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REVIEW ARTICLE

Role of Orai-family channels in the activation and regulation of transcriptional activity

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Abstract

Store operated Ca^{2+} entry (SOCE) is a cornerstone for the maintenance of intracellular Ca^{2+} homeostasis and the regulation of a variety of cellular functions. SOCE is mediated by STIM and Orai proteins following the activation of inositol 1,4,5-trisphosphate receptors. Then, a reduction of the endoplasmic reticulum intraluminal Ca^{2+} concentration is sensed by STIM proteins, which undergo a conformational change and activate plasma membrane Ca^{2+} channels comprised by Orai proteins. STIM1/Orai-mediated Ca^{2+} signals are finely regulated and modulate the activity of different transcription factors, including certain isoforms of the nuclear factor of activated T-cells, the cAMP-response element binding protein, the nuclear factor κ-light chain-enhancer of activated B cells, c-fos, and c-myc. These transcription factors associate SOCE with a plethora of signaling events and cellular functions. Here we provide an overview of the current knowledge about the role of Orai channels in the regulation of transcription factors through Ca^{2+}-dependent signaling pathways.

KEYWORDS

calcium signaling, CRAC channels, NFAT, Orai, SOCE, transcription factor

1 | INTRODUCTION TO ORAI CHANNELS

Ca^{2+} is a ubiquitous second messenger that operates over a wide temporal range to control a myriad of cellular events. To support this role, resting cells largely exclude Ca^{2+} from the cytosol maintaining a 20,000-fold gradient between the intracellular medium, the extracellular space and the internal Ca^{2+} stores, which are mainly formed by the endoplasmic reticulum (ER). Then, cell stimulation encodes a diversity of Ca^{2+} signals triggering the release of Ca^{2+} from internal stores, the entry of Ca^{2+} from the extracellular milieu or by regulating the activity of Ca^{2+}-ATPases and exchangers. Store operated Ca^{2+} entry (SOCE) is a widespread mechanism that maintains the intracellular Ca^{2+} homeostasis and plays key roles in gene transcription, cell proliferation, immune response, and memory formation among others (Emrich et al., 2022). SOCE is mediated by STIM and Orai protein families following Ca^{2+} stores depletion. STIM1 and STIM2 are single pass transmembrane (TM) proteins which sense the reticular Ca^{2+} concentration by their luminal EF-hand domains. When cell stimulation reduces the ER Ca^{2+} content, the luminal domain of these proteins unleashes a conformational change which favors the oligomerization of STIM proteins and their translocation into puncta clusters in the ER-plasma membrane (PM) junctions. Here, STIM molecules induce a Ca^{2+} influx from the extracellular milieu

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by opening Ca^{2+} release-activated Ca^{2+} (CRAC) channels formed by Orai proteins (Gudlur et al., 2018; Lunz et al., 2019). Although both STIM homologs can activate Orai channels they do not play redundant roles. STIM1 activates CRAC channels faster and more effectively, and therefore, it is considered the primary regulator of the CRAC channels after cell stimulation. By contrast, due to its lower Ca^{2+} affinity, STIM2 is activated under modest Ca^{2+} store depletions, playing a major role in preserving the resting Ca^{2+} levels and recruiting STIM1 under low stimulus intensity (Ahmad et al., 2022; Bird et al., 2009).

Orai family consists of three tetraspanning PM proteins (Orai1, Orai2, and Orai3) with their amino and carboxyl termini located in the cytosol (Figure 1). Orai1 was first described by Feske et al. in 2006 as the mutated gene responsible for the severe combined immunodeficiency. These authors proposed Orai1 as the molecular subunit of CRAC channels, underestimating the influence of Orai2 and Orai3 in the physiological roles of SOCE (Feske et al., 2006; Prakriya et al., 2006). However, this first model, which only considered STIM1 and Orai1, failed to replicate some of the properties of native CRAC currents, suggesting that this hypothesis must be honed with the inclusion of other proteins (Hoth & Niemeyer, 2013). The research about the molecular mediators of SOCE was boosted in 2012 with the resolution of the crystal structure of Orai from *Drosophila melanogaster*. The CRAC channel was described as an hexameric complex where the first TM domains line the ion permeation pathway and the remaining TM describe concentric rings around the pore (Hou et al., 2012) (Figure 1). This information has promoted our understanding about how CRAC channels are activated, event that requires the interaction between the C-terminal coiled coil domains of STIM and the three major cytosolic domains of Orai1 (N- and C-terminal regions and the intracellular loop) (Lunz et al., 2019). Upon activation, CRAC channels display a highly selective Ca^{2+} current, with a reversal potential of +60 mV that exhibits two inhibitory mechanisms: a fast Ca^{2+} dependent inactivation (CDI) that arises over milliseconds and is activated by the bulk of Ca^{2+} near the pore and a slow CDI, which depends on global rises in the cytosolic Ca^{2+} concentration and develops over tens of seconds (Mullins et al., 2009; Palty et al., 2012; Parekh, 2017).

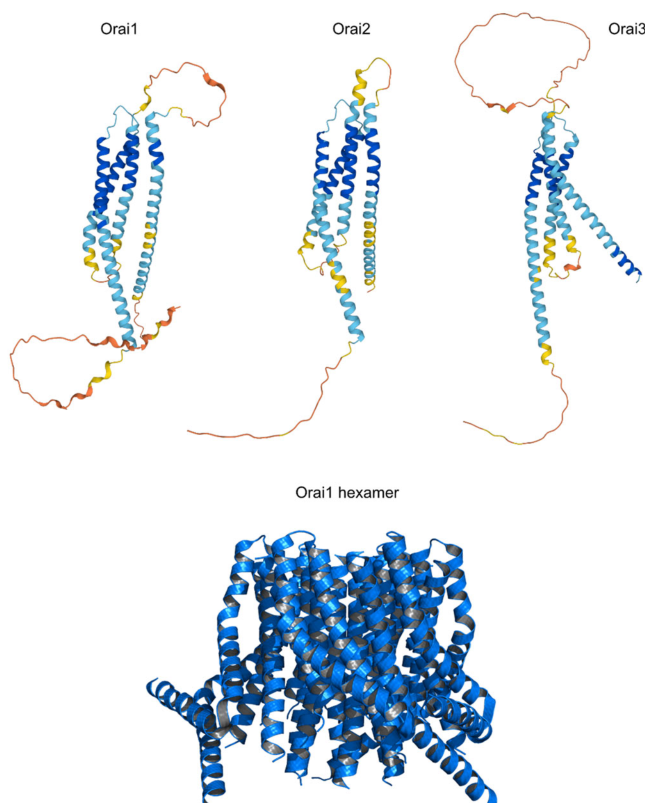

FIGURE 1 Orai protein structure. Orai family protein comprises three members that contain four transmembrane (TM) domains each and place their amino and carboxyl termini in the cytosol. Although the three proteins present a high homology in the TM segments, their sequence clearly differ in the extracellular loop and cytosolic regions (N and C-terminal domains and the intracellular loop) (Jumper et al., 2021; Varadi et al., 2022). CRAC channels exhibit a hexameric structure with the pore flanked by the first TM domains of the Orai subunits. CRAC, Ca^{2+} release-activated Ca^{2+}.

During the last few years, it has been proposed that CRAC channels are formed by the hexameric association of Orai1, Orai2, and Orai3 (Vaeth, Yang et al., 2017; Yoast et al., 2020). All three proteins form functional CRAC channel when ectopically expressed with STIM1, although they display slightly different biophysical and pharmacological properties (Zhang et al., 2020). CRAC currents mediated by Orai1 are larger than those mediated by Orai2 and Orai3, disparity explained by the fact that Orai proteins are not equally sensitive to CDI. Interestingly, Orai2 and Orai3 currents display a larger fast CDI, while Orai1 is more sensitive to slow CDI (DeHaven et al., 2007; Lis et al., 2007). In the model recently proposed, Orai2 and Orai3 are also involved in native CRAC channels, and the architecture of the pore would be influenced by the expression level of each Orai homolog. Then, in a heteromeric channel, the integration of Orai2 and Orai3 negatively regulates Orai1 function and adjust Ca^{2+} signals to the intensity of agonist stimulation (Vaeth, Yang et al., 2017; Yoast et al., 2020). Conversely, in cells where Orai2 or Orai3 protein expression dominates over the other member of the family these proteins became the major mediator of SOCE (Motiani et al., 2010).

By alternative translation initiation, Orai1 mRNA gives rise to two Orai1 forms: the full-length Orai1α contains 301 amino acids and the shorter variant, Orai1β, lacks the N-terminal 63 amino acids upstream the conserved start site (Desai et al., 2015; Fukushima et al., 2012). Both Orai1 variants can mediate I_{CRAC} currents and the alternative capacitative current $I_{SOC,}$ involving TRPC1 and Orai1 (Desai et al., 2015); however, the additional N-terminal sequence found in Orai1α supports some functional differences between isoforms. Upon channel activation, phosphorylation of Ser27 and Ser30, by protein kinase C (PKC), and Ser34, by protein kinase A (PKA), inhibits Orai1α channel activity (Kawasaki et al., 2010; Martínez-Martínez et al., 2022; Zhang et al., 2019). These serine residues are not present in Orai1β, making this variant less sensitive to phosphorylation-dependent channel inactivation. Within the same domain, Orai1α also contains an interacting sequence

(residues 23–34) with the Ca^{2+}-activated adenylyl cyclase 8 (AC8). AC8-Orai1α interaction was described by Cooper and coworkers as a linkage between Ca^{2+} and cAMP signaling pathways (Martin et al., 2009; Willoughby et al., 2012). However, Zhang et al. refined this model by suggesting that the interaction between AC8 and Orai1α also supports PKA-evoked Orai1α inactivation by Ser34 phosphorylation. Besides these domains, Orai1α N-terminus hosts a predicted PIP2 binding sequence (residues 28–33), a binding site for the scaffolding protein A-kinase anchoring protein 79 (AKAP79) (residues 39–59), known as AKAP association region (AKAR), and a caveolin binding domain (residues 52–60) (Kar, Lin et al., 2021; Zhang et al., 2019). Although the current model for CRAC channels proposes a heteromultimeric structure formed by the combination of all Orai family members, there is no evidence supporting the multimerization of Orai1 variants. Contrary, the analysis of Orai1α and Orai1β PM mobility suggests that these proteins could be assembled in different channels pools, a topic that awaits further investigations (Desai et al., 2015).

