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Activation of Farnesoid X Receptor Impairs The Tumor-Promoting Function of Breast Cancer-Associated Fibroblasts

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ABSTRACT

Cancer-associated Fibroblasts (CAFs), the principal components of tumor microenvironment, play multiple role in breast cancer progression. We have previously shown an oncosuppressive role of the nuclear Farnesoid X Receptor (FXR) in mammary epithelial cancer cells, here we assessed whether FXR activation may affect CAF tumor-promoting features.

We showed that FXR is expressed in human CAFs isolated from four patients and treatment with the selective FXR agonist GW4064 decreased CAF migration, stress-fiber formation and contractility. RNA-sequencing highlighted cell movement and pathways known to govern cell cytoskeleton organization and migration among the most down-regulated functions and ingenuity canonical pathways upon GW4064 treatment. FXR activation reduced expression of different secreted factors. Coculture experiments revealed a reduced growth and motility of breast cancer cells treated with conditioned-media derived from GW4064-treated CAFs. Increased FXR levels in bulk tumors correlated with a longer patient survival.

Our results evidence that FXR activation inhibits tumor-stimulatory activities of CAFs by impacting their mechanical properties and their paracrine signaling repertoire, suggesting that nuclear FXR ligands, by targeting both neoplastic cells and supportive stroma, may represent a promising avenue for the future management of breast cancer.