

Investigation of TRPM4 and its Role in Cell Migration and Proliferation of Prostate Cancer Cells

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Transient receptor potential melastatin 4 (TRPM4) is a monovalent cation channel, mainly conducting Na⁺ and K⁺. TRPM4 is expressed in a wide range of human tissues, although its expression is most prominent in the prostate and colon. Moreover, TRPM4 protein and RNA expression levels are increased in prostate cancer compared to normal prostate tissue and TRPM4 was recently identified as a cancer driver gene in androgen-insensitive prostate cancer. TRPM4 is activated by Ca²⁺ and plays an important role in intracellular Ca²⁺ signaling through the initiation of an important negative feedback mechanism of store-operated calcium entry (SOCE). As a universal second messenger calcium is regulating multiple biological processes. Therefore, it is important that calcium homeostasis is tightly regulated. However, in several cancers, SOCE and its signaling components are dysregulated, contributing to several cancer hallmarks such as increased proliferation and enhanced migration and inability to undergo apoptosis. Sodium influx via TRPM4 depolarizes the plasma membrane and by that reduces the driving force for further calcium influx. We hypothesize that TRPM4, as negative regulator of SOCE, plays a role in migration and proliferation of prostate cancer cells.

The effect of three novel TRPM4 inhibitors on proliferation of two prostate cancer cell lines, DU145 and LNCaP, cells was analyzed. We recently evaluated the new TRPM4 blocker, 4-Chloro-2-(2-(2-chlorophenoxy) acetamido) benzoic acid (CBA), as a potent inhibitor of TRPM4 current. In whole cell patch clamp experiments of LNCaP cells CBA was shown to block endogenous TRPM4 currents in a low micromolar range. Furthermore, LNCaP cells treated with CBA showed decreased proliferation. Two additional small molecule inhibitors were tested on the same cell line whereof one showed strong negative effect on the viability of LNCaP cells. Furthermore, DU145 cells treated with CBA demonstrated a decrease in migration compared to vehicle treated cells. However, no effect on proliferation was detected for these cells. To further study to role of TRPM4 in prostate cancer cell migration and proliferation, stable TRPM4-knockout cells were generated. In line with our previous data using the blockers, DU145-TRPM4-K.O. cells also displayed decreased migration and, additionally, decreased proliferation compared to DU145-wt cells. Altogether, our data presented here indicates a role of TRPM4 in cell proliferation and migration of prostate cancer cells.