In addition to store-operated channels, Orai1 and Orai3 have been proposed as the pore forming subunits of a store-independent Ca^{2+} channel that is activated in response to arachidonic acid (AA), the so called arachidonate-regulated Ca^{2+} (ARC) channels (Mignen et al., 2008; J. Thompson et al., 2010). Desai et al. (2015) have demonstrated that only Orai1α overexpression rescue AA-induced Ca^{2+} entry in cells where native Orai1 expression had been silenced, suggesting that Orai1α mediates this signaling event and supporting that both Orai1 variants do not play redundant roles. Concerning the functional roles of Orai1 isoforms, our group has recently reported that Orai1α mediates I_{SOC} currents in HeLa cells. In these cells, Orai1α modulates TRPC1 PM expression and channel function after agonist stimulation, roles that are absent in the short variant of Orai1 (Sanchez-Collado et al., 2022), suggesting that the role of the Orai1 variants in the activation of I_{SOC} might be cell specific. These data reveal that the generation of two Orai1 variants increases the versatility and diversity of Orai Ca^{2+} signals, making this protein family a precise switch for downstream cellular events.

As it has been previously mentioned, CRAC channels regulate gene expression by modulating the activity of a variety of Ca^{2+} dependent transcription factors. This function was initially found to be involved in the mediation of immunity and inflammatory responses; however, several studies have lately reported the role of Orai channels in genetic programming during myogenesis, cell cycle progression, cell proliferation and, after the influence of an oncogenic factor, the development of some cancer hallmarks. The nuclear factor of activated T cells (NFAT) family is the best characterized Orai-dependent transcription factor although others like NF-κB, c-myc, myocyte enhancer factor 2 (MEF2), or c-fos have been extensively associated to Orai channels. Herein, we summarize how Orai-mediated Ca^{2+} signals orchestrate a wide variety of cellular functions by tunning the activity of the above introduced transcription factors.

2 | NFAT

The mammalian NFAT family comprises five members including NFAT1, NFAT2, NFAT3, NFAT4, and NFAT5. Originally, the NFAT family was identified in immune cells, in which the role of these transcription factors in the activation, differentiation, and development of T-cells has been widely demonstrated (Mognol et al., 2016; Oh-hora & Rao, 2009). However, it is known that all members are ubiquitously expressed in a wide range of cells and tissue types, demonstrating their involvement in many cellular processes including osteoclastogenesis (Zhao et al., 2010), chondrogenesis (Tomita et al., 2002), differentiation of cardiac muscle cells (Chen & Cao, 2009), angiogenesis (Suehiro et al., 2014), myogenesis (Armand et al., 2008), or cardiac valve formation (Ranger et al., 1998). Deregulation of NFAT signaling is related with the pathogenesis and progression of many diseases including, among others, diabetes (Cai et al., 2021), autoimmune disorders (Park et al., 2020), atherosclerosis (Cai et al., 2021), inflammatory diseases (Pan et al., 2013), and cancer (Mognol et al., 2016), in which NFAT1 and NFAT2 act as oncogenes, although it has also been demonstrated that NFAT1 might be a tumor suppressor gene depending on the cell type (Mognol et al., 2016).

Four of the five members that comprises the NFAT family (NFAT1–4) are activated by rises in cytoplasmic free-Ca^{2+} concentration (Hogan et al., 2003; Vaeth, Maus et al., 2017), and it is well stablished that SOCE is the main source of Ca^{2+} to support the activation of NFATs after agonist stimulation (Kar & Parekh, 2015; Lin et al., 2019; Yoast et al., 2020; Zhang et al., 2019). In resting state, NFAT proteins are in a phosphorylated status that targeted them to the cell cytoplasm, but upon agonist-induced SOCE, NFAT proteins are dephosphorylated by a mechanism involving the Ca^{2+}/calmodulin (CaM)-dependent serine phosphatase calcineurin, promoting the exposition of the NFAT nuclear localization sequence and, subsequently, its nuclear translocation and activation (Figure 2) (Hogan et al., 2003; Kar & Parekh, 2015). The magnitude and selectivity of the activation of each NFAT isoform is matched to the amount of SOCE induced by a broad physiological range of agonist concentrations (Kar & Parekh, 2015; Yoast et al., 2020). Lastly, the activation of NFAT5, the other member of the family, is induced by osmotic stress and not by increases in cytosolic Ca^{2+} concentration (Kumar et al., 2020; Lee et al., 2019).

2.1 | NFAT1

NFAT1, also known as NFATp or NFATc2, has been described as a crucial regulator of the apoptotic signaling pathway mediating cell cycle arrest and cell death (Zhang et al., 2019). In the last decade, numerous articles have demonstrated the role of Orai1 in the induction of NFAT1 nuclear translocation and transcriptional activity (Kar, Lin et al., 2021; Kar et al., 2014; Robitaille et al., 2022; Son et al., 2020; Zhang et al., 2019). Interestingly, two alternative hypotheses try to explain how Orai1 activates NFAT1. The first model, described by Kar et al., suggests that Orai1 activation and the subsequent rise

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FIGURE 2 Cartoon summarizing the activation of transcription factors by Orai-forming channels. AC, adenylyl cyclase; ARC/LCT, arachidonic acid/leukotriene C4-activated channels; CaM, Ca^{2+}/calmodulin; CaMK, Ca^{2+}/calmodulin kinase; CREB, cAMP response element-binding protein; EGR-1, early growth response protein-1; IκB, inhibitor of nuclear factor kappa B; IKK, inase; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MEF-2, myocyte enhancer factor-2; NEMO, NF-κB essential modulator; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor-kappa B; PKA, protein kinase A; PKC, protein kinase C; SOCE, store-operated Ca^{2+} entry.

of the Ca^{2+} concentration near the channel trigger the interaction between AKAP79 and the AKAR region of Orai1. AKAP79 binds both calcineurin and NFAT1 leading the calcineurin-dependent NFAT1 dephosphorylation and the subsequent nuclear translocation and activation of transcription (Kar, Lin et al., 2021; Kar et al., 2014). Recently, it has been described that this mechanism requires of STIM2, which targets Orai1/STIM1 complexes to ER-PM junctions, a region where peripheral ER juxtaposes the PM and Ca^{2+} influx occurs (Son et al., 2020). The use of different N-terminal deletion mutants of Orai1 demonstrated that AKAR region comprises the N-terminal amino acids 39–59, which is not present in other Orai family members. Regarding the two Orai1 variants recently identified, AKAR region is present in the full-length Orai1α, but not in Orai1β variant. Nevertheless, the role of Orai1 variants in NFAT1 activation is

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controversial. A role for Orai1α, but not Orai1β, in the activation of NFAT1 after thapsigargin-induced SOCE has been reported by the expression of each Orai1 variant in HEK293 cells in which Orai1 expression was previously reduced by a siRNA or following *Orai* genes (*Orai1*, *2*, *and 3*) knocked out using CRISPR-Cas9 gene edition (Kar, Lin et al., 2021). Conversely, an alternative hypothesis proposed by Zhang et al. suggests that NFAT1 activation requires a large Ca^{2+} entry through Orai1. In this model, both Orai1 variants can equally support NFAT1 nuclear translocation after cell treatment with thapsigargin or with high concentrations of carbachol in HEK-293 cells. These authors suggest that the ability of Orai1β to drive NFAT1 activation is explained by its ability to drive a robust rise in the cytosolic Ca^{2+} concentration, because of the absence of Ser34 and its reduced CDI. The molecular basis described for this mechanism involve the Ca^{2+}/calmodulin-AC8, which can interact with the N-terminal amino acids 23–34 of Orai1, a sequence lacking in Orai1β variant. After SOCE activation, Ca^{2+} influx across Orai1 channel promotes AC8 activation and the subsequent generation of cAMP and PKA activation. By its interaction with AKAP79, PKA mediates Orai1 phosphorylation at Ser34 to induce CDI (Zhang et al., 2019). Interestingly, this mechanism is dampened in breast cancer cells. The AC8 overexpression observed in these cells enhances the pool of Orai1α associated with AC8, impairing the phosphorylation at Ser34 and Orai1α inactivation since this residue overlaps with the AC8-binding site. Consequently, SOCE is enhanced and supports the development of a variety of cancer hallmarks, including proliferation and migration (Sanchez-Collado et al., 2019; Sanchez-Collado, Lopez, Jardin et al., 2021; Sanchez-Collado, Lopez, & Rosado, 2021). However, Kar et al. have not detected protein expression or functional activity of AC8 or any other Ca^{2+}/CaM-activated adenylyl cyclase in HEK-293 cells and proposed an alternative PKA function that involves the association of AKAP79 with adenylyl cyclase 6 (AC6). Contrary to what happens with AC8, high increments in cytosolic Ca^{2+} concentration promoted by Ca^{2+} entry through store-operated channels reduce AC6 activity (Kar, Barak et al., 2021; Sanchez-Collado, Lopez, Jardin et al., 2021). Hence, in resting conditions, the AKAP79-AC6-PKA complex would maintain NFAT in a nonactivated state since it is phosphorylated by PKA at three serine residues, avoiding its calcineurin-mediated dephosphorylation and activation. After SOCE activation, this mechanism would be turn off due to AC6 inhibition, leading the NFAT dephosphorylation (Kar, Barak et al., 2021).

