Targeting Wnt pathway reduces primary tumor and metastasis in breast cancer models

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Background: Biomarkers CD44 and CD24 are routinely used to identify breast cancer stem cells (BCSGs). BCSGs are chemotherapy resistant and bear high tumorigenesis and metastatic capabilities. Wnt/β-catenin signaling is involved in maintaining CSCs and thus is responsible for recurrence and poor prognosis. Role of Wnt receptor LRP6 in breast cancer promotion and progression is well known. We hypothesized that interactions between cancer cells, macrophages, and endothelial cells induce cancer stemness via activation of Wnt/β-catenin pathway, and blocking that pathway will reduce primary and metastatic tumors.

Methods: Breast cancer cells were co-cultured with macrophages and endothelial cells with or without Wnt inhibitors, BCSC markers were quantified by flow cytometry. CD44+/CD24- cells were FACs sorted and applied to 3D cultures with or without Wnt inhibitors and/or Doxorubicin. In our in vitro studies we utilized two types of Wnt inhibitors, a small molecule LPR6 tyrosine kinase inhibitor Salinomycin and a function blocking monoclonal antibody (2F1)5. We tested the efficacy of 2F1 in two mouse models in combination with Doxorubicin. One model used SCID mice bearing allo grafts of MDA-MB-231 cells. The second used FvB mice bearing syngeneic Mct-1 tumors.

Results: Co-culture of breast cancer cells with macrophages and/or endothelial cells, significantly increases cells expressing BCSC markers, while inhibition of Wnt receptor significantly reduced them. The CD44+/24- cells are found highly resistant to Doxorubicin both in 2D and 3D cultures. In our in vitro experiments the 2F1-Doxorubicin combination significantly reduced primary tumors and lung and bone marrow metastasis as well as improved animal viability.

Conclusions: Inhibition of Wnt pathway significantly reduces the induction of BCSGs in vitro. In vivo both primary tumor and metastatic events were drastically reduced in two mouse models when treated with 2F1 and Doxorubicin. This study introduces LRP6 blocking antibody 2F1 as a promising antitumor agent that can be further developed for breast cancer targeted therapy in patients whose tumors express higher copy numbers of LRP6. Reference: A. Hu Y1, Chen Y, et al. Invest Ophthalmo Vis Sci. 2013 Jan 7;54(1):141-54.

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