Role of store-operated Ca2+ entry in cardiovascular disease

Ting Lu, Yihua Zhang, Yong Su, Dayan Zhou and Qiang Xu*

Abstract

Store-operated channels (SOCs) are highly selective Ca2+ channels that mediate Ca2+ influx in non-excitable and excitable (i.e., skeletal and cardiac muscle) cells. These channels are triggered by Ca2+ depletion of the endoplasmic reticulum and sarcoplasmic reticulum, independently of inositol 1,4,5-trisphosphate (InsP3), which is involved in cell growth, differentiation, and gene transcription. When the Ca2+ store is depleted, stromal interaction molecule 1 (STIM1) as Ca2+ sensor redistributes into discrete puncta near the plasma membrane and activates the protein Ca2+ release activated Ca2+ channel protein 1 (Orai1). Accumulating evidence suggests that SOC is associated with several physiological roles in endothelial dysfunction and vascular smooth muscle proliferation that contribute to the progression of cardiovascular disease. This review mainly elaborates on the contribution of SOC in the vasculature (endothelial cells and vascular smooth muscle cells). We will further retrospect the literature implicating a critical role for these proteins in cardiovascular disease.

Keywords: Stromal interaction molecule 1, Ca2+ release-activated Ca2+ channel protein 1, Store-operated channels, Transient receptor potential ion channels, Cardiovascular disease

Graphical Abstract

Background

Calcium ions (Ca2+) are second messengers and are widely involved in various physiological processes such as cell proliferation, muscle contraction, and enzyme...
regulation. The fluctuation of internal Ca2+ ions in response to receptor stimulation is usually achieved by releasing Ca2+ ions from intracellular Ca2+ ion stores or influx across the plasma membrane (PM) via Ca2+ ion-permeable channels and emerged as the Ca2+ release-activated Ca2+ channels (CRACs). CRAC is considered as prototypic SOC. Store-operated Ca2+ entry (SOCE) is a ubiquitous Ca2+ influx mechanism, expressed in non-excitable and excitable cells, triggered by the depletion of intracellular Ca2+ stores (ER or SR). SOCE is thus necessary to allow the entry of Ca2+ ions to replenish depleted ER/SR and initiate intracellular Ca2+ signals [1]. In 2005, STIM1 was identified as a member of SOCE that located in ER and translocated into puncta to induce extracellular Ca2+ influx [2], followed by the identification of Orai1 [3] and transient receptor potential channel of the canonical family (TRPC); interestingly, TRPC1 contributes to SOCE is not direct but requires the interplay between STIM1 and Orai1 [4–8]. While TRPC3, TRPC6, and TRPC7 mediate SOCE, it is still debated [4, 9, 10]. Previous studies have found that upon Ca2+ store depletion, stromal interaction molecule1 gets accumulated at the endoplasmic reticulum–plasma membrane (ER–PM) junction to interact with Orai1 leading to the activation of Ca2+–ion release-activated Ca2+ channels [11–14]. According to the genetic research highlights, the significance of SOC on human health is well explained. These studies have shown that patients lacking or having mutations in stromal interaction molecule1, or Orai1 may suffer from severe health problems, including immune deficiency, autoimmunity, bleeding disorders, skeletal muscle disease (i.e. tubular aggregate myopathy, Stormorken disease, and York-platelets disease), and cardiac diseases [15–18]. SOC serves to generate Ca2+ ion release-activated Ca2+ release phenomenon. The process mainly relies on a combination of Ca2+ channel and transporters, more importantly, their precise locations and spatial arrangement. Although early evidence has revealed SOCE in adult myocytes [32, 33], store-operated Ca2+ entry in C57BL/6 J mouse ventricular myocytes and its suppression by sevoflurane is also reported. SOCE is a relatively new phenomenon and also controversial in cardiac myocytes. It is generally accepted that SOCE is more evident in the developing heart [34]. A common function of SOCE is to replenish depleted sarcoplasmic reticulum (SR) Ca2+ stores [35]. It is first identified that SOCE microdomains located in catecholaminergic ventricular tachycardia myocytes contribute to arrhythmogenesis through Ca2+ “spillover” from the SOC-mediated Ca2+ entry pool to the ECC pool. Key SOCE constituents, STIM1 and Orai1, participated in the process [36]. The absence of structural heart disease characterizes arrhythmia, implying that SOCE enhancement is insufficient for hypertrophic remodeling. However, the role of other constituents, including TRPCs, must await further studies. A previous study found that over-expression of STIM1 exhibited sudden death and heart failure. The death may be due to arrhythmia, while heart failure develops with increased cardiac hypertrophy and reduced cardiac function. The result may be associated with partially co-localize with type 2 ryanodine receptor (RyR2) and dysregulation of type Ca2+ channel (LTCC), for cardiovascular diseases in VSMC [24–26]. However, evidence showed that Orai1 is independent of TRPC1-based SOC [23]. In contrast, using immunoprecipitation experiments, the passively depleted store with thapsigargin enhances TRPC1 association with Orai1 and STIM1 with Orai1 in VSMCs of aortic rats [27]. Moreover, data indicate for the first-time functional crosstalk between Orai1, TRPC1, and CaV1.2 channels, determining that upon agonist stimulation, vessel contraction involves Ca2+ entry due to co-localize of Orai1 and TRPC1 with CaV1.2 [28]. It is well known that phenotypic transformation of VSMCs is associated with cardiovascular disease, including hypertension and atherosclerosis [29]. The SOC has been reported to mediate the phenotypic switching of VSMC, which attribute to the activation of Ca2+ /calmodulin-dependent protein (CaMKII)δ [30]. However, Ziomek et al. found that tunicamycin induced a significant increase of intracellular Ca2+ in VSMC. Still, it was independent of the activation of Ca2+ channels instead of the direct permeability of the plasma membrane, ER, and sarcoplasmic reticulum to Ca2+ [31]. The different results may be due to other cell types.

