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Regulation of Ca^{2+} signaling in prostate cancer cells

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Upon store depletion, stromal interaction molecules (STIM) cluster and activate Orai Ca^{2+} channels in the plasma membrane, which mediate SOCE. The Orai protein family consists of 3 members: Orai1, Orai2, and Orai3. Several groups have demonstrated that these homologues can form heteromultimers. In contrast to Orai1 homomeric channels, Orai1/Orai3 heteromeric channels exhibit altered characteristics, such as altered pore properties and sensitivity to reactive oxygen species (ROS) in immune cells.[1,2] Our study[2] demonstrated that, in Orai1, a cysteine residue in position 195 (Cys-195) conferred ROS sensitivity. In Orai3, this cysteine is absent, and consequently, Orai3 lacks ROS sensitivity. However, a gain-of-function mutation in Orai3 (Gly-170 to Cys-170, which is the position equivalent to Cys-195 in Orai1) conferred ROS sensitivity on Orai3. Furthermore, it has been demonstrated that, when one Orai3 subunit is included in the store-operated heteromeric Orai1/Orai3 channel, it is sufficient to prevent ROS-induced block of SOCE.[3]

In 2013, we first described a store-operated heteromeric Orai1/Orai3 channel in human primary prostate epithelial cells (hPEC) and an increase in the Orai1/Orai3 ratio in prostate cancer cells.[4]

Our study, published in 2015, showed that SOCE was differentially regulated by ROS in hPECs and prostate cancer cells.[5] In these cells, as in immune cells, the ROS sensitivity of SOCE was highly correlated to the Orai1/Orai3 ratio.

When we stimulated the membrane androgen receptor (mAR), we observed submaximal store depletion, which was followed by low SOCE signals.[4] An siRNA-based knockdown of Orai3 resulted in a reduction of these low SOCE signals, which emphasized the role of Orai3 in the formation of store-operated Orai1/Orai3 heteromeric channels. Remarkably, when Ca^{2+} stores were extensively depleted with thapsigargin (TG), an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, SOCE was activated, but an siRNA-based knockdown of Orai3 only minimally altered store-operated Ca^{2+} entry, largely consistent with the findings of the Prevarskaya group.[6]

In one additional study, published in 2015, we showed that protein levels of transient receptor potential TRPM4 were elevated in malignant prostate cancer tissue.[7] As previously reported for other cell types, we showed that, in prostate cancer cells, TRPM4 was activated by a rise in intracellular Ca^{2+}. Upon activation, a Na^{+} influx via TRPM4 depolarized the membrane potential in prostate cancer cells, which reduced the driving force for Ca^{2+} and limited SOCE.

Figure 1 displays a simplified model of our findings on Ca^{2+} signaling in prostate cancer cells. TG leads to exhaustive Ca^{2+} depletion of the endoplasmic

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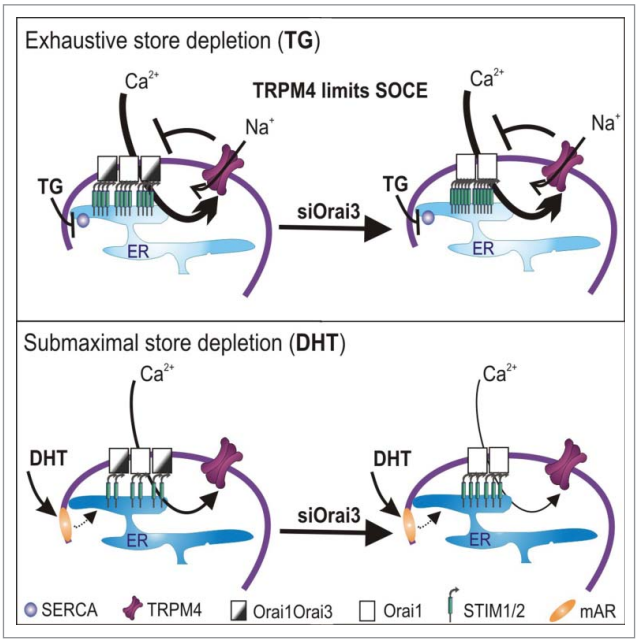

Figure 1. Ca^{2+} regulation in prostate cancer cells upon knockdown of Orai3. Upper panel: In prostate cancer cells, exhaustive store depletion by TG activates SOCE and subsequently TRPM4, as regulator of SOCE. An siRNA based knockdown of Orai3 does not reduce SOCE. Lower panel: Low SOCE signals do not activate TRPM4; thus, SOCE depends on the number of SOCE channels and the STIM/Orai ratio. siOrai3 reduces SOCE. Please see text for details.

reticulum and high SOCE signals. These high levels of intracellular Ca^{2+} activate TRPM4, which acts as an effective negative feedback mechanism for SOCE. In these conditions, a reduction in Orai3 may not be sufficient to reduce the SOCE signal to levels below the threshold for TRPM4 activation. Therefore, when SOCE signals exceed a certain threshold, and TRPM4 is activated, changes in the numbers of Orai1 homomeric channels, Orai1/Orai3 heteromeric channels, and the STIM/Orai ratio[8] may not determine the overall amplitude of SOCE.

In contrast, submaximal store depletion by an endogenous stimulus (dihydrotestosterone, DHT) activates a lower SOCE signal amplitude. Under these conditions, a knockdown of Orai3 leads to a reduction in SOCE. The low SOCE signals may be insufficient for full TRPM4 activation. Thus, changes in the numbers of Orai1 homomeric channels, Orai1/Orai3 heteromeric channels, and the STIM/Orai ratio can determine the amplitude of SOCE, due to little or no negative feedback from TRPM4.

In prostate cancer cells, Ca^{2+} signals contribute to several physiological and pathophysiological functions. Further investigation of the key players involved and their regulation may extend our understanding of Ca^{2+} signals in cancer cells and lead to the identification of putative therapeutic targets in the future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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