional coupling was described. This model assumes a reversible physical coupling between the ER and the plasma membrane where the actin cytoskeleton plays an essential role [106–109]. The de novo coupling between elements in the ER and the plasma membrane was found to be strongly dependent on actin filament reorganization. Thus, the actin network located underneath the plasma membrane acts as a negative clamp that prevents constitutive coupling [106, 109, 110]. According to this, stabilization of the cortical actin network has been reported to impair the activation of SOCE in a variety of cell types, including smooth muscle cell lines, human platelets, corneal endothelial cells, the human prostate adenocarcinoma cell line LNCaP, pancreatic acinar cells, smooth muscle cells or neutrophils [39, 45, 106, 107, 109, 111, 112]; however, in pancreatic β cells, thyroid FRTL-5 cells and *Aplisia* bag cell neurons, SOCE has been reported to be insensitive to stabilization of the cortical actin cytoskeleton by treatment with jasplakinolide [113–115], and stabilization of the peripheral cytoskeleton and disassembly of actin microfilaments have been shown to fail to alter the rate or extent of activation of I_{CRAC} in the RBL-1 rat basophilic cell line [116]. This discrepancies might be attributed to the different idiosyncrasy of the cells investigated. The role of the cortical cytoskeleton in the modulation of SOCE has been further supported by analysis of the actin polymerization and Ca^{2+} mobilization on a subsecond time scale. In human platelets stimulated with the physiological agonist thrombin we detected an initial decrease in the actin filament content within 0.1 s after stimulation that reached a minimum 0.9 s after the addition of thrombin. Actin depolymerization, involving the actin-binding protein cofilin, was observed before the initiation of SOCE, which occurred with a latency of 2.1 s after agonist stimulation [117], which is consistent with a role for the actin cortical cytoskeleton in the modulation of SOCE.

After the identification of STIM1 as the ER Ca^{2+} sensor [80, 118] and Orai1 as the prototypical CRAC/SOC channel [77, 119–122] the initial hypotheses had to be necessarily reconsidered and/or reinterpreted. Therefore, as described in a number of cells for SOCE, is the interaction between STIM1 and Orai1 modulated by the cortical actin cytoskeleton? There is a growing body of evidence supporting a role for the cytoskeleton in the interaction between STIM1 and Orai1. In HEK-293 cells and platelets, we have demonstrated that stabilization of the cortical actin cytoskeleton impairs de novo association between the ER Ca^{2+} sensor STIM1 and the SOC channel Orai1 [123, 124], without altering the coupling between plasma membrane-resident STIM1 and Orai1 [125]. These findings might explain why, in the presence of extracellular Ca^{2+}, treatment with jasplakinolide prevented Ca^{2+} entry but not the influx of other cations, such as Mn^{2+} or Na^{+} [126] that might permeate through non-selective cation channels containing TRP subunits. More recently, it has been reported in HeLa cells that calcineurin impairs cytoskeleton remodeling and STIM1/Orai1 puncta-like formation in a KSR-2-dependent manner [127]. Furthermore, in activated T cells, the Rac1 effector protein WAVE2 has been reported to modulate SOCE and STIM1/Orai1 interaction by regulation of actin filament reorganization [128]. Therefore, the participation of the cortical actin cytoskeleton in the modulation of the de novo interaction between STIM1 and Orai1 and, subsequently SOCE, might still be a potential model.

1.3 STIM1, Orai and TRPCs

As we discussed in the previous section, STIM1, originally named GOK, was presented in 2005 as an essential protein involved in the activation of SOCE [80, 81]. The initial studies on STIM1 were published in the mid-1990s, where STIM1 was described as a type-1 transmembrane glycoprotein of 685 amino acids involved in cell-cell interactions in hematopoietic cells [129] and as a cell growth suppressor that plays a pivotal role in the establishment and progression of rhabdomyosarcomas and rhabdoid tumors [130, 131]. Since then, several studies were focused on the study of the structure and function of STIM1 and the determination of the signaling pathways involving STIM1. In 2000, immunofluorescence and cell surface biotinylation analysis revealed that STIM1 is a 90-kDa integral transmembrane phosphoprotein ubiquitously expressed both in the plasma membrane and intracellular membranes of a variety human primary cells, including neonatal foreskin fibroblasts and MG63 osteoblast-like cells, and established tumor cell lines, such as the human leukemic K562, HL60 and U937 cell lines [132]. Later on, the same group demonstrated that the luminal N-terminal region of STIM1 includes an ER signal peptide, EF-hand Ca^{2+}-binding motif, and a single sterile alpha motif (SAM) involved in protein-protein interaction, whereas the cytosolic region consists of two coiled-coil domains, a proline/serine-rich region, and a lysine-rich region [132–134]. These studies also showed that STIM1 is subjected to different post-translational modifications, including phosphorylation on serine residues [133], and N-linked glycosylation in two sites within in the SAM domain [134].