A consensus is that beat-to-beat Ca2+ handling is regulated by excitation–contraction coupling (ECC). Canonical ECC in cardiomyocytes is a Ca2+-induced Ca2+ release phenomenon. The process mainly relies on a combination of Ca2+ channel and transporters, more importantly, their precise locations and spatial arrangement. Although early evidence has revealed SOCE in adult myocytes [32, 33], store-operated Ca2+ entry in C57BL/6 J mouse ventricular myocytes and its suppression by sevoflurane is also reported. SOCE is a relatively new phenomenon and also controversial in cardiac myocytes. It is generally accepted that SOCE is more evident in the developing heart [34]. A common function of SOCE is to replenish depleted sarcoplasmic reticulum (SR) Ca2+ stores [35]. It is first identified that SOCE microdomains located in catecholaminergic ventricular tachycardia myocytes contribute to arrhythmogenesis through Ca2+ “spillover” from the SOC-mediated Ca2+ entry pool to the ECC pool. Key SOCE constituents, STIM1 and Orai1, participated in the process [36]. The absence of structural heart disease characterizes arrhythmia, implying that SOCE enhancement is insufficient for hypertrophic remodeling. However, the role of other constituents, including TRPCs, must await further studies. A previous study found that over-expression of STIM1 exhibited sudden death and heart failure. The death may be due to arrhythmia, while heart failure develops with increased cardiac hypertrophy and reduced cardiac function. The result may be associated with partially co-localize with type 2 ryanodine receptor (RyR2) and dysregulation of type Ca2+ channel (LTCC),
which contributed to the enhancement of Ca2+ cycling in SR [37], the former distinct from in adult mouse skeletal muscle, which showed complete co-localization of STIM1 with RyR1 through the entire myofiber [38]. It is worth saying that accumulation of STIM1 and Orai1 have been found in muscles tubular aggregates of aged mice [39]. Still, it is difficult to determine whether tubular aggregates form due to altered Ca2+ handling or if they are the cause of muscle dysfunction.

Moreover, calsequestrin-1, a protein that acts as the main Ca2+ buffer in the SR and plays a central role in skeletal ECC, has been proposed to mediate SOCE by a retrograde signal that inhibits STIM1 aggregation. The role of calsequestrin-1 in cardiomyocytes and arrhythmia may deserve further study. There are no specific tools to define the contribution of SOCE constituents. Thus, the role of the contribution of these proteins in arrhythmogenesis must await further studies. The specific component of SOC involved in the above process needs to be studied in depth.

Pathological roles of store-operated channels in cardiovascular disease

Arterial thrombosis
At the site of vascular injury, loss of endothelial cells exposes the subendothelial extracellular matrix; soon, platelets are quickly adhered and activated and form a closed lesion embolism with the coagulation system. This process is essential to prevent excessive blood loss, but in pathological situations, it may result in arterial thrombosis that may play a critical role in myocardial infarction and stroke [40]. Myocardial infarction elicited by coronary atherosclerotic plaque corrosion or rupture is one of the two major diseases causing disability and mortality worldwide [41]. Human platelets contain significant levels of Orai1, Orai2, and Orai3 and different transient receptor potential ion channel subfamily members [42, 43]. Unlike a mouse, human platelets have been described as a significant inherent distinction between platelet count levels and the expression of specific Ca2+ ion signals. However, these differences do not exclude employing the mouse models to clarify the Ca2+ ion pathway on platelets. SOCE is the predominant mechanism of intracellular Ca2+ signals [44]. In STIM1-deficient platelets, a severe deficiency occurring in the Ca2+ ion response to all major agonists confirmed that SOC acts as the main pathway for Ca2+ ion entry in platelets, which is crucial for downstream pathway glycoprotein (GP) Ib-GPVI-immunoreceptor tyrosine-based activation motif [45]. However, platelets lack the normal endoplasmic reticulum, and the intriguing problem is that the exact location of STIM1 and the specific molecules involved in regulation is still unclear. Probably, but to a minor extent, STIM2 may be a candidate molecule that has been proven to initiate store-operated channels [46].

Moreover, it was reported that the critical role of Orai1 and TRPC6 in platelets is induced by G protein-coupled receptor activation and thrombosis [47, 48]. From arterial thrombosis of the mouse model, it was shown that cyclophilin A (CyPA) was identified as a Ca2+ ion modulator in platelets for the first time. CyPA deficiency is severely inhibited by activation-induced Ca2+ ion fluctuation in the cell and extracellular Ca2+ ion influx, which strongly impaired platelet activation. This study determined that CyPA in regulating Ca2+ ions was a key mechanism for arterial thrombosis [49]. Moreover, Karen Wolf and his colleagues concluded that secreted platelet serotonin 5-hydroxytryptamine (5-HT) was necessary to enhance the second stage of platelet activation through store-operated channel-mediated Ca2+ influx, as it played a significant role in thrombus stabilization, which is mainly dependent on 5-HT receptor 2A mediated phospholipase C β signaling and amplified Orai1 activity [50]. Consistent with these results [51], it is essential to elucidate the mechanisms of signaling pathways that require further research. Recently, S.K. Gotru et al. [52] found that thapsigargin-induced activation of the STIM1 function resulted in a significant reduction of store-operated Ca2+ entry in transient receptor potential melastatin 7 (TRPM7)-deficient platelets. The results suggested a functional interaction between STIM1 and TRPM7, which contains a cytoplasmic domain of serine/threonine alpha-kinase [52]. A significant observation was the function of Orai1, and STIM1 was regulated by multiple phosphorylations of serine residues [53, 54]. Hence, further research is needed to investigate whether TRPM7 kinase can phosphorylate these residues in the store-operated Ca2+ entry protein complex. Therefore, it can be considered that regulatory proteins are involved in store-operated Ca2+ entry, which could be the target for antithrombotic therapy.

