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Role of Farnesoid X Receptor Activation in Counteracting Tumor-promoting Functions of Cancer-Associated Fibroblasts in Breast Cancers

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Cancer-associated fibroblasts (CAFs), the principal components of the tumor microenvironment, play multiple roles in breast cancer onset and progression. While their significance is widely accepted, treatment options to target CAFs in clinical practice have not yet been well established. The nuclear receptor superfamily encompasses a druggable class of molecules, expressed in various stroma and parenchymal cell types, with the interesting therapeutic potential to modulate also the reactive microenvironment. Previously, we have demonstrated that activation of the nuclear Farnesoid X Receptor (FXR) in mammary epithelial cancer cells was associated with a reduction of cell proliferation, migration, and invasion 'in vitro' and tumor growth 'in vivo'. To extend these observations, here, we propose to assess the function of FXR in CAFs and evaluate whether this receptor may affect their tumor-promoting features.

Our results evidenced, for the first time, FXR mRNA and protein expression in CAFs isolated from biopsies of primary human breast tumors. Treatment with the FXR agonist GW4064 treatment was able to significantly decrease CAF motility, stress fiber formation and their contractility. RNA sequencing highlighted cell movement and migration of cells among the most down-regulated functions and identified signalings known to govern cell cytoskeleton organization and migration (i.e. ILK-actin cytoskeletal-Rho signalings) among the most down-regulated ingenuity canonical pathways in response to GW4064 treatment. Accordingly, decreased expression and activation of proteins and/or downstream effectors of these pathways were observed in GW4064-treated CAFs. Moreover, FXR activation reduced expression of different secreted factors, that act as mediators of tumor-stroma interaction. Indeed, coculture experiments revealed a significant inhibition in growth and motility of breast cancer cells treated with conditioned-media derived from GW4064-treated CAFs compared to vehicle-treated CAFs. All this sounds to fit with the clinical relevance that increased FXR levels in bulk tumors are associated with a statistically significant longer survival of patients.

In conclusion, FXR ligands, by targeting both breast cancer epithelial cells and tumor associated stroma, may represent emerging pharmacological tools to be exploited for the future management of breast cancer.

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