The role of STIM1 in the regulation of SOCE was initially discovered in 2005 by Roos and coworkers [80]. In this study, RNA interference (RNAi)-based screen of more than 170 proteins with known signaling motifs, was designed to identify genes that alter SOCE and the signal pathways controlling them in *Drosophila* S2 cells. With this approach, the *stim* gene and its product, STIM1, were identified as essential regulators of SOCE and CRAC channel activity since RNAi-mediated knockdown of the *stim* gene significantly blocked thapsigargin-induced Ca^{2+} influx in S2 cells. This new promising role of STIM1 was also confirmed in human cells. Suppression of STIM1 expression also significantly reduced thapsigargin-induced SOCE in Jurkat T cells expressing a short RNA hairpin loop (shRNA) targeting human STIM1. Moreover, Ca^{2+} influx was also diminished when STIM1 expression was down-regulated in HEK-293 and SH-SY5Y human cells transfected with STIM1 siRNA [80].

Since STIM1 overexpression in HEK-293 cells was not associated with an increased Ca^{2+} influx and detectable SOCE current, it was proposed that STIM1 could not function as SOC channel itself, and the intraluminal location of the EF-hand motif suggested that STIM1 might act as an ER Ca^{2+} sensor [80]. The report by Roos and coworkers was followed shortly thereafter by two studies from Liou and coworkers [81] and Zhang and coworkers [118]. Cell transfection with a mutated EF-hand motif of STIM1 or *Drosophila* Stim induced a constitutive Ca^{2+} influx mediated by CRAC channels and independent of the filling state of the Ca^{2+}

stores, and treatment with thapsigargin failed to further promote SOCE in HeLa [81], Jurkat and S2 cells [118]. Using different techniques, from immunofluorescence and electron microscopy to surface biotinylation, both studies also demonstrated that, once Ca^{2+} stores are depleted, STIM1 migrates from the ER to the proximity of the plasma membrane. Liou and coworkers first reported that upon store depletion STIM1 redistributes into *punctae* structures, ER regions enriched in STIM1 oligomers and located in close proximity to the plasma membrane [81]. Later on, it was demonstrated that SAM is an essential STIM1 domain for oligomerization and *punctae* formation, while the coiled-coil domains are involved in further stabilization of the STIM1 oligomers and also in functional protein-protein interactions of STIM1 with Ca^{2+} channels located in the plasma membrane [135].