Atherosclerosis
The complex interaction of modified lipoproteins and immune cells with arterial wall cellular components causes a chronic inflammatory process that promotes the formation and development of atherosclerosis [55–57]. For a long time, the formation of foam cells was considered an essential step in developing atherosclerosis. Recently it was demonstrated that knockdown of Orai1 with transfection small interfering RNA (siRNA) or SOCE inhibitor with SKF96365 dramatically inhibits atherosclerotic plaque development involved in macrophage scavenger receptors. This process is mainly dependent on calcineurin(CaN)-apoptosis signal-regulating kinase1
and its downstream effectors, c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase, but not on the nuclear factor of activated T4 [58]. Unexpectedly, Orai1-mediated Ca2+ entry via the CaN-nuclear aspect of activated T cells (NFATc) 4 signals is a key inflammatory pathway required for endothelial cell activation and vascular inflammation induced by tumor necrosis factor-α (TNFα) [59]. The critical role of Orai1 in regulating endothelial and macrophages has been confirmed in-vivo and in-vitro; the different target receptors might be related to cell type.

Moreover, TRPC3 shows its impact on endothelial dysfunction and is responsible for causing apoptosis of macrophages related to the pathogenesis of atherosclerosis. The relevance of TRPC3 with atherosclerosis has also been verified by in vivo studies [60], where the process is associated with endoplasmic reticulum stress that is considered the primary mechanism of cell apoptosis in atherosclerotic plaques [61]. It is well known that endothelial barrier function dysfunction is regarded as a leading cause of atherosclerotic plaque formation.

Interestingly, Stolwijk et al. found that STIM1 may regulate endothelial barrier functions independent of store-operated Ca2+ entry [62]. In contrast, knockdown or inhibition of STIM1 controlled the high-mobility group box 1 protein-induced Ca2+ entry followed by significantly reduced endothelial permeability [63]. However, the difference was correlated with other different agonists and pathological processes.

Endothelial progenitor cells (EPC) were considered the source of vascular repair [64]. Previous studies have shown that store-operated Ca2+ entry is a crucial regulator of EPC function [65, 66]. Wang LY et al. in his study found that endothelial progenitor cells proliferation and migration activities were significantly reduced in atherosclerotic mice, as well as store-operated Ca2+ entry amplitude, that could be due to the Ca2+ ion oscillations related to the reduced expression of Orai1, STIM1, and TRPC in these cells [67]. Moreover, early growth response protein-1 has been shown in atherosclerosis of animal models and response to growth stimuli in VSMC [68]. The data demonstrated that angiotensin II-induced early growth response protein-1 mediated the STIM1/Orai1/Ca2+-dependent pathway. The role of STIM1, Orai1, and TRPC1 regulating Ca2+ influx in the atherosclerosis model has not been elucidated clearly. Hence, SOC-mediated Ca2+ ion entry may be a promising therapeutic target for atherosclerosis.

Cardiac hypertrophy
Cardiac hypertrophy is the primary mechanism by which the heart responds to overloads such as myocardial infarction or hypertension to maintain pump function [17]. Calcium ion is an essential intracellular signal for cardiac hypertrophy to various stimulations [69]. The downstream signaling induced by Ca2+ ions initiates transcription procedures associated with cardiac hypertrophy, pathological growth, and cardiac remodeling, finally changing cardiac function. However, several studies have suggested that store-operated Ca2+ entry plays a key role in cardiac hypertrophy by altering the fetal genetic program controlled by the CaN/NFAT signals. In another study, Hulot et al. found that neonatal cardiomyocytes overexpress STIM1 and are significantly larger and showed an enhanced NFAT activity, which can be prevented in the presence of SKF-96365 [70]. Also, both STIM1 and Orai1 knockdown have entirely inhibited the growth of hypertrophic neonatal cardiomyocytes, which are mediated by phenylephrine and inhibited calmodulin kinase II and extracellular signal-regulated kinase 1/2 signaling, Orai1 deficiency occasionally prevented CaN-dependent hypertrophic pathway [71]. These data were obtained from in-vitro studies, which confirmed that store-operated Ca2+ entry is essential for developing pathological cardiac hypertrophy. However, its role in vivo models has not been studied.

From previous studies, it is understood that gastrin weakened the activity of store-operated Ca2+ entry by reducing the expression of two essential proteins, i.e., STIM1 and Orai1, in vivo and in vitro. The data suggested that inhibition of store-operated Ca2+ entry can reduce myocardial hypertrophy induced by phenylephrine, which indicates that the STIM1-Orai1-Ca2+ dependent pathway is located upstream of hypertrophy [72]. However, the SOC regulator involved in the process has not yet been fully elucidated. Store-manipulated Ca2+ entry-associated regulatory factor (SARAF) is an intrinsic regulator of store-manipulated Ca2+ entry, facilitating the weakening of STIM1-Orai1 interaction [35, 73]. Dai F et al. showed that store-manipulated Ca2+ entry-associated regulatory factor overexpression suppressed STIM1/Orai1 upregulation and cardiac hypertrophy induced by angiotensin II [74]. It is still unclear which specific mechanism of store-manipulated Ca2+ entry-associated regulatory factor regulates STIM1-Orai1; for example, store-manipulated Ca2+ entry-associated regulatory factor prevents STIM1 activation or affects the translocation of STIM1 from the endoplasmic reticulum to the plasma membrane. Also, TRPC is an essential mediator responsible for causing pathological myocardial hypertrophy. Moreover, it has been reported that TRPC1/5 dysregulation contributed to myocardial hypertrophy [75, 76]. However, in their study, the role of SOC in regulating TRPC1/5 has been reported to be unclear. A previous study found that inhibition of TRPC in transgenic mice or cultured neonatal cardiomyocytes remarkably
reduced the activity of CaN-NFAT, which is a known Ca$^{2+}$-dependent hypertrophy induction pathway. Therefore, TRPC contributes to the development of myocardial hypertrophy, partially through the CaN-NFAT signaling pathway [77]. Tang L and his coworkers recently established a stable human-based cardiomyocyte hypertrophy model and highlighted molecular mechanisms underlying TRPC1-mediated hypertrophy, which was related to abnormal activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [78]. Understanding the mechanism of STIM1, Orai1 and TRPC1 may prevent cardiac hypertrophy or heart failure.

