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Stim and Orai mediate constitutive Ca2+ entry and control endoplasmic reticulum Ca2+ refilling in primary cultures of colorectal carcinoma cells

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Store-operated Ca2+ entry (SOCE) provides a major Ca2+ entry route in cancer cells. SOCE is mediated by the assembly of Stim and Orai proteins at endoplasmic reticulum (ER)-plasma membrane junctions upon depletion of the ER Ca2+ store. Additionally, Stim and Orai proteins underpin constitutive Ca2+ entry in a growing number of cancer cell types due to the partial depletion of their ER Ca2+ reservoir. Herein, we investigated for the first time the structure and function of SOCE in primary cultures of colorectal carcinoma (CRC) established from primary tumor (pCRC) and metastatic lesions (mCRC) of human subjects. Stim1-2 and Orai1-3 transcripts were equally expressed in pCRC and mCRC cells, although Stim1 and Orai3 proteins were up-regulated in mCRC cells. The Mn2+-quenching technique revealed that constitutive Ca2+ entry was significantly enhanced in pCRC cells and was inhibited by the pharmacological and genetic blockade of Stim1, Stim2, Orai1 and Orai3. The larger resting Ca2+ influx in pCRC was associated to their lower ER Ca2+ content as compared to mCRC cells. Pharmacological and genetic blockade of Stim1, Stim2, Orai1 and Orai3 prevented ER-dependent Ca2+ release, thereby suggesting that constitutive SOCE maintains ER Ca2+ levels. Nevertheless, pharmacological and genetic blockade of Stim1, Stim2, Orai1 and Orai3 did not affect CRC cell proliferation and migration. These data provide the first evidence that Stim and Orai proteins mediate constitutive Ca2+ entry and replenish ER with Ca2+ in primary cultures of CRC cells. However, SOCE is not a promising target to design for alternative therapies for CRC.

References

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Key words

Colorectal cancer, store-operated Ca2+ entry, Stim, Orai, proliferation.

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