Calcium permeable ion channel remodelling in breast cancer

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Despite advances in early diagnosis and new molecular targeted therapies, some women with breast cancer still have a poor prognosis and those with triple negative breast cancers cannot be treated with hormone receptor targeted therapies or agents that target HER2. Triple negative breast cancers are more common in younger women and are more likely to be associated with metastasis to the brain than estrogen receptor positive breast cancers. Hence, there is a need to identify and define new drug targets for triple negative breast cancers which exhibit a significant overlap with the basal molecular subtype. Given the important role of calcium signalling in proliferation, invasion and cell death pathways, these studies sort to identify calcium permeable ion channels associated with the basal molecular subtype and assess the consequences of their pharmacological modulation. Levels of the Transient Receptor Potential (TRP) calcium permeable ion channel TRPV4 were identified as elevated in a subset of breast cancers of the basal molecular subtype and some basal-like breast cancer cell lines. Pharmacological activation of TRPV4 produced pronounced, rapid and sustained increases in cytosolic free calcium in cell lines with high levels of TRPV4 as assessed in Fluo-4 loaded breast cancer cell lines using a fluorescence imaging plate reader (FLIPR) assay. The functional consequences of TRPV4 pharmacological activation was assessed using live cell imaging (Juli Stage) and revealed distinct multiple cell death pathways with different times of onset. Pharmacological activation of TRPV4 was also identified as able to reduce breast cancer cell growth in vivo. These studies suggest that specific TRP channels may have pronounced overexpression in some triple negative breast cancers and that pharmacological modulation of TRP channels may represent unique opportunities to target this breast cancer subtype.