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In vitro modeling of Hedgehog signaling via mesenchymal cell subtypes in triple negative breast cancer

Triple negative breast cancer (TNBC) is a clinical therapeutic challenge due to the lack of receptors for estrogen, progesterone, and human epidermal growth factor receptor 2 which limits treatment options to chemotherapy and radiation. With current standard therapy less than 30% will survive the 5-year remission rate, especially Hispanic and African-American women where TNBC is more frequent and has the lowest (<14%) 5-year survival rates. Recent studies indicate that Hedgehog (Hh) signaling is active and correlates with reduced survival rates in TNBC patients. However, the role of the Hh signaling in the breast tumor microenvironment is not well understood. A main cellular mediator of Hh signaling is the adjacent mesenchyme which promotes tumor growth via a paracrine interaction, but which is also highly heterogeneous. As mesenchymal sub-types have been associated to specific pharmacological therapies, understanding of the mechanisms in mesenchymal-driven tumors is necessary for combinatorial pharmacological treatments that can increase survival rates and eliminate tumor relapse in patients. We developed a novel tumor-mesenchymal *in vitro* model to evaluate the role of mesenchymal cell sub-types from different sources in the proliferative potential and stem cell markers of breast cancer cells using a custom designed multiwell array. Cells were culture in adjacent compartments and active Hh signaling was confirmed by up-regulation of canonical Hh target genes Gli1, Patch1 and SMO. As a source of mesenchymal cell sub-types we evaluated TGF-b treated fibroblasts, cancer- associated and normal breast primary fibroblasts, and tumor epithelial cells that undergo epithelial-mesenchymal transition (EMT). Paracrine Hh signaling significantly increased proliferation of tumor cells after 72-96hrs in co-culture. Cells that undergo EMT promoted cell growth at higher rates than myofibroblasts. Observed increase in tumor cell proliferation was abolished when treated with the Hh signaling inhibitor cyclopamine. Similar results were observed in normal human breast cells suggesting that activation of Hh signaling in the mesenchyme is sufficient to promote cell growth in the epithelium. Computational analysis of a panel of genes associated to Hh signaling in breast cancer patients (>500 samples) show a strong correlation among TNBC patients and mesenchymal-driven Hh signaling in >80% of samples. We evaluated the

distribution of mesenchymal cell-sub-types and stem cells among the sub-set of basal TNBC samples (82 samples). Gene markers associated to myofibroblasts, EMT, mesenchymal stem cell and cancer stem cell were found in samples with active Hh signaling and co-expressed in groups of two or more which represented the 45.6% of the total samples. Together, these results indicate that the Hh-pathway and adjacent tumor microenvironment are key players in the progression of TNBC.Mesenchymal cell component can modulate tumor growth behavior induced by Hh signaling and is a potential new clinical target for TNBC.