Hypertension

Calcium ion is a central component that controls vascular contraction. It has been proposed that the abnormal treatment of cations in vascular myocytes may contribute to the response of vascular smooth muscle cells (VSMC) in contraction and stimulation that is enhanced by myogenic tension enhancement, which is a crucial marker of hypertension. Fernanda R.C reported that compared to age-matched male Wistar-Kyoto rats, blockade of SOC by 2-aminoethoxy diphenyl borate (2-APB) remarkably suppressed contraction in stroke-prone spontaneously hypertensive (SHRSP) rat aortas during the Ca$^{2+}$ loading period [79]. This accordingly enhanced the activation of STIM1/Orai1 in the aorta of male SHRSP, which represents a mechanism that leads to impaired control of sex-related intracellular Ca$^{2+}$ ion levels. In addition to this study, they even investigated female ovariectomy to understand whether it affects the activation of the Orai1/STIM1 pathway. The data suggested that female sex hormones may negatively regulate the STIM1/Orai1 pathway and contribute to vascular protection in female rats [80]. In a study conducted on smooth muscle-specific knockout of STIM1 of mice (stromal interaction molecule1 SMC$^{-/-}$ mice), Kassan et al. found that STIM1 was pivotal for causing hypertension. They demonstrated that after angiotensin II infusion at the 4th week, STIM1 was pivotal for causing hypertension. They demonstrated with hypertension and endothelial dysfunction; how mice was enhanced, which was found to be associated entry in this pathogenesis is undefined. TRPC$^{+}$ Ca$^{2+}$ hypertension, the specific molecule of SOC-mediated (SHRs) [82]. Although several molecules participated in hypertension, the specific molecule of SOC-mediated Ca$^{2+}$ entry in this pathogenesis is undefined. TRPC has been reported to increase in models of hypertension [83–85], especially a higher TRPC3 and change in TRPC 3/6 proportions in essential hypertension, which is associated with depolarization of vascular smooth muscle cells [86]. Liu D et al. found that TRPC3 was significant in controlling Ca$^{2+}$ ion entry in VSMC [87]. Previous research showed that TRPC3 transcription is closely related to systolic blood pressure ascribed to pro-inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α in essential hypertension [88].

Moreover, elevated TRPC3 messenger RNA (mRNA) levels in patients with hypertension were associated with increased salt intake and systolic blood pressure [89] but, its specific mechanism needs further investigation. The earlier studies were conducted in cultured rat and human embryonic kidney 293 cells; Parker et al. demonstrated that inhibition of sphingosine kinase 1 (SK1) attenuated the second phase of transmembrane Ca$^{2+}$ ion influx in Ang II-mediated hypertension, suggesting a role for sphingosine kinase 1 in Ang II-dependent activation of SOC [90]. However, different experimental conditions, including specific vascular bed studies and other vasoactive drugs and animal species, led to heterogeneity results. Considering the effect of different vasoactive agents (such as Ang-II, Noradrenaline) on blood pressure, multiple receptor blockers are used to treat hypertension [91, 92]. Pharmaceutical experiments using SKF-96465 suggested that inhibition of store-operated Ca$^{2+}$ entry positively affected blood pressure reduction and Ca$^{2+}$ ion release induced by Ang-II [93]. Moreover, the SOC activity was reduced by tyrosine kinase inhibitors, which control blood pressure [94]. Accordingly, it would be of great significance to investigate the effects of SOC inhibitors in hypertension.

Pulmonary arterial hypertension

The imbalance of pulmonary systolic and vasodilation is the cause of pulmonary hypertension. Importantly, pulmonary arterial remodeling is a pathological alteration. Mechanistically, it is involved in the proliferation of pulmonary artery smooth muscle cells (PASMC). Cytosolic free Ca$^{2+}$ ([$\text{Ca}^{2+}$]$\text{i}$) plays a pivotal role in pulmonary vascular remodeling [95]. Furthermore, the alteration in Ca$^{2+}$ ion signaling and profound pulmonary vascular remodeling may lead to pulmonary arterial hypertension (PAH) [96]. Accumulating evidence has implicated that store-operated Ca$^{2+}$ entry is responsible for developing pulmonary arterial hypertension [97–99]. Wang J et al. suggested that Orai1/2/3 and STIM1 contributed to SOC-mediated Ca$^{2+}$ influx in PASMCs, especially Orai2 is found to be a hypoxia-inducible factor-1α (HIF-1α)-dependent [98]. Following this, Fernandez et al. demonstrated that Orai2
knockdown reduced store-operated Ca\textsuperscript{2+} entry in proliferative PASMCs. The authors further found that proliferative pulmonary artery smooth muscle cells have enhanced store-operated Ca\textsuperscript{2+} entry. Moreover, STIM2 was implicated in increased activity of store-operated Ca\textsuperscript{2+} entry [100]. Interestingly, an increase of STIM2 in PASMC was observed in patients with idiopathic pulmonary hypertension. The role of STIM2 in store-operated Ca\textsuperscript{2+} entry may attribute to its effect on the augmentation of PASMC proliferation. However, STIM1 was not significantly changed in idiopathic pulmonary hypertension-PASMC [101]. Previously, STIM1 knockdown reduced store-operated Ca\textsuperscript{2+} entry and decreased hypoxia-induced PASMC proliferation, suggesting that STIM1 significantly impacts hypoxic pulmonary arterial hypertension [102], and CaN/NFAT shows increased activity in pulmonary arterial hypertension. Moreover, the CaN/NFAT signaling pathway has been involved in pulmonary artery smooth muscle cell proliferation through monocrotaline-induced pulmonary arterial hypertension [103]. Recently, Dong F et al. found that Chrysin inhibited the hypoxia-induced promotion of pulmonary artery smooth muscle cells proliferation and store-operated Ca\textsuperscript{2+} entry, which may be associated with inhibition of TRPC1 and TRPC6 [104]. Similarly, in vitro experiments suggested that the TRPC antagonist SKF-96365 controlled pulmonary artery smooth muscle cells proliferation and decreased expression of TRPC1, TRPC6, and CaN/NFATc3 caused by 5-HT [105]. The correlation between 5-HT and TRPC may promote the pathogenesis of pulmonary arterial hypertension. Previous studies confirmed that store-operated channels play a critical role in pulmonary arterial hypertension. However, different induced conditions can result in different pathogenesis and pathological manifestations. Notably, the models cannot accurately mimic human pulmonary arterial hypertension. The STIM, Orai, and TRPC in pulmonary arterial hypertension patients need further investigation. Future studies aim to understand the role of these proteins in pulmonary arterial hypertension patients and the irregulatory pathways.

