Inhibition of polyamine biosynthesis reverses Ca^{2+} channel remodeling in colon cancer cells

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Store-operated Ca^{2+} entry (SOCE) is the most important Ca^{2+} entry pathway in non-excitable cells. Colorectal cancer (CRC) show decreased Ca^{2+} store content and enhanced SOCE that correlate with cancer hallmarks and are associated to remodeling of store-operated channels (SOCs). Normal colonic cells display small, Ca^{2+}-selective currents driven by Orai1 channels. In contrast, CRC cells display larger, non-selective currents driven by Orai1 and TRPC1 channels. Difluoromethylornithine (DFMO), a suicide inhibitor of ornithine decarboxylase (ODC), the limiting step in polyamine biosynthesis, strongly prevents CRC, particularly when combined with sulindac. We asked whether DFMO may reverse SOC remodeling in CRC. We found that CRC cells overexpress ODC and treatment with DFMO decreases cancer hallmarks including enhanced cell proliferation and apoptosis resistance. Consistently, DFMO enhances Ca^{2+} store content and decreases SOCE in CRC cells. Moreover, DFMO abolish selectively the TRPC1-dependent component of SOCs characteristic of CRC cells and this effect is reversed by the polyamine putrescine. Combination of DFMO and sulindac inhibit both SOC components and abolish SOCE in CRC cells. Finally, DFMO treatment inhibits expression of TRPC1 and STIM1 in CRC cells. These results suggest that polyamines contribute to Ca^{2+} channel remodeling in CRC and DFMO may prevent CRC by reversing channel remodeling.

Keywords**:** Colorectal cancer; DFMO; Store-operated Ca^{2+} entry; Store-operated currents; Polyamines; TRPC1; Sulindac.

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