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"Lineage-Specific Insulin-Like Growth Factor 1 Receptor Deletion Reveals Protective Role in a Mouse Model of Basal-Like Breast Cancer"

By

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Friday, November 14th, 2025
11:00 A.M.
Cancer Center, G-1196

Join Zoom Meeting

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Password: 570304

ABSTRACT

Breast cancer is the most diagnosed cancer in women, and most breast cancer-related deaths result from the metastatic spread of malignant cells to distant organs. Triple-negative breast cancer (TNBC), an aggressive subtype lacking estrogen receptor, progesterone receptor, and HER2 amplification, accounts for about 15% of breast cancer cases, but nearly one-third of breast cancer deaths due to its heightened metastatic potential. Defining the molecular mechanisms that drive this process remains a critical challenge.

The insulin-like growth factor (IGF) signaling pathway has traditionally been considered a positive mediator of tumor growth and invasion. Paradoxically, our laboratory previously found that reducing insulin-like growth factor 1 receptor (IGF1R) signaling in a Wnt1 oncogene driven mouse model of basal-like breast cancer increased tumor metastatic potential. IGF1R is expressed throughout the mammary epithelium but is most highly expressed in the basal-myoepithelial cell lineage. Thus, to further understand the function of IGF1R in mammary tumorigenesis, we generated a new mouse model where *Igf1r* was conditionally deleted in the basal-myoepithelial lineage (tamoxifen-inducible Keratin 5-CreER^{T}; *Igf1r*$^{fl/fl}$) and crossed that mouse with the Wnt1 tumor model (K5-*Igf1r* KO; Wnt1). Using this novel mouse model, we tested the hypothesis that loss of IGF1R in the basal lineage is sufficient to promote an aggressive phenotype in Wnt1-driven basal-like tumors.

Loss of *Igf1r* in the keratin 5 lineage in Wnt1-driven mammary tumors significantly delayed primary tumor formation and increased both the frequency and size of lung metastases. Flow cytometry revealed a reduction in basal cells and a trending increase in luminal progenitors. Consistent with this shift, tumorsphere assays indicated reduced progenitor expansion capacity. Spatial transcriptomics and Ingenuity Pathway Analysis identified *Kras* as an activated upstream regulator across epithelial, fibroblast, and immune compartments, suggesting enhanced oncogenic signaling following *Igf1r* loss. Consistent with this finding, *Kras* and *Nras* mutations were increased, while *Hras* mutations were reduced in the K5-*Igf1r* KO; Wnt1 tumors. Epithelial-mesenchymal transition (EMT)-focused gene profiling revealed high upregulation of *Zeb2*, *Sox10*, and *Tgfβ3* expression, and immunostaining further exhibited reduced E-cadherin expression. Taken together, these data support increased epithelial plasticity and invasiveness in the *Igf1r* deficient, Wnt1 tumors. Notably, analysis of the METABRIC breast cancer dataset demonstrated an inverse correlation between ZEB2 and IGF1R expression across both TNBC and estrogen receptor-positive tumors, supporting a clinically relevant connection linking low IGF1R to elevated ZEB2 and aggressive breast cancer. Analyses of the tumor microenvironment further revealed a reduction of fibroblasts and macrophages, reduced collagen I deposition, and decreased iNOS expression, consistent with an immune-evasive, metastasis-permissive environment in the K5-*Igf1r* KO; Wnt1 tumors. Functionally, K5-*Igf1r* KO; Wnt1 tumor cells exhibited enhanced adhesion to fibronectin and increased endothelial intravasation, without changes in migration.

Together, these findings demonstrate that basal-myoepithelial loss of *Igf1r* delays tumor initiation but reprograms epithelial and stromal compartments toward *Kras*-driven oncogenic signaling and *Zeb2*-mediated EMT, which enhances their metastatic potential. This work identifies a basal, myoepithelial lineage-specific mechanism linking reduced IGF1R activity to *Zeb2*-associated epithelial plasticity and breast cancer aggressiveness.