Commentary on:
Feng M, Grice DM, Faddy HM, Nguyen N, Leitch S, Wang Y, Muend S, Kenny PA, Sukumar S, Roberts-Thomson S, Monteith GR and Rao R (2010)
Store-independent activation of Orai1 by SPCA2 in mammary tumors.
Cell (143) 84-98.

SIGNALLING

The calcium connection

> “oncogenic pathways are promoted by interactions between ORAI1 and SPCA2”

Changes in the cytosolic concentrations of Ca^{2+} can induce signalling pathways that regulate a broad range of cellular events, including those important in tumorigenesis. A recent study has characterized a new mechanism of constitutive Ca^{2+} signalling that involves the Ca^{2+} store-operated channel ORAI1 and ATP-powered calcium pumps.

One diagnostic feature of breast cancers is the formation of microcalcifications that can be seen on mammograms, suggesting that deregulation of Ca^{2+} signalling might be a characteristic of this type of cancer. To investigate the underlying mechanisms through which this might occur, Feng and colleagues examined the expression of secretory pathway Ca^{2+}-ATPase (Spca) family members in various human breast cancer cell lines and non-malignant cells. They found that the levels of SPCA1 were similar in all cells examined, whereas SPCA2 was upregulated in breast cancer cells compared with non-malignant cells. Knockdown of *SPCA2* in MCF-7 cells (a human breast adenocarcinoma cell line) led to inhibition of proliferation, reduced their ability to form colonies in soft agar and reduced tumour formation in a xenograft mouse model. By contrast, overexpression of SPCA2 in a non-malignant mammary epithelial cell line, MCF-10A, increased proliferation and conferred colony-forming potential: to these cells. Are these oncogenic activities of SPCA2 mediated through Ca^{2+} signalling? The authors found that intracellular Ca^{2+} levels in *SPCA2*-knockdown MCF-7 cells were reduced compared with control MCF-7 cells, and that overexpression of SPCA2 led to increased basal Ca^{2+} concentration, strongly suggesting that upregulation of SPCA2 in breast cancer cells leads to increased intracellular Ca^{2+} and thus tumorigenic capacity.


BANANASTOCK

Is the increased Ca^{2+} concentration observed in breast cancer cells dependent on the known Ca^{2+}-pumping ability of SPCA2? To test this, the authors created a mutant version of SPCA2 with impaired Ca^{2+}-ATPase activity and, surprisingly, expression of this mutant SPCA2 increased cytoplasmic Ca^{2+} levels in HEK293 cells and increased growth of MCF-10A cells on soft agar, similar to the effects of wild-type SPCA2. These results suggested that SPCA2 can induce Ca^{2+} influx independently of its ATPase function.

The authors found that SPCA2 localizes to the plasma membrane in MCF-7 cells, suggesting that it might interact with plasma membrane Ca^{2+} channels to mediate Ca^{2+} entry. Interestingly, although they observed that SPCA2-mediated Ca^{2+} entry was independent of the Ca^{2+} content of endoplasmic reticulum stores, they found that SPCA2 interacted with the store-operated calcium channel ORAI1. SPCA2 co-immunoprecipitated with ORAI1, and SPCA2–ORAI1 complexes could be found at the plasma membrane, indicating that ORAI1 is likely to regulate SPCA2-mediated Ca^{2+} influx in breast cancer cells. Consistent with this, *ORAI1* knockdown in MCF-7 cells reduced basal Ca^{2+} concentration, proliferation, colony formation and tumour formation in a xenograft model, similar to the phenotypes observed on *SPCA2* knockdown. Moreover, *ORAI1* knockdown in MCF-10A cells overexpressing SPCA2 reversed the tumorigenic abilities conferred by SPCA2 overexpression, confirming that oncogenic pathways are promoted by interactions between ORAI1 and SPCA2 in breast cancer cells. The results of Feng *et al.* therefore highlight SPCA2 and ORAI1 as potential targets for therapeutic intervention in breast cancer.

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ORIGINAL RESEARCH PAPER Feng, M. *et al.* Store-independent activation of Orai1 by SPCA2 in mammary tumors. *Cell* **143**, 84–98 (2010)