About the other members of Orai family, two different groups have proposed that neither Orai2 nor Orai3 are able to induce NFAT1 nuclear translocation and activation, supporting a major role of Orai1 for NFAT signaling. Kar et al. (2014) demonstrated that Orai3 failed to induce NFAT nuclear translocation and activation since AKAP79 cannot be recruited by Orai3. According to that, carbachol-induced NFAT1 nuclear translocation was strongly abolished in genetically modified HEK-293 cells in which Orai1 gene was knocked out using CRISPR-Cas9 gene editing compared with parental wild-type cells. Consistent with this, Trebak and coworkers showed that NFAT1 nuclear translocation resulted to be higher and faster in HEK-293 cells in which Orai2 or/and Orai3 expression were knocked out, suggesting that only Orai1 can mediate the large rise in cytosolic Ca^{2+} required for NFAT1 translocation and activation, while Orai2 and Orai3 act as negative modulators of Orai1 activity, matching the magnitude of Ca^{2+} signals to stimulation with high or low agonist concentration to fine tune NFAT1 activation (Emrich et al., 2021; Yoast et al., 2020). This regulatory role of Orai2 and Orai3 in NFAT1 activation in response to agonist were confirmed in two recent studies. In breast cancer cells, Orai2 expression varies according to the cell type. Thus, Orai2 expression is high in the triple negative breast cancer cell line BT20 and in the HER2 positive SKBR3 cells, while its expression is residual in the estrogen receptor positive (ER+) breast cancer cell line T47D. Knockdown of Orai2 expression in SKBR3 and BT20 cell lines, using a specific siRNA, increases the magnitude of agonist-induced SOCE and changes the pattern of Ca^{2+} responses from Ca^{2+} oscillations to plateaus. Consequently, these cells lose the ability to discriminate between low and high concentrations of agonist and NFAT1 nuclear translocation is enhanced after cell stimulation (Sanchez-Collado, Lopez et al., 2021). Otherwise, in primary lung fibroblast isolated from mice with pulmonary fibrosis, the attenuation of Orai3 expression, using a specific siRNA, decreased the TGF-β1-induced nuclear translocation of NFAT1. This effect is explained by a remodeling of the Orai channels due to an increase in Orai3 expression. Orai1 and Orai3 can form heteromultimeric channels that support both SOCE and AA-regulated store-independent Ca^{2+}entry. Hence, Orai3 overexpression in activated lung fibroblast leads to the formation of store-independent AA-regulated channels to detriment of SOC channels, with the consequent decrease in the magnitude of SOCE. This remodeling promotes and ensures a large extracellular Ca^{2+} influx responsible for NFAT1 activation, fibroblast proliferation, and pulmonary fibrosis development (Yu et al., 2022).

2.2 | NFAT2

The pivotal role of Orai1, but not Orai2 and Orai3, in the activation of NFAT2 (also known as NFATc, NFATc1) has been extensively demonstrated by using pharmacological or gene mutation approaches to inhibit channel function, or by gene silencing approaches to avoid protein expression (Carreras-Sureda et al., 2021; Choi et al., 2018; Hwang & Putney, 2012; Jans et al., 2013; Wang et al., 2022; Zhou et al., 2014). Hence, specific siRNA against Orai1 or the overexpression of the dominant-negative mutant Orai1R91W were used to demonstrate that Orai1-mediated Ca^{2+} entry promotes nuclear translocation and enhances transcriptional activity of NFAT2 after lysophosphatidic acid-induced SOCE in keratinocytes (Jans et al., 2013). Similar results were obtained in human umbilical vein endothelial cells (HUVEC) when Orai1 activity was impaired by overexpression of the dominant-negative mutants Orai1R91W or Orai1E106A. In these cells, histamine treatment failed to promote SOCE activation and NFAT2 nuclear translocation, events required for interleukine-8 (IL-8) secretion and the inflammatory response

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(Zhou et al., 2014). Furthermore, the attenuation of Orai1 activity or expression in HUVEC cells, using the Orai1 channel inhibitor BTP2 or a specific siRNA against Orai1 respectively, also impaired NFAT2 nuclear translocation and transcriptional activity, compromising cell migration, and proliferation (Wang et al., 2022). The role of Orai1 in NFAT2 activation was also demonstrated by the generation of Orai1 knock-out (Orai1KO) Jurkat cells using CRISPR-mediated gene editing. In Orai1KO cells, treatment with thapsigargin failed to induce NFAT2 nuclear translocation and activation, an event required for T cell activation. As expected, Orai1 overexpression was able to rescue thapsigargin-induced NFAT2 nuclear translocation and activation in these cells. Interestingly, overexpression of a S-acylation-deficient mutant of Orai1 (Orai1C143A) did not rescue thapsigargin-induced SOCE and NFAT2 nuclear translocation and activation, suggesting that the S-acylation of Orai1 at Cys-143 is required for channel function (Carreras-Sureda et al., 2021). NFAT2 nuclear translocation and transcriptional activity have been also shown to be required for bone remodeling, including bone formation by osteoblasts and bone resorption by osteoclasts. So, phorbol-12-myristate-13-acetate (PMA) and ionomycin-induced NFAT2 nuclear translocation and activation have been shown to be reduced in primary osteoblasts isolated from Orai1KO mice, resulting in a deficient differentiation and cell proliferation (Choi et al., 2018). Moreover, Orai1 knockdown using a specific shRNA in mouse monocyte/macrophage-like RAW264.7 cells, reduced receptor activator of nuclear factor-κB ligand (RANKL)-induced NFAT2 activation required for osteoclast formation (Hwang & Putney, 2012). Finally, in patients with generalized vitiligo, a reduced intracellular Ca^{2+} concentration and Orai1 transcripts levels have been linked to a decrease in extracellular Ca^{2+} uptake in regulatory T-cells. As consequence, these cells showed a defective calcineurin and NFAT2 activation, with the subsequent decrease in immunosuppressive response. Ca^{2+} treatment of these cells significantly increased intracellular Ca^{2+} and Orai1 transcripts and restores calcineurin and NFAT2 activity (Giri et al., 2022).

2.3 | NFAT4

Although a reduced number of studies have addressed the topic, there is a wide agreement about the role of CRAC channels in the activation NFAT4 (also known as NFATx or NFATc3). This signaling pathway is involved in cellular functions like myogenesis, cell proliferation and secretion as well as in the regulation of oncogenic genes (Kim et al., 2019; Liu et al., 2018; Robbs et al., 2008; Srikanth et al., 2017). However, the physiological conditions that mediate this event is the subject of an intense scientific debate. Yoast and coworkers have reported that NFAT4 nuclear translocation is mediated by discrete rises in cytosolic Ca^{2+} concentration following stimulation with low agonists concentrations. Furthermore, these authors described Orai1 as the unique CRAC channel member that supports NFAT4 nuclear translocation, meanwhile Orai2 or Orai3 play a regulatory role in the activation of NFAT4 by shaping the Ca^{2+} signals evoked by the channels (Yoast et al., 2020). Interestingly, due to its lower sensibility to CDI mechanism, Orai1β shows a greater capacity to trigger NFAT4 nuclear translocation as compared to the longer Orai1 variant, Orai1α (Zhang et al., 2019). By contrast, Kar et al. have proposed that NFAT4 activation and nuclear translocation are not mediated by low agonist concentrations and require a strong cell stimulation (Kar & Parekh, 2015). Although both groups described that NFAT4 nuclear translocation is faster than that observed for NFAT1, Parekh and coworkers proposed that NFAT4 nuclear accumulation and transcriptional activity demands for intense stimuli which induce a large Ca^{2+} entry and the rise of nuclear Ca^{2+} concentration. This Ca^{2+} dependent regulatory mechanism is mediated by the translocation of calcineurin into the nucleus, where it would counterbalance NFAT4 phosphorylation, its main inhibitory mechanism (Kar & Parekh, 2015).

2.4 | NFAT3 and NFAT5

Regarding the other members of NFAT family, NFAT3 and NFAT5 (also known as NFATc4 and TonEBP, respectively), the role of Orai proteins in their activation has not been extensively studied and demonstrated. STIM1-Orai1 mediated SOCE induces NFAT3 activation and initiates signaling pathways involved in the hypertrophic growth of cardiomyocytes (Lu et al., 2017). No evidence has been shown on the involvement of Orai proteins in the activation of NFAT5, since this member lacks calcineurin docking sites which are required for the Ca^{2+} dependent nuclear translocation and activation (Lee et al., 2019). However, it has been demonstrated that NFAT5 activation promotes an increase in the expression of the serum-glucocorticoid-inducible kinase 1 (SGK1), which is responsible for an increase of Orai1 and Orai2 expression (Sahu et al., 2017).

3 | cAMP-RESPONSE ELEMENT BINDING PROTEIN (CREB)

CREB is a ubiquitous protein which was first described in 1987 as a key cAMP-responsive transcription factor regulating somatostatin gene expression (Montminy & Bilezikjian, 1987). CREB belongs to the region-leucine zipper family of transcription factors which is also comprised by CREM (cAMP-response element modulator) and ATF-1 (activation of transcription factor-1) (Pearce et al., 2017). In resting cells, CREB is located inside the nucleus and has no transcriptional activity. Upon cell stimulation, signaling pathways such as Ca^{2+}/CaM, Ras/MAPK, or even an increase of cAMP concentration, mediate the phosphorylation of CREB at Ser-133 and its subsequent activation (Pearce et al., 2017; Purves, 2004; Sheng et al., 1991; West et al., 2001). After its phosphorylation, CREB forms homo or heterodimers and binds to its DNA binding site, known as CRE (c-AMP response element), mediating gene expression and controlling several cell functions, mainly in brain tissue (Figure 2) (Purves, 2004).

Many authors have described SOCE as a powerful CREB activator. Hence, following cell stimulation, CRAC channels opening

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leads to the interaction of Ca^{2+}-CaM, which, in turn, causes autophosphorylation and activation of different calmodulin kinase (CaMK) subtypes that undergo nuclear translocation and phosphorylate CREB at Ser-133 (Bito et al., 1996; Ho et al., 2000; Purves, 2004; Simo-Cheyou et al., 2017). Simultaneously, SOCE impairment either using cell treatment with 2-aminoethoxydiphenyl borate (2-APB), silencing STIM1 and Orai1 gene expression, or overexpressing Orai1 dominant negative mutants induced the inhibition of CREB transcriptional activity (Rodríguez-Moyano et al., 2013; Shanmughapriya et al., 2015; Simo-Cheyou et al., 2017).