The role of store-operated channels in cardiovascular diseases has been summarized in Fig. 1.
Conclusion

Accumulating evidence indicates that approaches aimed at store-operated Ca2+ entry in the cardiovascular system may be therapeutic. The pharmacological tools have demonstrated the contribution of SOCE constituents in cardiovascular diseases; while useful for initial investigation and analysis, they lack specificity. Although the constituents of SOCE were shown to play a central role in Ca2+ signals, their absolute requirement for store-operated Ca2+ entry regulation is helpful to carry out further investigation. The Cav1.2 and colocalization with SOCE have been reported for the first time in vessel contraction. The effect of functional crosstalk in hypertension and atherosclerosis might be worthy of further study. Besides, Ca2+ originating from SOCE could modulate cell adhesion and ECC by influencing intercalated disk-residing proteins’ functions. The role of SOCE in maintaining the intercalated disk structure and function via regulation of protein synthesis, trafficking, and targeting may be a future research direction of arrhythmia. There is a hope that future studies will reveal further signaling molecules regulating cardiovascular Orai1/STIM1 and TRPC abundance and its function. Evaluation of SOC channels will shed new light on the treatment of cardiovascular disease.

Abbreviations

SOCs: Store-operated channels; ER: Endoplasmic reticulum; SR: Sarcoplasmic reticulum; InsP3: Inositol 1,4,5-triphosphate; STIM1: Stromal interaction molecule 1; Ca2+: Calcium ions; Orai 1: Ca2+ release-activated Ca2+ channel protein 1; PM: Plasma membrane; CRACs: Ca2+ ion release-activated Ca2+ channels; TRPCs: Transient receptor potential channel of canonical family; Cav 1.2: L-type channels; VSMC: Vascular smooth muscle cells; eNOS: Endothelial nitric oxide synthase; CAMKII: Ca2+/calmodulin-dependent protein; ECC: Excitation-contraction coupling; SR: Sarcoplasmic reticulum; GP: Glicycroprotein; CyPA: CyclophilinA; 5-HT: 5-Hydroxytryptamine; TRPM7: Transient receptor potential melastatin 7; siRNA: Small interfer RNA; CaN: Calcineurin; JNK: C-Jun N-terminal kinase; NFAT: Nuclear aspect of activated T cells; TNFa: Tumor necrosis factor-c; EPIC: Endothelial progenitor cell; SARAF: Associated regulatory factor; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; 2-APB: 2-Aminoethoxy diphenyl borate; SHRP2: Stroke-prone spontaneously hypertensive; IL-1β: Interleukin-1β; mRNA: Messenger RNA; SK1: Sphingosine kinase 1; PASMSC: Pulmonary artery smooth muscle cells; PAH: Pulmonary arterial hypertension; HIF-1α: Hypoxia-inducible factor-1α.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12964-022-00829-z.

Acknowledgements

None.

Authors’ contributions

QX conceived of the manuscript and participated in the design of the manuscript. TL carried out the original draft and image processing. YZ was responsible for manuscript revision. DZ was responsible for proofreading the manuscript. YS participated in revising the image. All authors contributed to and have approved the final manuscript.

Funding

This article is funded by the scientific research project of Chongqing Nanan District Health Commission and Nanan District Science and Technology Bureau; the project number is 2020-06.

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Declarations

Ethics approval and consent to participate

Not applicable, this manuscript does not report on or involve the use of any animal or human data or tissue.

Consent for publication

Not applicable, this manuscript does not report on or involve the use of any animal or human data or tissue.

Competing interests

The authors declare that they have no competing interests.