The identification of STIM1 as the intraluminal Ca^{2+} sensor provided an explanation for the communication between the intracellular Ca^{2+} stores and the CRAC/SOC channels located in the plasma membrane, whose identity still remained elusive. In 2006, Orai1 was identified as the pore subunit of the CRAC channels [77, 121, 136–138]. Initially Feske and coworkers [77] and soon thereafter Vig et al. [136] presented Orai1, also named as CRAC modulator 1 (CRACM1), as an essential component regulator of the CRAC channel. Both studies identified *Drosophila* gene *olf186-F* as an essential gene in the activation of thapsigargin-induced SOCE by using a genome-wide RNAi screen in *Drosophila* S2 cells to identify the genes encoding the CRAC channel or other proteins involved in its regulation [77, 136]. The *Drosophila olf186-F* gene has three human homologues that encode the proteins named, for the first time, as Orai1, Orai2 and Orai3 [77]. The term "orai" is referred to the three keepers of heaven's gate in Greek mythology. The gene encoding human Orai1 was mapped on chromosome region 12q24 and was shown to be mutated in the hereditary severe combined immune deficiency (SCID) syndrome patients. Collected T cells from these patients are characterized by an impaired SOCE and CRAC channel activity. This mutation consists in a C→T transition at position 271 of the coding sequence of the human *orai1* gene, leading to replacement of a highly conserved arginine residue by tryptophan at position 91 of the protein (R91W). Expression of an exogenous wild-type Orai1 in SCID T-cells restored store depletion-evoked Ca^{2+} influx, suggesting that this single point mutation R91W in Orai1 sequence was responsible of the defective I_{CRAC}. However, expression of wild-type Orai1 in SCID T-cells did not promote Ca^{2+} influx per se in resting conditions, suggesting that Orai1 is not a Ca^{2+} channel constitutively activated. Furthermore, electrophysiological and pharmacological properties of the restored Ca^{2+} influx current were fully consistent with those observed in I_{CRAC} in normal T cells [77]. According to these results, the selective small interfering RNA (SiRNA)-mediated knockdown of Orai1 reduced both Ca^{2+} influx and I_{CRAC} in response to thapsigargin in human HEK-293 and Jurkat T cells [136]. In addition to the demonstration that Orai1 plays a pivotal role in CRAC current generation, both studies also predicted the topology Orai1 as a membrane protein with four transmembrane domains and cytosolic N- and C- termini, which shows no structural homology to other known ion-channels [77, 136].

Soon after the identification of Orai1 as a the pore forming subunit of the CRAC channel published studies demonstrated the earliest pieces of evidence for the functional interaction between STIM1 and Orai1 in the activation of CRAC currents were reported. Co-expression of STIM1 and Orai1 resulted in a significantly enhanced CRAC current in HEK-293, Jurkat T cells [119, 120, 122] and *Drosophila* S2 cells [139]. The generated current showed Ca^{2+} selectivity, development and inactivation kinetics, pharmacological profiles and biophysical properties indistinguishable from native CRAC current [120, 139].

According to the idea that conserved acidic residues are essential for ion permeation through known Ca^{2+} channels, three simultaneous studies analyzed highly conserved glutamate residues across species and the most interesting results come from the residues E178 and E262 in *Drosophila* and their corresponding human homologues E106 and E190. Mutation of E106 to alanine or glutamine greatly impaired channel function. However, the conservative mutations of E106 to an aspartate (E106D) resulted in a channel with reduced selectivity for Ca^{2+}, thus indicating that this residue functions as part of the selectivity filter, and confirms that Orai1 is a pore forming subunit of the CRAC channel [121, 137, 138]. While mutation of E190 to aspartate or alanine had no significant effect on channel function, the substitution by glutamine (E190Q) resulted in diminished Ca^{2+} selectivity [121, 138]. These studies also demonstrated, for the first time, the STIM1-Orai1 protein interaction upon Ca^{2+} store depletion to initiate CRAC channel activation, by using co-immunoprecipitation in co-transfected HEK-293 cells [138] and *Drosophila* S2 cells [137]. The STIM1/Orai1 complex was reported to be located in the *punctae* region on the plasma membrane after CRAC current activation by fluorescence microscopy [140, 141].

The identification of Orai1 as the pore forming region of the CRAC channel raised the question concerning the architecture of the channel, with reports proposing tetrameric and even higher-order multimeric structures [142–144]. Hou and coworkers [145] reported in 2012 the crystal structure of *Drosophila* Orai channel, which shares 70 % homology with human Orai1. The crystal structure indicates that the pore of *Drosophila* Orai is formed by six subunits, each containing four transmembrane regions (M1 to M4). The transmembrane helices are arranged in three concentric circles around the pore, where the inner ring is formed of six M1 helices, the middle ring consists of M2 and M3 helices and the outer ring is formed of M4 helices located at the periphery of the channel. The side chains of M1 line the pore of Orai, which is composed of four different sections: a selectivity filter formed by a ring of glutamates at the extracellular end of the channel, followed by a hydrophobic section, a basic region spanning near the intracellular side of the channel, which might contribute to the stabilization of the closed state of the channel, and a wider section that extends into the cytosol. The pore region of Orai shows biochemical differences with the known K^+ channels, which emphasizes the distinct mechanisms of ion selectivity and permeation between Orai and K^+ channels.