Alternatively, as mentioned above, CREB might be activated by the MAPK/ERK pathway in a SOCE-dependent manner. Some studies have demonstrated that SOCE mediates CREB phosphorylation through the activation of different PKC subtypes after Ca^{2+} entry through Orai1, which, in turn, triggers MAPK/ERK-mediated CREB phosphorylation. Thus, SOCE blocking agents have been shown to reduce ERK1/2 phosphorylation and CREB activation (Pulver-Kaste et al., 2006; Soltoff & Lannon, 2013). Simo-Cheyou and coworkers have described the involvement of STIM1-Orai signaling mechanism in the modulation of Early growth response protein-1 (Egr-1) expression in vascular smooth muscle cells (VSMCs). These authors suggest that the expression and transcriptional activity of Egr-1 is promoted by the previous activation of ERK1/2 and CREB phosphorylation, a signaling pathway that mediates the vasoactive effects of angiotensin II (Simo-Cheyou et al., 2017).

Furthermore, Orai1 could influence CREB-mediated gene transcription through its interaction with several subtypes of Ca^{2+}-dependent adenylate cyclase (AC), such as AC1, AC8, and AC10 (Parker et al., 2019; Sanchez-Collado, Lopez, Jardin et al., 2021). The activation of these ACs is mediated by a Ca^{2+}/CaM-dependent conformational change that triggers an increase of intracellular cAMP and activates PKA. This kinase, besides mediating Orai1 CDI (Hofer, 2019; Zhang et al., 2019), can enter the nucleus and activate CREB transcriptional activity by its phosphorylation at Ser-133.

4 | NF-KB

NF-κB is a dimeric transcription factor, formed mainly by heterodimers of p50/p65, first described in 1986 as a transcription factor capable to interact with the κ-immunoglobulin (Igκ) light chain gene enhancer in B cells (Sen & Baltimore, 1986b). Its transcriptional activity can be triggered by many extracellular signals, like TNF-α, IL-1β, or lipopolysaccharides, and has a pivotal role in the transcription of several genes involved in the inflammatory response (Karin & Ben-Neriah, 2000; Nelson et al., 2004; Sen & Baltimore, 1986a; Siebenlist et al., 1994). These genes include proinflammatory cytokines and chemokines (TNF-α, IL-6, IL-8, etc.), enzymes (COX2, iNOS, etc.), adhesion molecules (ICAM-1 or E-selectin, among others), receptors (IL2R, T-cell receptor, MHC-I/II, etc.), growth factors (M-CSF, TGF-β2, GM-CSF, G-CSF, etc.), and transcription factors and regulators (Baeuerle & Baichwal, 1997; Barnes & Karin, 1997; Siebenlist et al., 1994). To play this role, it is necessary for the complex to be activated and translocated to the nucleus because, at resting state, NF-κB remains at the cytoplasm binding its inhibitory proteins IκBs. The canonical activation pathway of NF-κB requires the proteolytic degradation of IκB by the IκB kinase (IKK), formed by IKKα, IKKβ, and the regulatory protein NEMO (NF-KB essential modifier), which mediated IκB phosphorylation at Ser-32 and Ser-36 and also phosphorylates NF-κB at Ser-536 (DiDonato et al., 1997; May et al., 2000; Nelson et al., 2004). Subsequently, IκB undergoes ubiquitination and is degraded by the proteasome. This mechanism releases NF-κB from its inhibitory proteins, favors NF-κB nuclear translocation and support the expression of many genes, including those that encode NF-κB inhibitors (Karin & Ben-Neriah, 2000; Nelson et al., 2004; Sen & Baltimore, 1986a; Siebenlist et al., 1994).

Considering the role of NF-κB in the mediation of the inflammatory response, some studies have addressed a functional relationship between CRAC signaling pathway and NF-κB phosphorylation and nuclear translocation (Figure 2) (Berry et al., 2018; Chaudhari et al., 2020; Dolmetsch et al., 1998; Kanno & Siebenlist, 1996; Liu et al., 2016; Mizuma et al., 2019; Singh et al., 2020; Xu et al., 2014). To confirm this hypothesis, the NF-κB transcriptional activity following cell stimulation using G protein-coupled receptor agonists has been investigated, reporting that NF-κB-mediated gene transcription requires both, the intracellular Ca^{2+} stores depletion evoked by the opening of IP_3R and the entry of Ca^{2+} through CRAC channels. Furthermore, Liu and coworkers have reported that CRAC channel inhibition by Synta66 or by the overexpression of the dominant negative mutant Orai1E106A impairs IκBα degradation and NF-κB phosphorylation following cell treatment with Ionomycin and PMA (Chaudhari et al., 2020; Liu et al., 2016). This mechanism for NF-κB activation involves several key steps of the noncanonical pathway. First, the activation of different Ca^{2+}-dependent PKC subtypes trigger CARMA-BCL10-MALT1 complex (CBM complex), which is necessary for the subsequent NEMO-IKK interaction and the final degradation of NF-kB inhibitory proteins (Figure 2) (Berry et al., 2018; Steffan et al., 1995). It is also important to mention that several Ca^{2+}-dependent proteins, such as CaMK and calcineurin, are also able to control the phosphorylation status and activation of the CBM complex (Ishiguro et al., 2007; Oruganti et al., 2011; Palkowitsch et al., 2011). From this point on, the degradation of IκBα/β will release the transcription factor triggering its phosphorylation and subsequent translocation to the nucleus (Berry et al., 2018; Mizuma et al., 2019; Xu et al., 2014). To our knowledge, there is no evidence supporting the contribution of Orai2 and Orai3 in NF-κB activation, a topic that deserves further investigation.

5 | C-MYC

The transcription factor c-myc, which is encoded by the proto-oncogene *c-myc*, is involved in vital processes for the cell such as cell growth, proliferation, and apoptosis as it is an important modulator of cell cycle progression through G1 phase (E. B. Thompson, 1998). Interestingly, alterations in c-myc expression and its regulation contribute to

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tumorigenesis and tumor growth (Dang, 2012). The activity of this transcription factor is known to be regulated by several mechanisms in which Ca^{2+} signaling and SOCE play a key role (Putney, 2009).

Considering Orai channels, many studies have described a correlation between the expression and activity of these channels and the cellular hallmarks associated with different cancer types. Then, as it has been proposed that Orai3 is involved in the regulation of G1 phase and G1/S transition in tumor cells (Chamlali et al., 2021; Sanchez-Collado, Jardin et al., 2021), Faouzi et al. aimed to elucidate the relationship between Orai3 and c-myc. To identify the connection between them, authors have simultaneously compared the expression of both proteins in breast cancer tumor samples and cell lines. The results obtained show that Orai3 and c-myc expression is significantly correlated and both present a higher expression in cancer cells when compared with noncancerous cells (Faouzi et al., 2013).

In addition, Faouzi and coworkers studied the effect of Orai3 downregulation on c-myc expression and function. First, they observed that silencing Orai3 channels in ER+ breast cancer MCF-7 cells induced a significant decrease both in the expression and activity of c-myc, while this correlation was not reported when studying the non-tumoral MCF-10A breast epithelial cell line. Considering the obtained results, these authors took a step forward and analyzed their impact on cell viability and proliferation, concluding that *Orai3* and *c-myc* gene silencing separately decreased MCF-7 cell survival, but have no additive effect when combined. The analysis of the phosphorylation level of different proteins involved in the MAPK pathway, such as ERK1/2, reported that *Orai3* knockdown decreases protein phosphorylation levels in MCF-7 cells, in comparison with control cells, which indicates that Orai3 potentially impacts c-myc function and activity through the MAPK cascade (Figure 2) (Faouzi et al., 2013).

6 | MEF2

MEF2 protein family comprises a group of transcription factors implicated in myogenesis and its associated mechanisms (Brand, 1997; Taylor & Hughes, 2017). In this process, somatic cells transform into muscle cells thanks to different signaling pathways in which SOCE is critically important (Arnaudeau et al., 2006). As it has been introduced, Orai and STIM protein families are the main regulators of SOCE, so that some authors hypothesized and tried to clarify if they also played a role in MEF2 expression and function. In this sense, Darbellay and coworkers have explored the role of Orai proteins in the regulation of MEF2 expression during myoblasts differentiation reporting that Orai1 and Orai3 knockdown decreases MEF2 nuclear expression, while the inhibition of Orai2 expression did not exert a significant role (Figure 2). Furthermore, it has been reported that STIM1 and Orai1 overexpression results in an increased *MEF2* gene expression and accelerate differentiation. Altogether, these findings demonstrate that Orai1 and Orai3 regulate MEF2 expression in myoblasts, and SOCE plays an essential role in myoblasts differentiation (Darbellay et al., 2009). Conversely, in VSMCs Ren et al. (2010) have reported that cell treatment with thapsigargin had no effect on MEF2 expression, concluding that SOCE might not be relevant for MEF2 expression in VSMCs. These observations suggest that the functional role of SOCE in MEF2 expression might be cell specific.

7 | C-FOS

c-fos proto-oncogene is part of the *Fos* superfamily in which *FosB*, *FosL1*, and *FosL2* genes are also included. It encodes a transcription factor that forms AP-1 (activator protein-1) together with c-jun, a heterodimeric complex involved in multiple functions, such as cell proliferation, differentiation, or survival, among others (Manios et al., 2020; Piechaczyk & Blanchard, 1994). Chang et al. reported that c-fos transcription and translation to the nucleus was boosted in RBL-1 cells following Ca^{2+} store depletion using thapsigargin. This event was impaired in the absence of external Ca^{2+} or after treatment with 2-APB as CRAC channel blocker. Unexpectedly, the modulation of c-fos expression by SOCE was mediated by an alternative pathway that seems to be independent from MAPK/ERK1/2 cascade (Figure 2) (Chang et al., 2006).

The role of SOCE in the modulation of c-fos expression and activation was confirmed by Ren and coworkers in VSMC. These authors reported that SOCE-mediated c-fos expression counterbalance stretch stimulus and the acquisition of a contractile phenotype in these cells (Ren et al., 2010). In addition, this model has been completed suggesting that NFAT and c-fos transcriptional activities are complementary promoted by SOCE, adapting the intensity of agonist stimulation to the downstream cellular events (Lin et al., 2019).

