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Store-Operated Calcium Channel and Cancer

Editorial

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The increase of intracellular Ca^{2+} concentration is an important mechanism that regulates a variety of physiological processes ranging from exocytosis to gene regulation and cell proliferation [1]. Calcium release from intracellular stores (mainly endoplasmic reticulum, ER) or calcium entry through calcium channels can be used by cells to evoke a higher level of cytosolic Ca^{2+} concentration. In non-excitable cells, a major pathway for Ca^{2+} influx is via store-operated Ca^{2+} channels (also known as capacitative calcium entry) [2]. The concept of Store-operated calcium (SOC) channel was first proposed by James Putney in 1986 [3]. In this model, the depletion of intracellular calcium stores triggers calcium entry across the plasma membrane. In 1992, Hoth & Penner identified the presence of this a Ca^{2+} release-activated Ca^{2+} current (CRAC) [4]. Using RNA interference (RNAi)-based approaches, STIM1, an intracellular calcium sensor, was found in 2005 [5, 6]. One year later, Orai1 (CRACM1) was discovered as an essential component of store-operated calcium channel in T cells and mast cells [7, 8]. The role of Ca^{2+} in cell motility has been known for a long time. There is evicence that Ca^{2+} influx is more important than Ca^{2+} release in the migration of fibroblast and breast cancer cells [9, 10].

SOC channel is the major Ca^{2+} entry mechanism in non-excitable cells, including most cancer cells [11]. However, the roles of SOCE in cancer metastasis have not been recognized until very recently. In 2009, Yang and colleagues reported that STIM1 and Orai1 were critical for the migration, invasion of breast cancer cells in vitro, and metastasis in mouse models [10]] . Since this initial report, STIM1 and Orai1 have also been implicated in the dissemination and progression of cervical cancer, colorectal cancer, non-small cell lung cancer, prostate cancer and melanoma [12, 18]. Moreover, the protein levels of STIM1 in cervical cancer specimens and the mRNA ratio of STIM1/STIM2 in breast cancer patients were significantly associated with metastasis and survival [15, 19]. Store-independent activation of Orai1 by SPCA2 also contributes to breast cancer tumorigenesis [20]. Recent genetic association studies further identified a strong correlation between ORAI1 polymorphism and estrogen receptors (ERs) positive breast cancer [21]. Despite differences in experimental design and analytic method, these studies, came to a similar conclusion that SOC channel is clearly associated with the pathogenesis of cancer.

Advances in approaches and techniques have made it possible for scientists to regulate STIM1-Orai1 communication signaling pathways. There is now a growing body of literature supporting important roles of STIM1 and Orai1 in the invasion and metastasis of various tumors. Although the molecular mechanisms by which hyperactive SOC channel promote cancer metastasis is still not fully understood, several pathways including small GTPase Rac and Ras mediated focal adhesion turnover, adhesion regulated tyrosine kinase Pyk2 and mitogen-activated protein kinases have been implicated in mediating signal transductions downstream of SOC channel. We may look forward in the future to having more information on the role of store-operated calcium channels in tumor progression as well as in the cancer therapy.

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