Received: 14 October 2021 Accepted: 14 January 2022 Published online: 18 March 2022

References

1. Shim AH, Tirado-Lee L, Prakriya M. Structural and functional mechanisms of CRAC channel regulation. J Mol Biol. 2015;427(1):77–93. https://doi.org/10.1016/j.jmb.2014.09.021.
2. Liu J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE Jr, et al. STIM is a Ca2+-sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol. 2005;15(13):1235–41. https://doi.org/10.1016/j.cub.2005.05.055.
3. Prakriya M, Feske S, Gwack Y, Srikanth S, Rao A, Hogan PG. Orai1 is an essential pore subunit of the CRAC channel. Nature. 2006;443(7108):230–3. https://doi.org/10.1038/nature05122.
4. Liao Y, Erxleben C, Abramowitz J, Flockerzi V, Zhu MX, Armstrong DL, et al. Functional interactions among Orai1, TRPCs, and STIM1 suggest a STIM-regulated heteromeric Orai/TRPC model for SOCE/ICRAC channels. Proc Natl Acad Sci U S A. 2008;105(8):2895–900. https://doi.org/10.1073/pnas.0712288105.
5. Gross SA, Guzman GA, Wissenbach U, Philipp SE, Zuo MX, Bruns D, et al. TRPC5 is a Ca2+-activated channel functionally coupled to Ca2+-selective ion channels. J Biol Chem. 2009;284(49):34423–32. https://doi.org/10.1074/jbc.M109.018192.
6. Sundivakkam PC, Freichel M, Singh V, Yuan JP, Vogel SM, Flockerzi V, et al. The Ca(2+) sensor stromal interaction molecule 1 (STIM1) is necessary and sufficient for the store-operated Ca(2+) entry function of transient receptor potential canonical (TRPC) 1 and 4 channels in endothelial cells. Mol Pharmacol. 2012;81(4):510–26. https://doi.org/10.1124/mol.111.074658.
7. Antony F, Sabourin J, Sauc S, Bernheim L, Koenig S, Frieden M. TRPC1 and TRPC4 channels functionally interact with STIM1 to promote myogenesis and maintain fast repetitive Ca2+ release in human myotubes. Biochim Biophys Acta Mol Cell Res. 2017;1864(5):806–13. https://doi.org/10.1016/j.bbamcr.2017.02.003.
8. Qu YY, Wang JW, Zhong H, Liu YM, Tang N, Zhu LP, et al. TRPC1 stimulates calcium-sensing receptor-induced store-operated Ca2+ entry and nitric oxide production in endothelial cells. Mol Med Rep. 2017;16(4):4613–9. https://doi.org/10.3892/mmr.2017.7164.
9. Liao Y, Erxleben C, Yildirim E, Abramowitz J, Armstrong DL, Birnbaumer L. Orai proteins interact with TRPC channels and confer responsiveness to store depletion. Proc Natl Acad Sci U S A. 2007;104(11):4682–7. https://doi.org/10.1073/pnas.0611660104.
10. Liao Y, Plumfer NW, George MD, Abramowitz J, Zhu MX, Birnbaumer L. A role for Orai in TRPC-mediated Ca2+ entry suggests that a TRPC-Orai complex may mediate store and receptor operated Ca2+ entry. Proc.
Lu et al. Cell Communication and Signaling  (2022) 20:33

Natl Acad Sci U S A. 2009;106(9):3202–6. https://doi.org/10.1073/pnas.0813346106.

11. Luik RM, Wang B, Prakriya M, Wu MM, Lewis RS. Oligomerization of STIM1 couples ER calcium depletion to CRAC channel activation. Nature. 2008;454(7203):538–42. https://doi.org/10.1038/nature06705.

12.Navarro-Borelly L, Somasundaram A, Yamashita M, Ren D, Miller RJ, Prakriya M. STIM1-ORAI1 interactions and OrAI1 conformational changes revealed by live-cell FRET microscopy. J Physiol. 2008;586(22):5383–401. https://doi.org/10.1113/jphysiol.2008.162503.

13. Peroni S, Dynes JL, Yeromin AV, Cahalan MD, Franzini-Armstrong C. Nanoscale patterning of STIM1 and ORAI1 during store-operated Ca2+ entry. Proc Natl Acad Sci U S A. 2015;112(40):E5333–42. https://doi.org/10.1073/pnas.1515606112.

14. Butorac C, Mulk M, Derler I, Stadlbauer M, Lunz V, Krozova A, et al. A novel STIM1-ORAI1 gating interface essential for CRAC channel activation. Cell Calcium. 2019;79:57–67. https://doi.org/10.1016/j.ceca.2019.02.009.

15. Feske S. CRAC channelopathies. Pflugers Arch. 2010;460(2):417–35.

16. Nesin V, Wiley G, Kousi M, Ong EC, Lehmann T, Nicholl DJ, et al. Activating mutations in STIM1 and ORAI1 cause overlapping syndromes of tubulopathy and congenital miosis. Proc Natl Acad Sci U S A. 2014;111(11):4197–202. https://doi.org/10.1073/pnas.1312535111.

17. Eder P. Cardiac remodeling and disease: SOCE and TRPC signaling in cardiac pathology. Adv Exp Med Biol. 2017;983:505–21. https://doi.org/10.1007/978-3-319-57752-6_25.

18. Michelucci A, Garcia-Castañeda M, Boncompagni S, Dirksen RT. Role of STIM1/ORAI1-mediated SOCE in skeletal muscle physiology and disease. Cell Calcium. 2018;76:101–15. https://doi.org/10.1016/j.ccl.2018.04.008.

19. Zhang W, Trebak M. STIM1 and Orai1: novel targets for vascular smooth muscle myocytes and its suppression by sevofurane. Br J Anaesth. 2012;109(3):352–60. https://doi.org/10.1093/bja/aej121.

20. Collins HE, Zhu-Mauldin X, Marchase RB, Chatham JC. STIM1/ORAI1-mediated SOCE: current perspectives and potential roles in cardiac function and pathology. Am J Physiol Heart Circ Physiol. 2013;305(4):H446–58. https://doi.org/10.1152/ajpheart.00301.2013.

21. Palty R, Raev R, Kamiński I, Meller R, Reuveny E. SARAF inactivates the store operated calcium entry machinery to prevent excess calcium refilling. Cell. 2012;149(2):425–38. https://doi.org/10.1016/j.cell.2012.01.055.

22. Bonilla IM, Belevych AE, Baine S, Stepanov A, Mezache L, Bodnar T, et al. Enhancement of cardiac store-operated calcium entry (SOCE) within novel intercalated disk microdomains in arrhythmic disease. Sci Rep. 2019(9):10179. https://doi.org/10.1038/s41598-019-46427-x.