8 | CONCLUDING REMARKS

SOCE is a major mechanism for Ca^{2+} influx that is required for the activation of a variety of cell functions ranging from secretion and motility to gene expression (Putney, 2009). Cells typically respond to stimulation with physiological concentrations of agonists with transient regenerative Ca^{2+} oscillations, which play a crucial role in gene transcription. While Ca^{2+} oscillations are mediated by Ca^{2+} release via IP_3 receptors, SOCE plays a relevant role sustaining long-term Ca^{2+} oscillations. Native CRAC channels, consisting in the heteromeric assembly of Orai isoforms, have been reported to play an essential role matching gene transcription to the magnitude of agonist stimulation (Yoast et al., 2020). Orai channels activate a variety of transcription factors acting as a point of convergence between agonist stimulation and gene expression.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Ethical Committee of the University of Extremadura (protocol code 195/2019 and date of approval 24 July 2019).

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REFERENCES

Ahmad, M., Ong, H. L., Saadi, H., Son, G. Y., Shokatian, Z., Terry, L. E., Trebak, M., Yule, D. I., & Ambudkar, I. (2022). Functional communication between IP(3)R and STIM2 at subthreshold stimuli is a critical checkpoint for initiation of SOCE. *Proc Natl Acad Sci USA*, *119*(3), e2114928118. https://doi.org/10.1073/pnas.2114928118

Armand, A. S., Bourajjaj, M., Martínez-Martínez, S., Azzouzi, H., da Costa Martins, P. A., Hatzis, P., Seidler, T., Redondo, J. M., & De Windt, L. J. (2008). Cooperative synergy between NFAT and MyoD regulates myogenin expression and myogenesis. *Journal of Biological Chemistry*, *283*(43), 29004–29010. https://doi.org/10.1074/jbc.M801297200

Arnaudeau, S., Holzer, N., König, S., Bader, C. R., & Bernheim, L. (2006). Calcium sources used by post-natal human myoblasts during initial differentiation. *Journal of Cellular Physiology*, *208*(2), 435–445. https://doi.org/10.1002/jcp.20679

Baeuerle, P. A., & Baichwal, V. R. (1997). NF-kappa B as a frequent target for immunosuppressive and anti-inflammatory molecules. *Advances in Immunology*, *65*, 111–137.

Barnes, P. J., & Karin, M. (1997). Nuclear factor-κB—A pivotal transcription factor in chronic inflammatory diseases. *New England Journal of Medicine*, *336*(15), 1066–1071. https://doi.org/10.1056/NEJM199704103361506

Berry, C. T., May, M. J., & Freedman, B. D. (2018). STIM- and Orai-mediated calcium entry controls NF-κB activity and function in lymphocytes. *Cell Calcium*, *74*, 131–143. https://doi.org/10.1016/j.ceca.2018.07.003

Bird, G. S., Hwang, S. Y., Smyth, J. T., Fukushima, M., Boyles, R. R., & Putney, J. W., Jr. (2009). STIM1 is a calcium sensor specialized for digital signaling. *Current Biology*, *19*(20), 1724–1729. https://doi.org/10.1016/j.cub.2009.08.022.

Bito, H., Deisseroth, K., & Tsien, R. W. (1996). CREB phosphorylation and dephosphorylation: A Ca(2+)- and stimulus duration-dependent switch for hippocampal gene expression. *Cell*, *87*(7), 1203–1214. https://doi.org/10.1016/s0092-8674(00)81816-4

Brand, N. J. (1997). Myocyte enhancer factor 2 MEF2. *The International Journal of Biochemistry & Cell Biology*, *29*(12), 1467–1470. https://doi.org/10.1016/s1357-2725(97)00084-8

Cai, Y., Yao, H., Sun, Z., Wang, Y., Zhao, Y., Wang, Z., & Li, L. (2021). Role of NFAT in the progression of diabetic atherosclerosis. *Frontiers in Cardiovascular Medicine*, *8*, 635172. https://doi.org/10.3389/fcvm.2021.635172

Carreras-Sureda, A., Abrami, L., Ji-Hee, K., Wang, W. A., Henry, C., Frieden, M., Didier, M., van der Goot, F. G., & Demaurex, N. (2021). S-acylation by ZDHHC20 targets ORAI1 channels to lipid rafts for efficient Ca(2+) signaling by Jurkat T cell receptors at the immune synapse. *eLife*, *10*. https://doi.org/10.7554/eLife.72051

Chamlali, M., Kouba, S., Rodat-Despoix, L., Todesca, L. M., Pethö, Z., Schwab, A., & Ouadid-Ahidouch, H. (2021). Orai3 calcium channel regulates breast cancer cell migration through calcium-dependent and -independent mechanisms. *Cells*, *10*(12), 3487. https://doi.org/10.3390/cells10123487

Chang, W. C., Nelson, C., Parekh, A. B., Chang, W. C., Nelson, C., & Parekh, A. B. (2006). Ca2+ influx through CRAC channels activates cytosolic phospholipase A2, leukotriene C4 secretion, and expression of c-fos through ERK-dependent and -independent pathways in mast cells. *The FASEB Journal*, *20*(13), 2381–2383. https://doi.org/10.1096/fj.06-6016fje

Chaudhari, S., Yazdizadeh Shotorbani, P., Tao, Y., Davis, M. E., Mallet, R. T., & Ma, R. (2020). Inhibition of interleukin-6 on matrix protein production by glomerular mesangial cells and the pathway involved. *American Journal of Physiology-Renal Physiology*, *318*(6), F1478–F1488. https://doi.org/10.1152/ajprenal.00043.2020

Chen, Y., & Cao, X. (2009). NFAT directly regulates Nkx2-5 transcription during cardiac cell differentiation. *Biology of the Cell*, *101*(6), 335–350. https://doi.org/10.1042/BC20080108

Choi, H., Srikanth, S., Atti, E., Pirih, F. Q., Nervina, J. M., Gwack, Y., & Tetradis, S. (2018). Deletion of Orai1 leads to bone loss aggravated with aging and impairs function of osteoblast lineage cells. *Bone Reports*, *8*, 147–155. https://doi.org/10.1016/j.bonr.2018.03.007

Dang, C. V. (2012). MYC on the path to cancer. *Cell*, *149*(1), 22–35. https://doi.org/10.1016/j.cell.2012.03.003

Darbellay, B., Arnaudeau, S., König, S., Jousset, H., Bader, C., Demaurex, N., & Bernheim, L. (2009). STIM1- and Orai1-dependent store-operated calcium entry regulates human myoblast differentiation. *Journal of Biological Chemistry*, *284*(8), 5370–5380. https://doi.org/10.1074/jbc.M806726200

DeHaven, W. I., Smyth, J. T., Boyles, R. R., & Putney, J. W., Jr. (2007). Calcium inhibition and calcium potentiation of Orai1, Orai2, and Orai3 calcium release-activated calcium channels. *Journal of Biological Chemistry*, *282*(24), 17548–17556. https://doi.org/10.1074/jbc.M611374200.

Desai, P. N., Zhang, X., Wu, S., Janoshazi, A., Bolimuntha, S., Putney, J. W., & Trebak, M. (2015). Multiple types of calcium channels arising from alternative translation initiation of the Orai1 message. *Science Signaling*, *8*(387), ra74. https://doi.org/10.1126/scisignal.aaa8323

DiDonato, J. A., Hayakawa, M., Rothwarf, D. M., Zandi, E., & Karin, M. (1997). A cytokine-responsive IκB kinase that activates the transcription factor NF-κB. *Nature*, *388*(6642), 548–554. https://doi.org/10.1038/41493

10974652, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcp.30971 by Readcube (Labtiva Inc.), Wiley Online Library on [04/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Dolmetsch, R. E., Xu, K., & Lewis, R. S. (1998). Calcium oscillations increase the efficiency and specificity of gene expression. *Nature*, *392*(6679), 933–936. https://doi.org/10.1038/31960

Emrich, S. M., Yoast, R. E., & Trebak, M. (2022). Physiological functions of CRAC channels. *Annual Review of Physiology*, *84*, 355–379. https://doi.org/10.1146/annurev-physiol-052521-013426

Emrich, S. M., Yoast, R. E., Xin, P., Arige, V., Wagner, L. E., Hempel, N., Gill, D. L., Sneyd, J., Yule, D. I., & Trebak, M. (2021). Omnitemporal choreographies of all five STIM/Orai and IP(3)Rs underlie the complexity of mammalian Ca(2+) signaling. *Cell Reports*, *34*(9), 108760. https://doi.org/10.1016/j.celrep.2021.108760

Faouzi, M., Kischel, P., Hague, F., Ahidouch, A., Benzerdjeb, N., Sevestre, H., Penner, R., & Ouadid-Ahidouch, H. (2013). ORAI3 silencing alters cell proliferation and cell cycle progression via c-myc pathway in breast cancer cells. *Biochimica et Biophysica Acta (BBA)—Molecular Cell Research*, *1833*(3), 752–760. https://doi.org/10.1016/j.bbamcr.2012.12.009

Feske, S., Gwack, Y., Prakriya, M., Srikanth, S., Puppel, S. H., Tanasa, B., Hogan, P. G., Lewis, R. S., Daly, M., & Rao, A. (2006). A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature*, *441*(7090), 179–185. https://doi.org/10.1038/nature04702

Fukushima, M., Tomita, T., Janoshazi, A., & Putney, J. W. (2012). Alternative translation initiation gives rise to two isoforms of Orai1 with distinct plasma membrane mobilities. *Journal of Cell Science*, *125*(Pt 18), 4354–4361. https://doi.org/10.1242/jcs.104919

Giri, P. S., Bharti, A. H., Begum, R., & Dwivedi, M. (2022). Calcium controlled NFATc1 activation enhances suppressive capacity of regulatory T cells isolated from generalized vitiligo patients. *Immunology*, *167*(3), 314–327. https://doi.org/10.1111/imm.13538

Gudlur, A., Zeraik, A. E., Hirve, N., Rajanikanth, V., Bobkov, A. A., Ma, G., Zheng, S., Wang, Y., Zhou, Y., Komives, E. A., & Hogan, P. G. (2018). Calcium sensing by the STIM1 ER-luminal domain. *Nature Communications*, *9*(1), 4536. https://doi.org/10.1038/s41467-018-06816-8

