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Induction of DUSP9 in Xenografts from Human Breast Cancer Cell Lines increases Mammary Cancer Stem Cells

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ABSTRACT

Breast cancer remains a complex disease that kills 40,000 women every year. Initiation and progression of breast cancer is influenced by heterogeneous groups of cells, including mammary cancer stem cells (MCSCs). Progression of this dreadful disease is driven by many signaling pathways among which MAPK pathway is highly prominent. Since targeting prominent kinases in MAPK pathway has been unsuccessful to control breast cancer, it is important to examine the phosphatases that regulate the activity of these kinases.

Using xenograft model from breast cancer cell lines, our lab has found that during the initial stages of xenograft development (week 1-4, 100-200mg weight), ERK1/2 remains inactive. However, during the later stages of tumor development (week 5-15, 300-700mg weight), we found phospho-ERK1/2, which is the active form of ERK1/2 remains highly up regulated. Our lab has also found that presence of inactive ERK1/2 during the initial stages of tumor development was independent of pMEK1/2, which is the upstream kinase that activates ERK1/2. We have also found that a specific dual specific phosphatase (DUSP9) was induced in the xenografts from breast cancer cell lines during initial stages of their development.

I will be examining the significance of DUSP9 induction in the early stages of xenograft development. There are reports that DUSP9-mediated pERK1/2 inactivation has been found to increase mouse embryonic stem cell content. I have been examining the expression levels of MCSCS (Aldehyde dehydrogenase 1(ALDH1)/ OCT3/4 / CD44/SOX2) in various stages of xenograft development and correlating them with DUSP9 expression and pERK1/2. I am examining the expression levels of MCSCs by Western blot analysis as well as qPCR. I have also been treating breast cancer cell line HMLE^{HRASV12} with MEK inhibitors, *in vitro*, for inactivating ERK to analyze the levels of mammary cancer stem cells (ALDH1)/ OCT3/4 /

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CD44/SOX2. I am also examining the levels of DUSP9 as well as the levels of ERK/pERK1/2 /AKT /pAKT in cells treated with MEK1/2 inhibitors *in vitro*. I intend to determine whether inhibition of pERK1/2 could influence embryonic stem cell content as analyzed by the expression of markers Oct ³/₄ and Sox2.

Keywords: Breast Cancer, Mammary Cancer Stem Cells, Xenograft

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