STIM and Orai Proteins in Calcium Signaling: an *AJP-Cell Physiology* series of Themed Reviews

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CALCIUM RELEASE-ACTIVATED CURRENTS (CRAC) were first described in the early 1990s and shown to carry out key cellular functions. As examples, CRAC channels mediate the depolarizing effect of muscarinic receptor activation in pancreatic β cells (1) and promote cell cycle progression, proliferation, and acquisition of specific immune functions in T lymphocytes (2). It took another 10 years for the two key molecular components that reconstitute this system to be identified. First, in 2005, a protein called stromal interacting molecule 1 (or STIM1), which was originally recognized as a tumor-linked human gene mapping to 11p15.5 (4), was identified in a RNAi screen in *Drosophila* as a key component of CRAC channel function (7). The importance of the finding earned this publication an associated commentary by James W. Putney, who was first in proposing a functional link between intracellular Ca\(^{2+}\) stores (e.g., endoplasmic reticulum) and the plasma membrane (6). The commentary highlighted the resolution of a long-standing mystery on the nature of the link between these intracellular Ca\(^{2+}\) stores and the plasma membrane Ca\(^{2+}\) channels (5). STIM proteins (as there are two genes in mammals) sense endoplasmic reticulum (ER) Ca\(^{2+}\) levels via an EF-hand motif located in the ER lumen, and, upon Ca\(^{2+}\) store depletion, they undergo structural changes, aggregate into oligomers, and translocate close to the plasma membrane (PM) where they enter into interaction with Ca\(^{2+}\) channels to activate them. Second, a year later, through a combined approach of genome-wide RNAi screen for NFAT (a transcription factor selectively activated by CRAC-mediated calcium microdomains) regulators in *Drosophila* and of gene mapping in an extended family of Severe Combined Immune Deficiency (SCID) patients, the plasma membrane calcium channel, named Orai, that responds to Ca\(^{2+}\) store depletion was identified in both human and fly (3). As three genes were in fact identified as encoding Orai channels, the name of the channel was given from Greek mythology: Orai being three sister keepers of the gate of heaven.

The interplay between Orai calcium channels at the plasma membrane and calcium stores within the cell involves not only STIM proteins, but also membrane lipids and a multitude of associated proteins. Over a 9 year period, over 400 publications involving these specialized Ca\(^{2+}\) channels have appeared in PubMed, validating the physiological importance of the Orai/STIM field. This series of *AJP-Cell Physiology* Reviews emphasizes the complexity of this biological system and highlights its significance. The series begins with a review by Amy Spinelli and Mohamed Trebak on Orai channel-mediated Ca\(^{2+}\) signals in vascular and airway smooth muscle cells. This issue also features a review article by Shmuel Mulalle and colleagues on Orai1 and STIM1 in ER/PM junctions in pancreatic cell function and dysfunction. Additional review articles in the next issues will summarize in depth the molecular details of STIM-Orai interaction (Christoph Romanin and colleagues), cover gene expression, alternative splicing, posttranslational modification and trafficking (Barbara Niemeyer), and highlight the importance of this Ca\(^{2+}\) communication system in phagocytic immune cells (Nicolas Demaurex and Paula Nunes) and cancer biology (Natalia Prevarskaya and colleagues).

DISCLOSURES

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AUTHOR CONTRIBUTIONS

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REFERENCES


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