Hofer, A. M. (2019). cAMPing out with the keepers of the gate: Adenylyl cyclases get cozy with Orai. *Cell Calcium*, *82*, 102054. https://doi.org/10.1016/j.ceca.2019.102054

Hogan, P. G., Chen, L., Nardone, J., & Rao, A. (2003). Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes & Development*, *17*(18), 2205–2232. https://doi.org/10.1101/gad.1102703

Ho, N., Liauw, J. A., Blaeser, F., Wei, F., Hanissian, S., Muglia, L. M., Wozniak, D. F., Nardi, A., Arvin, K. L., Holtzman, D. M., Linden, D. J., Zhuo, M., Muglia, L. J., & Chatila, T. A. (2000). Impaired synaptic plasticity and cAMP response element-binding protein activation in Ca2+/calmodulin-dependent protein kinase type IV/Gr-deficient mice. *The Journal of Neuroscience*, *20*(17), 6459–6472. https://doi.org/10.1523/JNEUROSCI.20-17-06459.2000

Hoth, M., & Niemeyer, B. A. (2013). The neglected CRAC proteins: Orai2, Orai3, and STIM2. *Current Topis in Membranes*, *71*, 237–271. https://doi.org/10.1016/B978-0-12-407870-3.00010-X

Hou, X., Pedi, L., Diver, M. M., & Long, S. B. (2012). Crystal structure of the calcium release-activated calcium channel Orai. *Science*, *338*(6112), 1308–1313. https://doi.org/10.1126/science.1228757

Hwang, S. Y., & Putney, J. W. (2012). Orai1-mediated calcium entry plays a critical role in osteoclast differentiation and function by regulating activation of the transcription factor NFATc1. *The FASEB Journal*, *26*(4), 1484–1492. https://doi.org/10.1096/fj.11-194399

Ishiguro, K., Ando, T., Goto, H., & Xavier, R. (2007). Bcl10 is phosphorylated on Ser138 by Ca2+/calmodulin-dependent protein kinase II. *Molecular Immunology*, *44*(8), 2095–2100. https://doi.org/10.1016/j.molimm.2006.09.012

Jans, R., Mottram, L., Johnson, D. L., Brown, A. M., Sikkink, S., Ross, K., & Reynolds, N. J. (2013). Lysophosphatidic acid promotes cell migration through STIM1- and Orai1-mediated Ca2+(i) mobilization and NFAT2 activation. *Journal of Investigative Dermatology*, *133*(3), 793–802. https://doi.org/10.1038/jid.2012.370

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2

Kanno, T., & Siebenlist, U. (1996). Activation of nuclear factor-kappaB via T cell receptor requires a Raf kinase and Ca2+ influx. Functional synergy between Raf and calcineurin. *The Journal of Immunology*, *157*(12), 5277–5283.

Karin, M., & Ben-Neriah, Y. (2000). Phosphorylation meets ubiquitination: The control of NF-κB activity. *Annual Review of Immunology*, *18*, 621–663. https://doi.org/10.1146/annurev.immunol.18.1.621

Kar, P., Barak, P., Zerio, A., Lin, Y. P., Parekh, A. J., & Parekh, A. B. (2021). AKAP79 orchestrates a cyclic AMP signalosome adjacent to Orai1 Ca(2+) channels. *Function*, *2*(5), zqab036. https://doi.org/10.1093/function/zqab036

Kar, P., Lin, Y. P., Bhardwaj, R., Tucker, C. J., Bird, G. S., & Parekh, A. B. (2021). The N terminus of Orai1 couples to the AKAP79 signaling complex to drive NFAT1 activation by local Ca(2+) entry. *Proc Natl Acad Sci USA*, *118*(19), e2012908118. https://doi.org/10.1073/pnas.2012908118

Kar, P., & Parekh, A. B. (2015). Distinct spatial Ca2+ signatures selectively activate different NFAT transcription factor isoforms. *Molecular Cell*, *58*(2), 232–243. https://doi.org/10.1016/j.molcel.2015.02.027

Kar, P., Samanta, K., Kramer, H., Morris, O., Bakowski, D., & Parekh, A. B. (2014). Dynamic assembly of a membrane signaling complex enables selective activation of NFAT by Orai1. *Current Biology*, *24*(12), 1361–1368. https://doi.org/10.1016/j.cub.2014.04.046

Kawasaki, T., Ueyama, T., Lange, I., Feske, S., & Saito, N. (2010). Protein kinase C-induced phosphorylation of Orai1 regulates the intracellular Ca2+ level via the store-operated Ca2+ channel. *Journal of Biological Chemistry*, *285*(33), 25720–25730. https://doi.org/10.1074/jbc.M109.022996

Kim, K. M., Rana, A., & Park, C. Y. (2019). Orai1 inhibitor STIM2β regulates myogenesis by controlling SOCE dependent transcriptional factors. *Scientific Reports*, *9*(1), 10794. https://doi.org/10.1038/s41598-019-47259-5

Kumar, R., DuMond, J. F., Khan, S. H., Thompson, E. B., He, Y., Burg, M. B., & Ferraris, J. D. (2020). NFAT5, which protects against hypertonicity, is activated by that stress via structuring of its intrinsically disordered domain. *Proceedings of the National Academy of Sciences*, *117*(33), 20292–20297. https://doi.org/10.1073/pnas.1911680117

Lee, N., Kim, D., & Kim, W. U. (2019). Role of NFAT5 in the immune system and pathogenesis of autoimmune diseases. *Frontiers in Immunology*, *10*, 270. https://doi.org/10.3389/fimmu.2019.00270

Lin, Y. P., Bakowski, D., Mirams, G. R., & Parekh, A. B. (2019). Selective recruitment of different Ca(2+)-dependent transcription factors by STIM1-Orai1 channel clusters. *Nature Communications*, *10*(1), 2516. https://doi.org/10.1038/s41467-019-10329-3

Lis, A., Peinelt, C., Beck, A., Parvez, S., Monteilh-Zoller, M., Fleig, A., & Penner, R. (2007). CRACM1, CRACM2, and CRACM3 are store-operated Ca2+ channels with distinct functional properties. *Current Biology*, *17*(9), 794–800. https://doi.org/10.1016/j.cub.2007.03.065

Liu, X., Berry, C. T., Ruthel, G., Madara, J. J., MacGillivray, K., Gray, C. M., Madge, L. A., McCorkell, K. A., Beiting, D. P., Hershberg, U., May, M. J., & Freedman, B. D. (2016). T cell receptor-induced nuclear factor κB (NF-κB) signaling and transcriptional activation are regulated by STIM1- and Orai1-mediated calcium entry. *Journal of Biological Chemistry*, *291*(16), 8440–8452. https://doi.org/10.1074/jbc.M115.713008

10974652, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcp.30971 by Readcube (Labtiva Inc.), Wiley Online Library on [04/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Liu, X., Wang, T., Wang, Y., Chen, Z., Hua, D., Yao, X., Ma, X., & Zhang, P. (2018). Orai1 is critical for Notch-driven aggressiveness under hypoxic conditions in triple-negative breast cancers. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease*, *1864*(4 Pt A), 975–986. https://doi.org/10.1016/j.bbadis.2018.01.003

Lunz, V., Romanin, C., & Frischauf, I. (2019). STIM1 activation of Orai1. *Cell Calcium*, *77*, 29–38. https://doi.org/10.1016/j.ceca.2018.11.009

Lu, Y., Zhao, M., Liu, J. J., He, X., Yu, X. J., Liu, L. Z., Sun, L., Chen, L. N., & Zang, W. J. (2017). Long-term administration of pyridostigmine attenuates pressure overload-induced cardiac hypertrophy by inhibiting calcineurin signalling. *Journal of Cellular and Molecular Medicine*, *21*(9), 2106–2116. https://doi.org/10.1111/jcmm.13133

Manios, K., Tsiambas, E., Stavrakis, I., Stamatelopoulos, A., Kavantzas, N., Agrogiannis, G., & C Lazaris, A. (2020). c-Fos/c-Jun transcription factors in non-small cell lung carcinoma. *Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology*, *25*(5), 2141–2143.

Martin, A. C. L., Willoughby, D., Ciruela, A., Ayling, L. J., Pagano, M., Wachten, S., Tengholm, A., & Cooper, D. M. F. (2009). Capacitative Ca2+ entry via Orai1 and stromal interacting molecule 1 (STIM1) regulates adenylyl cyclase type 8. *Molecular Pharmacology*, *75*(4), 830–842. https://doi.org/10.1124/mol.108.051748

Martínez-Martínez, E., Sánchez-Vázquez, V. H., León-Aparicio, D., Sanchez-Collado, J., Gallegos-Gómez, M. L., Rosado, J. A., Arias, J. M., & Guerrero-Hernández, A. (2022). PKC-mediated Orai1 channel phosphorylation modulates Ca(2+) signaling in HeLa cells. *Cells*, *11*(13), 2037. https://doi.org/10.3390/cells11132037

May, M. J., D'Acquisto, F., Madge, L. A., Glöckner, J., Pober, J. S., & Ghosh, S. (2000). Selective inhibition of NF-κB activation by a peptide that blocks the interaction of NEMO with the IκB kinase complex. *Science*, *289*(5484), 1550–1554. https://doi.org/10.1126/science.289.5484.1550

Mignen, O., Thompson, J. L., & Shuttleworth, T. J. (2008). Both Orai1 and Orai3 are essential components of the arachidonate-regulated Ca2+-selective (ARC) channels: Orai1 and Orai3 are both required for functional ARC channels. *The Journal of Physiology*, *586*(1), 185–195. https://doi.org/10.1113/jphysiol.2007.146258

Mizuma, A., Kim, J. Y., Kacimi, R., Stauderman, K., Dunn, M., Hebbar, S., & Yenari, M. A. (2019). Microglial calcium release-activated calcium channel inhibition improves outcome from experimental traumatic brain injury and microglia-induced neuronal death. *Journal of Neurotrauma*, *36*(7), 996–1007. https://doi.org/10.1089/neu.2018.5856