In addition to the small families of STIM and Orai, another somewhat larger family of ion channels are also linked to SOCE. These are a subfamily of the larger family of TRP channels, called TRPC for classical or canonical TRPs, because it is

comprised of those proteins most highly related to the *Drosophila* TRP channel [146].

The origin of the *Drosophila* TRP goes back to 1969, when Cosens and coworkers identified a spontaneously formed mutant on the basis of a behavioral phenotype [147], but it was not until 1975 that Minke described and named it as "Transient Receptor Potential" (TRP) because of the transient depolarization of the photoreceptors due to Na^+ and Ca^{2+} entry [148]. The identity of the mutated protein was reported in 1989 by Montell and coworkers who cloned, sequenced and presented a molecular characterization of the *Drosophila trp* gen and highlighted its similarity with the Ca^{2+} channels [149]. Later studies characterized TRP and its homologue TRPL as Ca^{2+} permeable channels activated downstream of phospholipase C [150].

After the initial identification of the *Drosophila* TRPs, all the attempts were focused on finding its counterpart in mammals. In 1995, regarding its high homology to the TRP protein sequence, an expressed sequence from a human fetal brain cDNA library was reported by two groups as the first homologue in human (TRPC1) [151, 152]. Since the identification of TRPC1, several mammalian homologues have been described and are classified into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin). In addition, a less related TRPN has been reported in worms and fish and TRPY in fungi [153].

The DNA and corresponding amino acid sequence of the previously called TRPC1, the expression pattern as well as another general features of the novel protein were described by Wes and coworkers and Zhu and coworkers, who characterized it as a polypeptide of 793 amino acids expressed at the highest levels in the fetal brain and in the adult heart, brain, testis and ovaries [151, 152]. The primary structure was supposed to present six transmembrane domains with a pore region between the fifth (S5) and sixth (S6) transmembrane segments and both C and N termini located intracellularly [154]. This structure is shared by all the members of the TRP family. Furthermore, Wes also described that the most highly conserved domain among all TRP family members contains three ankyrin repeats which are thought to play key roles in protein-protein interactions [151, 155]. Later on the whole structure of the protein was reported, with the N-terminus containing three to four ankyrin repeats, a predicted coiled-coil motif and a caveolin binding region. By the way, the citoplasmic C-terminus includes an EWKFAR TRP box, a highly conserved proline rich domain, a coiled-coil motif and a *C*aM/*I*P_3 *r*eceptor *b*inding (CIRB) domain [98, 156]. The presence of coiled-coil domains, commonly involved in subunit oligomerization suggest that they are probably involved in homo-and heteromerization of TRPCs or in linking TRPCs to other proteins also containing coiled-coil domains [157, 158].

Despite the key role of TRPs in receptor-operated Ca^{2+} entry (ROCE) and in SOCE has been reported in different cell types, the latter has been a matter of intense debate, and the role of TRPCs in SOCE has not been demonstrated in all the cellular models investigated. Among the first pieces of evidence for a role of TRPC1 in SOCE comes from a study made in Chinese hamster ovary cells (CHO), where expression of TRPC1A, a splice variant of TRPC1, resulted in a linear nonselective

cation current with similar permeabilities for Na^+, Ca^{2+}, and Cs^+, activated by intracellular infusion of either IP_3 or thapsigargin to deplete intracellular Ca^{2+} stores [159]. At the same time, Zhu and coworkers demonstrated that expression in COS cells of full-length cDNA encoding human TRPC1 increased SOCE while expression of antisense sequences suppressed it [160]. Further evidence supporting the role of TRPC1 in SOCE comes from studies based on overexpression of TRPC1 proteins or knockdown of the endogenous TRPC1 channels in several cell types, including human cells. In human submandibular gland cells and vascular endothelial cells, the overexpression of TRPC1 increased SOCE while the silencing of the endogenous protein by using antisense oligonucleotides reduced thapsigargin-evoked influx [161, 162]. In general, the key role of TRPC1 in SOCE has been supported by several research groups by means of different experimental maneuvers in many cell types, such as DT40-B-lymphocytes, endothelial cells, rat cardiac myocytes, the human megakaryoblastic cell line MEG01, the C2C12 mouse myoblastic cell line, rat kidney fibroblasts or human platelets [162–166]. Other members of the TRPC family have also been reported to be activated by store depletion or to be involved in SOCE both in excitable and non-excitable cells. For instance, the transient expression of the full length cDNA of mouse TRPC2, the homologue of the human *trp2* pseudogene, was reported to evoke a Ca^{2+} entry that was shown to be readily activated not only after agonist stimulation but also by store depletion in the absence of an agonist [167]. In addition, in 1996 Zhu and coworkers observed that the heterologous expression of the human TRPC3 in COS cells enhanced SOCE [160] and similar results were obtained by Boulay and coworkers by expressing the murine TRPC6 in this cells [168]. Over the years, some studies have highlighted that there is also a growing body of evidence supporting a role of TRPC6 in the conduction of SOCE in different cells [169, 170].

