The Many Faces of Orai

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Three decades ago, Putney\(^1\) forwarded the idea of store-operated Ca\(^{2+}\) entry in mammalian cells. He rationalized that after the discharge of Ca\(^{2+}\) from an intracellular pool, an undefined signaling pathway would enhance extracellular Ca\(^{2+}\) influx and promote store refilling. Using concurrent advancements in pharmacology, biochemistry, and Ca\(^{2+}\) measurement techniques, the endoplasmic reticulum was readily identified as the intracellular Ca\(^{2+}\) pool and inositol trisphosphate receptor activation as central to the depletion process. The molecular identity of store-operated Ca\(^{2+}\) channels remained unclear till 2005 when unbiased screening arrays first identified stromal interacting molecule-1 (STIM1). This single transmembrane spanning protein resides primarily, although not exclusively in the endoplasmic reticulum, and it retains a luminal EF-hand motif. On internal store depletion, it has been argued that Ca\(^{2+}\) dissociates from this motif and initiates a response that promotes STIM1 aggregation and the direct physical gating to the pore (Figure). The pore-forming subunits of the store-operated Ca\(^{2+}\) channel were later isolated by genetic approaches and the product was termed Orai after the mythological keepers of Heaven’s gate. Multiple Orai subunits, either 4 or 6 based on current literature, constitute a functional channel and when reconstructed, its electrical properties are reminiscent of the Ca\(^{2+}\) release–activated Ca\(^{2+}\) current. Three Orai gene products are expressed in mammals, and it is generally accepted that the pore-forming region of classical store-operated Ca\(^{2+}\) channel singularly comprises Orai1.

Perspectives, however, started to shift in 2008 when STIM1 and Orai1 were observed at low levels in contractile smooth muscle cells.\(^{3,4}\) Expression levels were subsequently found to increase in proliferative smooth muscle, leading to the suggestion that STIM1/Orai1 channels not only enable store refilling but also drive gene transcription and cellular proliferation.

In the current issue of Circulation Research, Gonzalez-Cobes et al\(^{3}\) broaden our understanding of vascular Orais by refocusing the investigative lens from Orai1 to Orai3. Using cultured smooth muscle cells and low noise/high resistance whole cell electric recordings, the authors begin by isolating an Orai1 store-operated Ca\(^{2+}\) current activated by the platelet-derived growth factor. During this examination, the authors unexpectedly observed a distinct thrombin-activated Ca\(^{2+}\) conductance, which operated in a unique store-independent manner. To ascertain the molecular identity of this novel conductance, short hairpin-encoded lentiviruses, small interference RNA sequences, and dominant negative constructs were used to alter channel activity. This examination revealed that STIM1, Orai1, and Orai3 were constitutive members of the thrombin-activated Ca\(^{2+}\) channel, whereas transient receptor potential channel/4/6 were not. It was then revealed that this store-independent Ca\(^{2+}\) current displayed properties akin to the elusive arachidonic acid–regulated Ca\(^{2+}\) channel as activation depended on leukotriene C\(_4\) production.\(^6\) Extending beyond cultured cell lines to native tissue, Gonzalez-Cobes et al concluded their examination by noting that a balloon model of vascular injury augments the thrombin-activated, store-independent Ca\(^{2+}\) current and that in vivo Orai3 knockdown suppresses neointima formation.

The vascular findings of Gonzalez-Cobes et al\(^{3}\) are notable in 3 key aspects. First, they establish that Orai subunits encode for at least 2 distinct conductances, only 1 of which operates as a typical store-operated Ca\(^{2+}\) channel. Second, they highlight that Orai3 is an integral part of arachidonic acid–regulated-like channels in smooth muscle and that their upregulation is integral to transcriptional control and neointimal formation in disease states. Finally, this article furthers our understanding of discrete Ca\(^{2+}\) signaling and how defined Ca\(^{2+}\) channels control cellular processes beyond tissue contraction. Looking forward, this article opens new investigative avenues particularly in the area of regulatory control. What is the mechanism by which a thrombin receptor acutely elevates leukotriene C\(_4\) production and the activity of ORAI3 containing channels? What pool of STIM1 is involved in channel activation and how does this occur independent of store depletion? Likewise, what controls the expression of Orai3 and how does it drive neointima formation? With time, the many faces of Orai should reveal themselves.

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References


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