Mognol, G. P., Carneiro, F. R. G., Robbs, B. K., Faget, D. V., & Viola, J. P. B. (2016). Cell cycle and apoptosis regulation by NFAT transcription factors: New roles for an old player. *Cell Death & Disease*, *7*(4), e2199. https://doi.org/10.1038/cddis.2016.97

Montminy, M. R., & Bilezikjian, L. M. (1987). Binding of a nuclear protein to the cyclic-AMP response element of the somatostatin gene. *Nature*, *328*(6126), 175–178. https://doi.org/10.1038/328175a0

Motiani, R. K., Abdullaev, I. F., & Trebak, M. (2010). A novel native store-operated calcium channel encoded by Orai3. *Journal of Biological Chemistry*, *285*(25), 19173–19183. https://doi.org/10.1074/jbc.M110.102582

Mullins, F. M., Park, C. Y., Dolmetsch, R. E., & Lewis, R. S. (2009). STIM1 and calmodulin interact with Orai1 to induce Ca2-dependent inactivation of CRAC channels. *Proceedings of the National Academy of Sciences*, *106*(36), 15495–15500. https://doi.org/10.1073/pnas.0906781106

Nelson, D. E., Ihekwaba, A. E. C., Elliott, M., Johnson, J. R., Gibney, C. A., Foreman, B. E., Nelson, G., See, V., Horton, C. A., Spiller, D. G., Edwards, S. W., McDowell, H. P., Unitt, J. F., Sullivan, E., Grimley, R., Benson, N., Broomhead, D., Kell, D. B., & White, M. R. H. (2004). Oscillations in NF-κB signaling control the dynamics of gene expression. *Science*, *306*(5696), 704–708. https://doi.org/10.1126/science.1099962

Oh-hora, M., & Rao, A. (2009). The calcium/NFAT pathway: Role in development and function of regulatory T cells. *Microbes and Infection*, *11*(5), 612–619. https://doi.org/10.1016/j.micinf.2009.04.008

Oruganti, S. R., Edin, S., Grundström, C., & Grundström, T. (2011). CaMKII targets Bcl10 in T-cell receptor induced activation of NF-κB. *Molecular Immunology*, *48*(12–13), 1448–1460. https://doi.org/10.1016/j.molimm.2011.03.020

Palkowitsch, L., Marienfeld, U., Brunner, C., Eitelhuber, A., Krappmann, D., & Marienfeld, R. B. (2011). The Ca2+-dependent phosphatase calcineurin controls the formation of the Carma1-Bcl10-Malt1 complex during T cell receptor-induced NF-κB activation. *Journal of Biological Chemistry*, *286*(9), 7522–7534. https://doi.org/10.1074/jbc.M110.155895

Palty, R., Raveh, A., Kaminsky, I., Meller, R., & Reuveny, E. (2012). SARAF inactivates the store operated calcium entry machinery to prevent excess calcium refilling. *Cell*, *149*(2), 425–438. https://doi.org/10.1016/j.cell.2012.01.055

Pan, M. G., Xiong, Y., & Chen, F. (2013). NFAT gene family in inflammation and cancer. *Current Molecular Medicine*, *13*(4), 543–554. https://doi.org/10.2174/1566524011313040007

Parekh, A. B. (2017). Regulation of CRAC channels by Ca(2+)-dependent inactivation. *Cell Calcium*, *63*, 20–23. https://doi.org/10.1016/j.ceca.2016.12.003

Parker, T., Wang, K. W., Manning, D., & Dart, C. (2019). Soluble adenylyl cyclase links Ca(2+) entry to Ca(2+)/cAMP-response element binding protein (CREB) activation in vascular smooth muscle. *Scientific Reports*, *9*(1), 7317. https://doi.org/10.1038/s41598-019-43821-3

Park, Y. J., Yoo, S. A., Kim, M., & Kim, W. U. (2020). The role of calcium-calcineurin-NFAT signaling pathway in health and autoimmune diseases. *Frontiers in Immunology*, *11*, 195. https://doi.org/10.3389/fimmu.2020.00195

Pearce, A., Sanders, L., Brighton, P. J., Rana, S., Konje, J. C., & Willets, J. M. (2017). Reciprocal regulation of β 2-adrenoceptor-activated cAMP response-element binding protein signalling by arrestin2 and arrestin3. *Cellular Signalling*, *38*, 182–191. https://doi.org/10.1016/j.cellsig.2017.07.011

Piechaczyk, M., & Blanchard, J. M. (1994). c-fos proto-oncogene regulation and function. *Critical Reviews in Oncology/Hematology*, *17*(2), 93–131. https://doi.org/10.1016/1040-8428(94)90021-3

Prakriya, M., Feske, S., Gwack, Y., Srikanth, S., Rao, A., & Hogan, P. G. (2006). Orai1 is an essential pore subunit of the CRAC channel. *Nature*, *443*(7108), 230–233. https://doi.org/10.1038/nature05122

Pulver-Kaste, R. A., Barlow, C. A., Bond, J., Watson, A., Penar, P. L., Tranmer, B., & Lounsbury, K. M. (2006). Ca2+ source-dependent transcription of CRE-containing genes in vascular smooth muscle. *American Journal of Physiology-Heart and Circulatory Physiology*, *291*(1), H97–H105. https://doi.org/10.1152/ajpheart.00753.2005

Purves, D. (2004). Neuroscience (3rd ed.). Sinauer Associates, Publishers.

Putney, J. W. (2009). Capacitative calcium entry: From concept to molecules. *Immunological Reviews*, *231*(1), 10–22. https://doi.org/10.1111/j.1600-065X.2009.00810.x

Ranger, A. M., Grusby, M. J., Hodge, M. R., Gravallese, E. M., de la Brousse, F. C., Hoey, T., Mickanin, C., Baldwin, H. S., & Glimcher, L. H. (1998). The transcription factor NF-ATc is essential for cardiac valve formation. *Nature*, *392*(6672), 186–190. https://doi.org/10.1038/32426

Ren, J., Albinsson, S., & Hellstrand, P. (2010). Distinct effects of voltage- and store-dependent calcium influx on stretch-induced differentiation and growth in vascular smooth muscle. *Journal of Biological Chemistry*, *285*(41), 31829–31839. https://doi.org/10.1074/jbc.M109.097576

Robbs, B. K., Cruz, A. L. S., Werneck, M. B. F., Mognol, G. P., & Viola, P. B. (2008). Dual roles for NFAT transcription factor genes as oncogenes

10974652, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcp.30971 by Readcube (Labtiva Inc.), Wiley Online Library on [04/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and tumor suppressors. *Molecular and Cellular Biology*, *28*(23), 7168–7181. https://doi.org/10.1128/MCB.00256-08

Robitaille, M., Chan, S. M., Peters, A. A., Dai, L., So, C. L., Bong, A. H. L., Sadras, F., Roberts-Thomson, S. J., & Monteith, G. R. (2022). ORAI1-regulated gene expression in breast cancer cells: Roles for STIM1 binding, calcium influx and transcription factor translocation. *International Journal of Molecular Sciences*, *23*(11), 5867. https://doi.org/10.3390/ijms23115867

Rodríguez-Moyano, M., Díaz, I., Dionisio, N., Zhang, X., Ávila-Medina, J., Calderón-Sánchez, E., Trebak, M., Rosado, J. A., Ordóñez, A., & Smani, T. (2013). Urotensin-II promotes vascular smooth muscle cell proliferation through store-operated calcium entry and EGFR transactivation. *Cardiovascular Research*, *100*(2), 297–306. https://doi.org/10.1093/cvr/cvt196

Sahu, I., Pelzl, L., Sukkar, B., Fakhri, H., al-Maghout, T., Cao, H., Hauser, S., Gutti, R., Gawaz, M., & Lang, F. (2017). NFAT5-sensitive Orai1 expression and store-operated Ca(2+) entry in megakaryocytes. *The FASEB Journal*, *31*(8), 3439–3448. https://doi.org/10.1096/fj.201601211R

Sanchez-Collado, J., Jardin, I., Lopez, J. J., Ronco, V., Salido, G. M., & Rosado, J. A. (2021). Role of Orai3 in the pathophysiology of cancer. *Int J Mol Sci*, *22*(21), 11426. https://doi.org/10.3390/ijms222111426

Sanchez-Collado, J., Lopez, J. J., Cantonero, C., Jardin, I., Regodon, S., & Rosado, J. A. (2021). Orai2 modulates store-operated Ca(2+) entry and cell cycle progression in breast cancer cells. *Cancers (Basel)*, *14*(1), 114. https://doi.org/10.3390/cancers14010114

Sanchez-Collado, J., Lopez, J. J., Jardin, I., Berna-Erro, A., Camello, P. J., Cantonero, C., Smani, T., Salido, G. M., & Rosado, J. A. (2022). Orai1α, but not Orai1β, co-localizes with TRPC1 and is required for its plasma membrane location and activation in HeLa cells. *Cellular and Molecular Life Sciences*, *79*(1), 33. https://doi.org/10.1007/s00018-021-04098-w

Sanchez-Collado, J., Lopez, J. J., Jardin, I., Camello, P. J., Falcon, D., Regodon, J. A., Salido, G. M., Smani, T., & Rosado, J. A. (2019). Adenylyl cyclase type 8 overexpression impairs phosphorylation-dependent Orai1 inactivation and promotes migration in MDA-MB-231 breast cancer cells. *Cancers*, *11*(11), 1624. https://doi.org/10.3390/cancers11111624

Sanchez-Collado, J., Lopez, J. J., Jardin, I., Salido, G. M., & Rosado, J. A. (2021). Cross-talk between the adenylyl cyclase/cAMP pathway and Ca(2+) homeostasis. *Reviews of Physiology, Biochemistry and Pharmacology*, *179*, 73–116. https://doi.org/10.1007/112_2020_55

Sanchez-Collado, J., Lopez, J. J., & Rosado, J. A. (2021). The Orai1-AC8 interplay: How breast cancer cells escape from Orai1 channel inactivation. *Cells*, *10*(6), 1308. https://doi.org/10.3390/cells10061308

Sen, R., & Baltimore, D. (1986a). Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. *Cell*, *47*(6), 921–928. https://doi.org/10.1016/0092-8674(86)90807-x

Sen, R., & Baltimore, D. (1986b). Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell*, *46*(5), 705–716. https://doi.org/10.1016/0092-8674(86)90346-6