Nevertheless, several studies have failed to observe store-operated behavior of exogenously expressed TRPC channels in different cell types, thus demonstrating that TRPCs did not account for SOCE in all cellular models investigated [171]. Moreover, the mode of expression of TRPCs might determine its involvement in SOCE or ROCE in the same cell type, as it was reported by Lievremont and coworkers in 2004, who described that TRPC7 activation mode was different in cells transiently or stably expressing this channel [172].

With the identification of STIM1 and Orai1 as the key molecular players of CRAC currents, most studies focused on the possible interaction between these proteins and TRPC channels. In 2006, after Spassova and coworkers confirmed the crucial functional role of STIM1 over the regulation of SOC channels by using electrophysiological analysis [173], two independent studies demonstrated for the first time that STIM1 is associated with TRPC1, in the plasma membrane upon Ca^{2+} store depletion, and that the STIM1-TRPC1 interaction promotes channel activation and SOCE [174, 175]. In HEK-293 cells expressing exogenous STIM1, Ca^{2+} store depletion increased the association between STIM1 and TRPC1, while the expression of the EF-hand mutant STIM1 yield a constitutive STIM1-TRPC1 complex formation and subsequent TRPC1 activation and Ca^{2+} influx [174]. According to this, electrotransjection of human platelets with anti-STIM1 antibody, directed

toward the EF-hand Ca^{2+}-binding motif, prevented the migration of STIM1 toward the plasma membrane, the interaction between endogenously expressed STIM1 and TRPC1 and reduced SOCE [175]. Functional interaction between STIM1 and TRPC1 has also been reported, among others cellular types, in intestinal epithelial cells [176], salivary and pancreatic acinar cells [79, 177], pulmonary artery cells [178] or messanglial cells [179].

STIM1 also interacts directly with other members of TRPC family involved in SOCE, such as TRPC4 and TRPC5 in HEK293 cells [180] and TRPC6 in human platelets [24], regulating their activation. STIM1 also indirectly regulates TRPC3 and TRPC6 by mediating the heteromultimerization of TRPC3 with TRPC1 and TRPC4 with TRPC6 [180]. Direct STIM1/TRPC interaction has been reported to require interaction of the STIM1 SOAR region with the TRPC C-terminal coiled-coil domains, as well as electrostatic interactions involving the lysine-rich domain of STIM1 [181, 182]. This association is supported by the actin cytoskeleton [175] and plasma membrane lipid rafts domains [183–185].

In addition to the STIM1-TRPC coupling previously described, there is a body of evidence supporting the formation of ternary complexes among the three main elements involved in SOCE, STIM, Orai and TRPCs. In HEK293 cells, SOCs were reported to be built by TRPC pore-forming subunits and Orai regulatory subunits that transduce the Ca^{2+} store depletion signal from STIM1 to TRPCs [186]. Supporting this hypothesis, a dynamic assembly among STIM1, Orai1 and TRPC1 has been proposed to be essential for SOCE in human salivary gland cells [187] and human platelets [123]. Interestingly, the association of these proteins has been reported to occur in specific plasma membrane microdomains known as lipid rafts which provide the adequate environment for the formation of the store-operated Ca^{2+} influx complex (SOCIC) or receptor-operated Ca^{2+} entry complexes [184, 185]. The following chapters will highlight recent advances in the Ca^{2+} entry mechanisms, involving store-operated and receptor-operated signaling pathways, in non-excitable cells.

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