Role of TRPV4 (Transient Receptor Potential Vanniloid type 4) Channel in colorectal cancer

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Colorectal cancer (CRC) is the largest tumour onset in the Italian population. To date our knowledge of the molecular mechanisms involved in CRC are still poorly understood. TRPV4, the fourth member of the vanilloid subfamily of TRP channels, has been found to be involved in carcinogenic processes by acting as a regulator of tumor angiogenesis (Adapala *et al.*, 2016). Nevertheless, the drastic reduction of TRPV4 expression in human tumor cells suggests a direct role of TRPV4 also on tumor functions, however its role in CRC is largely unexplored. Here, we have investigated the role of TRPV4 in experimental colon carcinogenesis.
We observed that, TRPV4 is constitutively expressed in the gut mainly by epithelium and vascular vessels demonstrated by immunohistochemical localization. We found a dramatic down-regulation of TRPV4 expression revealed by qPCR on primary epithelial cells taken from healthy and tumor-affected area of CRC patients who were staged as pT4N2 at diagnosis. Interestingly, the mRNA expression analysis of TRPV4 in human colon cancer cell lines revealed a very low TRPV4 expression in cell lines with metastatic capacity (Lovo and RKO) compared to Caco-2, as though, TRPV4 decreases over tumor in correlation with the tumor stage. We also observed that GSK1016790A and RN1747 exogenous stimulation (two potent and selective TRPV4 agonists) were able to reduce the proliferation rate of the tumoral Caco-2 epithelial cells revealed by ^{3}H-thymidine incorporation assay. Finally, the intra-tumoral injections of the TRPV4 activator GSK1016790A, was able to reduce tumor growth *in vivo* induced by the subcutaneous injection of Caco-2 cells in nude mice. Overall these ongoing data support our hypothesis that TRPV4 is involved in colorectal carcinogenesis.

Thoppil RJ, Cappelli HC, Adapala RK, Kanugula AK, Paruchuri S, Thodeti CK. TRPV4 channels regulate tumor angiogenesis via modulation of Rho/Rho kinase pathway. Oncotarget. 2016 Mar 26. doi: 10.18632/oncotarget.8405.