Shanmughapriya, S., Rajan, S., Hoffman, N. E., Zhang, X., Guo, S., Kolesar, J. E., Hines, K. J., Ragheb, J., Jog, N. R., Caricchio, R., Baba, Y., Zhou, Y., Kaufman, B. A., Cheung, J. Y., Kurosaki, T., Gill, D. L., & Madesh, M. (2015). Ca2+ signals regulate mitochondrial metabolism by stimulating CREB-mediated expression of the mitochondrial Ca2+ uniporter gene MCU. *Science Signaling*, *8*(366), ra23. https://doi.org/10.1126/scisignal.2005673

Sheng, M., Thompson, M. A., & Greenberg, M. E. (1991). CREB: A Ca(2+)-regulated transcription factor phosphorylated by calmodulin-dependent kinases. *Science*, *252*(5011), 1427–1430. https://doi.org/10.1126/science.1646483

Siebenlist, U., Franzoso, G., & Brown, K. (1994). Structure, regulation and function of NF-kappa B. *Annual Review of Cell Biology*, *10*, 405–455. https://doi.org/10.1146/annurev.cb.10.110194.002201

Simo-Cheyou, E. R., Tan, J. J., Grygorczyk, R., & Srivastava, A. K. (2017). STIM-1 and ORAI-1 channel mediate angiotensin-II-induced expression of Egr-1 in vascular smooth muscle cells. *Journal of Cellular Physiology*, *232*(12), 3496–3509. https://doi.org/10.1002/jcp.25810

Singh, A. K., Roy, N. K., Bordoloi, D., Padmavathi, G., Banik, K., Khwairakpam, A. D., Kunnumakkara, A. B., & Sukumar, P. (2020). Orai-1 and Orai-2 regulate oral cancer cell migration and colonisation by suppressing Akt/mTOR/NF-κB signalling. *Life Sciences*, *261*, 118372. https://doi.org/10.1016/j.lfs.2020.118372

Soltoff, S. P., & Lannon, W. A. (2013). Activation of ERK1/2 by store-operated calcium entry in rat parotid acinar cells. *PLoS One*, *8*(8), e72881. https://doi.org/10.1371/journal.pone.0072881

Son, G. Y., Subedi, K. P., Ong, H. L., Noyer, L., Saadi, H., Zheng, C., Bhardwaj, R., Feske, S., & Ambudkar, I. S. (2020). STIM2 targets Orai1/STIM1 to the AKAP79 signaling complex and confers coupling of Ca(2+) entry with NFAT1 activation. *Proceedings of the National Academy of Sciences*, *117*(28), 16638–16648. https://doi.org/10.1073/pnas.1915386117

Srikanth, S., Woo, J. S., Sun, Z., & Gwack, Y. (2017). Immunological disorders: Regulation of Ca(2+) signaling in T lymphocytes. *Advances in Experimental Medicine and Biology*, *993*, 397–424. https://doi.org/10.1007/978-3-319-57732-6_21

Steffan, N. M., Bren, G. D., Frantz, B., Tocci, M. J., O'Neill, E. A., & Paya, C. V. (1995). Regulation of IkB alpha phosphorylation by PKC- and Ca(2+)-dependent signal transduction pathways. *The Journal of Immunology*, *155*(10), 4685–4691.

Suehiro, J., Kanki, Y., Makihara, C., Schadler, K., Miura, M., Manabe, Y., Aburatani, H., Kodama, T., & Minami, T. (2014). Genome-wide approaches reveal functional vascular endothelial growth factor (VEGF)-inducible nuclear factor of activated T cells (NFAT) c1 binding to angiogenesis-related genes in the endothelium. *Journal of Biological Chemistry*, *289*(42), 29044–29059. https://doi.org/10.1074/jbc.M114.555235

Taylor, M. V., & Hughes, S. M. (2017). Mef2 and the skeletal muscle differentiation program. *Seminars in Cell & Developmental Biology*, *72*, 33–44. https://doi.org/10.1016/j.semcdb.2017.11.020

Thompson, E. B. (1998). The many roles of c-Myc in apoptosis. *Annual Review of Physiology*, *60*, 575–600. https://doi.org/10.1146/annurev.physiol.60.1.575

Thompson, J., Mignen, O., & Shuttleworth, T. J. (2010). The N-terminal domain of Orai3 determines selectivity for activation of the store-independent ARC channel by arachidonic acid. *Channels*, *4*(5), 398–410. https://doi.org/10.4161/chan.4.5.13226

Tomita, M., Reinhold, M. I., Molkentin, J. D., & Naski, M. C. (2002). Calcineurin and NFAT4 induce chondrogenesis. *Journal of Biological Chemistry*, *277*(44), 42214–42218. https://doi.org/10.1074/jbc.C200504200

Vaeth, M., Maus, M., Klein-Hessling, S., Freinkman, E., Yang, J., & Feske, S. (2017). Store-operated Ca(2+) entry controls clonal expansion of T cells through metabolic reprogramming. *Immunity*, *47*(4), 664–679. https://doi.org/10.1016/j.immuni.2017.09.003

Vaeth, M., Yang, J., Yamashita, M., Zee, I., Eckstein, M., & Feske, S. (2017). ORAI2 modulates store-operated calcium entry and T cell-mediated immunity. *Nature Communications*, *8*, 14714. https://doi.org/10.1038/ncomms14714

Varadi, M., Anyango, S., Deshpande, M., Nair, S., Natassia, C., Yordanova, G., Yuan, D., Stroe, O., Wood, G., Laydon, A., Žídek, A., Green, T., Tunyasuvunakool, K., Petersen, S., Jumper, J., Clancy, E., Green, R., Vora, A., Lutfi, M., … Velankar, S. (2022). AlphaFold protein structure database: Massively expanding the structural coverage of protein-sequence space with high-accuracy models. *Nucleic Acids Research*, *50*(D1), D439–D444. https://doi.org/10.1093/nar/gkab1061

Wang, S., Xu, L., Wu, Y., Shen, H., Lin, Z., Fang, Y., Zhang, L., Shen, B., Liu, Y., & Wu, K. (2022). Parathyroid hormone promotes human

10974652, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcp.30971 by Readcube (Labtiva Inc.), Wiley Online Library on [04/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

umbilical vein endothelial cell migration and proliferation through Orai1-mediated calcium signaling. *Frontiers in Cardiovascular Medicine*, *9*, 844671. https://doi.org/10.3389/fcvm.2022.844671

West, A. E., Chen, W. G., Dalva, M. B., Dolmetsch, R. E., Kornhauser, J. M., Shaywitz, A. J., Takasu, M. A., Tao, X., & Greenberg, M. E. (2001). Calcium regulation of neuronal gene expression. *Proceedings of the National Academy of Sciences*, *98*(20), 11024–11031. https://doi.org/10.1073/pnas.191352298

Willoughby, D., Everett, K. L., Halls, M. L., Pacheco, J., Skroblin, P., Vaca, L., Klussmann, E., & Cooper, D. M. F. (2012). Direct binding between Orai1 and AC8 mediates dynamic interplay between Ca2+ and cAMP signaling. *Science Signaling*, *5*(219), ra29. https://doi.org/10.1126/scisignal.2002299

Xu, Z. P., Song, Y., Yang, K., Zhou, W., Hou, L. N., Zhu, L., Chen, H. Z., & Cui, Y. Y. (2014). M3 mAChR-mediated IL-8 expression through PKC/NF-κB signaling pathways. *Inflammation Research*, *63*(6), 463–473. https://doi.org/10.1007/s00011-014-0718-4

Yoast, R. E., Emrich, S. M., Zhang, X., Xin, P., Johnson, M. T., Fike, A. J., Walter, V., Hempel, N., Yule, D. I., Sneyd, J., Gill, D. L., & Trebak, M. (2020). The native ORAI channel trio underlies the diversity of Ca (2+) signaling events. *Nature Communications*, *11*(1), 2444. https://doi.org/10.1038/s41467-020-16232-6

Yu, C., Zhou, Z., Huang, W., Li, X., Zou, F., Meng, X., & Cai, S. (2022). Orai3 mediates Orai channel remodelling to activate fibroblast in pulmonary fibrosis. *Journal of Cellular and Molecular Medicine*, *26*(19), 4974–4985. https://doi.org/10.1111/jcmm.17516

Zhang, X., Pathak, T., Yoast, R., Emrich, S., Xin, P., Nwokonko, R. M., Johnson, M., Wu, S., Delierneux, C., Gueguinou, M., Hempel, N., Putney, J. W., Gill, D. L., & Trebak, M. (2019). A calcium/cAMP signaling loop at the ORAI1 mouth drives channel inactivation to shape NFAT induction. *Nature Communications*, *10*(1), 1971. https://doi.org/10.1038/s41467-019-09593-0

Zhang, X., Xin, P., Yoast, R. E., Emrich, S. M., Johnson, M. T., Pathak, T., Benson, J. C., Azimi, I., Gill, D. L., Monteith, G. R., & Trebak, M. (2020). Distinct pharmacological profiles of ORAI1, ORAI2, and ORAI3 channels. *Cell Calcium*, *91*, 102281. https://doi.org/10.1016/j.ceca.2020.102281

Zhao, Q., Wang, X., Liu, Y., He, A., & Jia, R. (2010). NFATc1: Functions in osteoclasts. *The International Journal of Biochemistry & Cell Biology*, *42*(5), 576–579. https://doi.org/10.1016/j.biocel.2009.12.018

Zhou, M. H., Zheng, H., Si, H., Jin, Y., Peng, J. M., He, L., Zhou, Y., Muñoz-Garay, C., Zawieja, D. C., Kuo, L., Peng, X., & Zhang, S. L. (2014). Stromal interaction molecule 1 (STIM1) and Orai1 mediate histamine-evoked calcium entry and nuclear factor of activated T-cells (NFAT) signaling in human umbilical vein endothelial cells. *Journal of Biological Chemistry*, *289*(42), 29446–29456. https://doi.org/10.1074/jbc.M114.578492

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10974652, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcp.30971 by Readcube (Labtiva Inc.), Wiley Online Library on [04/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License