Orai1, STIM1, and iPLA$_2$β Determine Arterial Vasoconstriction

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There is no need to emphasize the role of Ca$^{2+}$ entry as one of the major factors that determine constriction of arterial smooth muscle cells (SMC). For many years voltage-gated Ca$^{2+}$ channels were thought to be a main path for Ca$^{2+}$ entry, but recently it became clear that a variety of other Ca$^{2+}$-conducting channels exist in vascular SMC, can respond to contractile agonists, and may play important roles in cardiovascular function. One of them is a store-operated channel (SOC) that many thought to be critically important only for store-operated Ca$^{2+}$ entry (SOCE) in nonexcitable cells (that lack voltage-gated Ca$^{2+}$ channels) but recently made its triumphant breakthrough into the reality of the excitable cells. Presently there is no doubt that SOCE is involved in SMC function, but debate continues on whether molecular determinants and mechanism of SOCE found in nonexcitable cells and heterologous systems may be directly applied to vascular SMC. It also remains unclear how important SOCE mechanism is for responses of small pressurized vessels to vascular SMC. It also remains unclear how important SOCE mechanism is for responses of small pressurized vessels to vascular SMC. Importantly, a new article by Smani’s group, demonstrate that Orai1, STIM1, and iPLA$_2$β are equally important not only for SOCE in isolated SMC, but also for Urotensin-induced vasoconstriction of intact coronary arteries. The new findings of the essential role of iPLA$_2$β in agonist-induced Ca$^{2+}$ influx and contractile responses in carotid arteries, together with some earlier findings of the role of iPLA$_2$β in agonist-induced constriction of cerebral, carotid, and mesenteric arteries, established the important role of iPLA$_2$β in agonist-induced constriction of the major arterial beds.

And last but not least, molecular evidence for the critical role of Orai1 in nonselective cat-SOC current and SOCE in primary vascular SMC was finally obtained: The current paper from Smani’s group and an independent study recently published by our group demonstrated that molecular knockdown of Orai1 impairs whole-cell cat-SOC current and SOCE, as well as agonist-induced Ca$^{2+}$ and Mn$^{2+}$ entry in primary vascular SMC. Because of poor cation selectivity, cat-SOC in vascular SMC can serve not only as an important path for Ca$^{2+}$ entry, but also as a depolarizing trigger for a secondary activation of voltage-gated Ca$^{2+}$ channels thus amplifying agonist-induced Ca$^{2+}$ influx, that triggers vascular SMC constriction. Pharmacological inhibitors of Orai1-encoded channel were shown to significantly attenuate agonist-induced constrictions in coronary, as well as cerebral, carotid, and mesenteric arteries.

The Figure illustrates a likely signaling pathway that can be triggered by contractile agonists in vascular SMC, with each step in this pathway now being supported by strong experimental evidence. Physiological activation of SOCE can be triggered by agonist-induced IP$_3$-mediated Ca$^{2+}$ release from ER that leads to Ca$^{2+}$ loss from luminal EF hand of STIM1. This event triggers STIM1 oligomerization and accumulation in ER-PM junctions, which we have shown to be accompanied by production of calcium influx factor. Calcium influx factor was shown to displace inhibitory CaM from plasma membrane-associated variant of iPLA$_2$β leading to localized production of lysophospholipids in plasma membrane, that can in turn activate cardiovascular diseases such as arteriosclerosis, hypertension, and heart failure. In their new article, Smani and coworkers highlight mechanistic interplay between STIM1, iPLA$_2$β, and Orai1 involved in Ca$^{2+}$ entry and coronary artery constriction and demonstrate that molecular knockdown of Orai1 and STIM1 impairs Urotensin-II–induced responses. They also confirmed the role of iPLA$_2$β (and its lysophospholipid product) as endogenous mediators of SOCE, which are required for signal transduction from STIM1 to Orai1, and extended our earlier findings of the functional role of iPLA$_2$β downstream of STIM1 and upstream of Orai1 to coronary SMC. Importantly, a new article by Smani’s group, demonstrate that Orai1, STIM1, and iPLA$_2$β are equally important not only for SOCE in isolated SMC, but also for Urotensin-induced vasoconstriction of intact coronary arteries. The new findings of the essential role of iPLA$_2$β in agonist-induced Ca$^{2+}$ influx and contractile responses in carotid arteries, together with some earlier findings of the role of iPLA$_2$β in agonist-induced constriction of cerebral, carotid, and mesenteric arteries, established the important role of iPLA$_2$β in agonist-induced constriction of the major arterial beds.

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In nonexcitable cells SOCE is mediated by Ca$^{2+}$-selective channel, historically called CRAC (Ca$^{2+}$ release-activated Ca$^{2+}$ channel). This channel is encoded by Orai1 and is thought to be directly activated by ER membrane-resident STIM1, which senses depletion of Ca$^{2+}$ in the lumen of the ER and, through a sequence of molecular interactions, can activate Orai1 in plasma membrane. In contrast, SOCE and agonist-induced contractile responses in primary vascular SMC are known to be mediated by nonselective cation channel (cat-SOC), and additional endogenous mediators (like iPLA$_2$β and its lysophospholipid products) were found to be required for signal transduction from ERresident STIM1 to plasma membrane SOC channels.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Dr Smani and coworkers present compelling evidence for the equally important role of Orai1, STIM1, and iPLA$_2$β in Urotensin-II–induced constriction of coronary arteries. Urotensin-II is one of the strongest known vasoconstrictors and it is related to voltage-gated Ca$^{2+}$ channels.
Orai1-dependent cat-SOC and SOCE. Such cat-SOC not only provides Ca\(^{2+}\) entry into the cell, but can also serve as a depolarizing stimulus leading to activation of voltage-gated Ca\(^{2+}\) channels, thus amplifying and fine-tuning Ca\(^{2+}\) entry and agonist-induced constriction in vascular SMC. Experimentally, activation of Orai1-mediated cat-SOC and CRAC channels can be achieved even in the absence of STIM1, via a number of shortcuts in this pathway: by (1) C-terminal domain of STIM1, (2) calcium influx factor, or CaM inhibitor peptide-induced displacement of CaM from iPLA\(_2\)\(^{\beta}\), and (3) lysophospholipids.

Thus, Orai1, STIM1, and iPLA\(_2\)\(^{\beta}\) are all involved in agonist-induced Ca entry and constriction of vascular SMC and may present attractive targets for development of new pharmacological treatments that, by inhibiting SOCE pathway in SMC, may attenuate pathological vasoconstriction and help treat a broad range of cardiovascular diseases.

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**Disclosures**

None.

**References**

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