23. Correll RN, Goonasekera SA, van Berlo JH, Burr AR, Accornero F, Zhang H, et al. STIM1 elevation in the heart results in aberrant Ca2+ handling and cardiomyopathy. J Mol Cell Cardiol. 2015;87:38–47. https://doi.org/10.1016/j.yjmcc.2015.07.032.

24. Goonasekera SA, Davis J, Kwong JQ, Accornero F, Wei-LaPierre L, Sergent MA, et al. Enhanced Ca2+ influx from STIM1-ORAI1 induces muscle pathology in mouse models of muscular dystrophy. Hum Mol Genet. 2014;23(14):3706–15. https://doi.org/10.1093/hmg/ddu079.

25. Boncompagni S, Pecorai C, Michelucci A, Pietrangelo L, Protasi F. Long-term exercise reduces formation of tubular aggregates and promotes maintenance of Ca2+ entry units in aged muscle. Front Physiol. 2020;11:601057. https://doi.org/10.3389/fphys.2020.601057.

26. Braun A, Vogtle T, Varga-Szabo D, Nieswandt B. STIM and ORAI in hemostasis and thrombosis. Front Biosci (Landmark Ed). 2011;16:2144–60. https://doi.org/10.2741/3844.

27. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367(9524):1747–57. https://doi.org/10.1016/S0140-6736(06)68770-9.

28. Tolhurst G, Carter RN, Amisten S, Holdich JP, Erlinge D, Mahaut-Smith MP. Expression profiling and electrophysiological studies suggest a major role for ORAI1 in the store-operated Ca2+ influx pathway of platelets and megakaryocytes. Platelets. 2008;19(4):308–13. https://doi.org/10.1080/09538080801935710.

29. Bena-Erra A, Galán C, Dionisio N, Gomez LJ, Salido GM, Rosado JA. Capacitative and non-capacitative signaling complexes in human platelets. Biochim Biophys Acta. 2012;1823(8):1242–51. https://doi.org/10.1016/j.bbamac.2012.05.023.
47. Ramanathan G, Gupta S, Thielmann I, Pleines I, Varga-Szabo D, May F, et al. Defective diacylglycerol-induced Ca2+-entry but normal agonist-induced activation responses in TRPC6-deficient mouse platelets. J Thromb Haemost. 2012;10(3):419–29. https://doi.org/10.1111/j.1538-7836.2011.04586.x.

48. Harper MT, Londoño JE, Quick K, Londoño JC, Flocke CV, Philipp SE, et al. Transient receptor potential channels function as a coincidence signal detector mediating phosphatidylserine exposure. Sci Signal. 2013;6(281):ra50. https://doi.org/10.1126/scisignal.2003701.

49. Elvers M, Herrmann A, Seizer P, Munzer P, Beck S, Schönberger T, et al. Intracellular cyclin A is an important Ca2+-+ regulator in platelets and critically involved in arterial thrombus formation. Blood. 2012;119(6):1317–26. https://doi.org/10.1182/blood-2011-12-394384.

50. Wolf K, Braun A, Haining E, Tseng YL, Kraft P, Schuhmann MK, et al. Partially defective store operated calcium entry and hematopoietic stem cell progenitor deficiency. PLoS ONE. 2016;11(1):e0147664. https://doi.org/10.1371/journal.pone.0147664.

51. Chen W, Thielmann I, Gupta S, Subramanian H, Stegner D, van Pozo-Guisado E, Martin-Romero FJ. The regulation of STIM1 by phosphatidylinositol(4,5)bisphosphate activity and modulates canonical transient receptor potential channel 6 function in murine platelets. J Thromb Haemost. 2014;12(4):528–39. https://doi.org/10.1111/jth.12525.

52. Goto SK, Chen W, Kraft P, Becker IC, Wolf K, Strotz S, et al. TRPM7 kinase controls calcium responses in arterial thrombosis and stroke in mice. Arterioscler Thromb Vasc Biol. 2018;38(2):544–52. https://doi.org/10.1161/ATVBAHA.117.310391.

53. Kawasaki T, Ueyama T, Lange I, Feske S, Saito N. Protein kinase C-induced phosphorylation of Orai1 regulates the intracellular Ca2+-+ level via the store-operated Ca2+-+ channel. J Biol Chem. 2010;285(33):25720–30. https://doi.org/10.1074/jbc.M109.022996.

54. Pozo-Guisado E, Martin-Romero FJ. The regulation of STIM1 by phosphorylation. Commun Integr Biol. 2013;6(6):e26283. https://doi.org/10.4161/cib.26283.

55. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from gene expression during cardiac hypertrophy. Curr Vasc Pharmacol. 2013;11(4):497–506. https://doi.org/10.2174/1570157611311040013.

56. Hulot JS, Fauchon J, Ramanujam D, Chaanine A, Aubart F, Sassi Y, et al. Critical role for stromal interaction molecule 1 in cardiac hypertrophy. Circulation. 2011;124(7):796–805. https://doi.org/10.1161/circulationaha.111.013122.

57. Voelkers M, Salz M, Herzog N, Frank D, Dolatabadi N, Frey N, et al. Orai and Stim1 regulate normal and hypertrophic growth in cardiomyocytes. J Mol Cell Cardiol. 2010;48(6):1293–304. https://doi.org/10.1016/j.yjmcc.2009.06.008.

58. Dai C, Zhang Y, Wang Q, Li D, Yang Y, Ma S, et al. Overexpression of TRPC1 reduces the proliferation and migration of endothelial progenitor cells. Stem Cells Dev. 2014;23(2):394–502. https://doi.org/10.1089/scd.2013.0580.

