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**A novel function for ALK4 in suppressing breast cancer progression**

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**Public Abstract:**

Most breast cancer patients die because of a process called metastasis in which the breast cancer cells spread to distant vital organs. Once breast cancer advances to the metastatic stage, current therapeutic strategies are largely ineffective. Therefore, identification of novel therapeutic targets for metastatic breast cancer are urgently needed. Metastatic breast cancer develops from localized lesions where the cancer cells are restricted by the basement membrane. The cancer cells acquire mutations that allow them to invade through the basement membrane, leading to disease progression. Breast cancer metastasis involves multiple steps, including cell migration and invasion that allows cancer cells to enter blood vessels, survive in the circulation, and colonize the second organ. In addition, the cancer cells undergo a process termed epithelial to mesenchymal transition (EMT) by which the cancer cells lose epithelial cell features and gain connective tissue cell features. The cancer cells that have undergone EMT have enhanced migration and invasion capabilities and increased survival. Here, we aim to identify the changes that increase the ability of breast cancer cells to spread, and aim to develop novel therapeutics for treating breast cancer metastasis. We recently uncovered that activin receptor-like kinase 4 (ALK4), a transforming growth factor-beta (TGF-β) superfamily receptor, is mutated in some breast cancers, with decreased ALK4 expression correlating with high grade breast cancer, advanced stage, and a poorer prognosis. TGF-β is a family of related proteins that binds cell membrane receptors and sends signals into the nucleus to regulate gene expression. We utilized a genetic approach to...
decrease ALK4 protein levels in cultured human mammary epithelial cells and breast cancer cells and demonstrated that loss of ALK4 results in enhanced migration, invasion and EMT, which is often induced by TGF-β. Conversely, restoring ALK4 expression in ALK4 silenced highly metastatic cells and suppressed breast cancer metastasis in a mouse model of breast cancer. In the absence of ALK4, TGF-β signaling was increased in these breast cancer cells. Interestingly, we also found that decreased ALK4 increases TGF-β levels at the cell surface. Therefore, we hypothesize that loss of ALK4 increases TGF-β receptors and their signaling to promote breast cancer progression and metastasis by increasing cell invasion and EMT. In our proposed study, we will investigate how ALK4 expression is decreased during breast cancer progression. We will also assess how loss of ALK4 enhances TGF-β receptors and their signaling, and test whether inhibition of TGF-β signaling can block breast cancer metastasis induced by ALK4 loss in a murine model. The scientific findings of this proposed work could identify ALK4 as a novel biomarker to predict breast cancer progression and a therapeutic target in the treatment of metastatic breast cancer.