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LETTER

Reply to Thinnes: Is There Competition in Trafficking of VDAC-cored VRAC and SOC in NE Differentiation of Cells?

This is a response to the letter by Friedrich Thinnes (1).

As you point out, it is important to clarify the role of store-operated calcium (SOC) channels in VRAC (volume-regulated anion channel), because calcium entry through SOC channels seems to inhibit Cl^- efflux through VRAC and further induces apoptosis of cancer cell line LNCaP cells (2–4). Some TRP (transient receptor potential) channels involved in SOC entry have been picked up as candidates for the SOC channel in LNCaP cells (5–7), but interaction between these channels and VRAC has not been sufficiently clarified. Furthermore, because Orai1 and STIM1 distribute ubiquitously in our body, they are expected to have a regulatory role over VRAC in various cells. Indeed, the SOC current in LNCaP cells exhibits some CRAC (Ca^{2+} release-activated Ca^{2+})-like properties (5). Their involvement in VRAC, however, has not yet been reported. Therefore, the present discussion should provide new insights as to how we can integrate ongoing research into VRAC and store-operated channels.

In addition to the present three-dimensional structure of Orai1, we have described some TRP channel structures using EM (electron microscopy) image analysis (8, 9). The swollen structures of both store-operated Orai1 and TRPC3 channels should be able to accommodate and/or associate with various components, like the VRAC complex. Single particle reconstruction from EM images is very promising for the analysis of such "super" complexes because it does not require crystallization. Since volume control of cells is universal to physiological functions, including apoptosis in our body, single particle reconstruction of an SOC channel-VRAC "super complex" should enhance the analysis of cell-volume control machinery, which may be general to its related physiology.

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