59. Gómez AM, Ruiz-Hurtado G, Benitah JP, Domínguez-Rodríguez A. The role of TRPC channels in cardiovascular disease. Curr Cardiol Rep. 2014;16(9):46418. https://doi.org/10.1007/s11886-014-0464-1.
83. Noorani MM, Noel RC, Marrelli SP. Upregulated TRPC3 and downregulated TRPC1 channel expression during hypertension is associated with increased vascular contractility in rat. Front Physiol. 2011;2(4):22. https://doi.org/10.3389/fphys.2011.00042.

84. Wang M, Tang YB, Ma MM, Chen JH, Hu CP, Zhao SP, et al. TRPC3 channel confers cerebrovascular remodelling during hypertension via transactivation of EGFR receptor signalling. Cardiovasc Res. 2016;109(1):34–43. https://doi.org/10.1093/cvr/cvq246.

85. Wang B, Xiong S, Lin S, Xia W, Li Q, Zhao Z, et al. Enhanced mitochondrial transient receptor potential channel, canonical type 3-mediated calcium handling in the vasculature from hypertensive rats. J Am Heart Assoc. 2017;6.7. https://doi.org/10.1161/JAHA.0005812.

86. Álvarez-Miguel I, Cidad P, Pérez-García MT, López-López JR. Differences in TRPC3 and TRPC6 channels assembly in mesenteric vascular smooth muscle cells in essential hypertension. J Physiol. 2017;595(5):1497–513. https://doi.org/10.1113/jphysiol.2017.153553.

87. Liu D, Yang D, He H, Chen X, Cao T, Feng X, et al. Increased transient receptor potential canonical type 3 channel expression during hypertension is associated with enhanced Ca(2+)-channel blockers. J Cell Mol Med. 2015;19(12):2763–70. https://doi.org/10.1002/jcm.2012.0006.

88. Hu Y, Xia W, Li Y, Wang Q, Lin S, Wang B, et al. High-salt intake increases TRPC3 expression and enhances TRPC3-mediated calcium influx and systolic blood pressure in hypertensive patients. Hypertens Res. 2020;43(7):679–87. https://doi.org/10.1002/hr.14460.02.00499.1.

89. Wilson PC, Fitzgibbon WR, Garrett SM, Jaffa AA, Luttrell LM, Brands MD, et al. Inhibition of phosphoglycerate kinase 1 ameliorates angiotensin II-induced hypertension and inhibits transmembrane calcium entry via store-operated calcium channel. Mol Endocrinol. 2015;29(6):896–908. https://doi.org/10.1210/me.2014-1388.

90. Kohan DE, Rossi NF, Inosco EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. Physiol Rev. 2011;91(1):1–77. https://doi.org/10.1152/physrev.00060.2009.

91. Unger T, Paulis L, Sica DA. Therapeutic perspectives in hypertension: novel means for renin-angiotensin-aldosterone system modulation and emerging device-based approaches. Eur Heart J. 2011;32(22):2739–47. https://doi.org/10.1093/eurheartj/ehr253.

92. Xu Y, Elimbah V, Dhalla NS. Reduction of blood pressure by store-operated calcium channel blockers. J Cell Mol Med. 2015;19(12):2763–70. https://doi.org/10.1111/jcmm.12684.

93. Zuo WL, Du JH, Huang JH, Li S, Zhang G, Chen SL, et al. Tyrosine phosphorylation modulates store-operated calcium entry in cultured rat epididymal basal cells. J Cell Physiol. 2011;226(4):1069–74. https://doi.org/10.1002/jcp.22429.

94. Smith KA, Ayon RJ, Tang H, Makino A, Yuan JX. Calcium-sensing receptor regulates cytosolic [Ca(2+)] and plays a major role in the development of pulmonary hypertension. Front Physiol. 2016;7:517. https://doi.org/10.3389/fphys.2016.00517.

95. Liu XR, Zhang MF, Yang N, Liu Q, Wang RX, Cao YN, et al. Enhanced store-operated Ca(2+) entry and TRPC channel expression in pulmonary arteries of monocrotaline-induced pulmonary hypertensive rats. Am J Physiol Cell Physiol. 2012;302(1):C77–87. https://doi.org/10.1152/ajpcell.00247.2011.

96. Zhoub C, Townsley ML, Alexeyev M, Voelkel NF, Stevens T. Endothelial hyperpermeability in severe pulmonary arterial hypertension: role of store-operated calcium entry. Am J Physiol Lung Cell Mol Physiol. 2016;311(3):L560–9. https://doi.org/10.1152/ajplung.0057.2016.

97. Wang J, Xu C, Zheng Q, Yang K, Lai N, Wang T, et al. ORAI 1, 2, 3 and STIM1 promote store-operated calcium entry in pulmonary arterial smooth muscle cells. Cell Death Discov. 2017;3:17074. https://doi.org/10.1038/cddiscovery.2017.74.

98. Miao R, Wan J, Liu J, Yuan JX, Wang J, Xie W, et al. Bone marrow-derived endothelial progenitor cells contribute to monocrotaline-induced pulmonary arterial hypertension in rats via inhibition of store-operated Ca(2+) channels. Biomed Res Int. 2018;2018:4892349. https://doi.org/10.1155/2018/4892349.

100. Fernandez RA, Wan J, Song S, Smith KA, Gu Y, Tauseef M, et al. Upregulated expression of STIM2, TRPC6, and ORA12 contributes to the transition of pulmonary arterial smooth muscle cells from a contractile to proliferative phenotype. Am J Physiol Cell Physiol. 2015;308(8):C581–93. https://doi.org/10.1152/ajpcell.00202.2014.

101. Song MY, Makino A, Yuan JX. STIM2 contributes to enhanced store-operated Ca entry in pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. Pulm Circ. 2011;1(1):84–94. https://doi.org/10.4103/2045-8932.78106.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.