Stromal protein expression in breast cancer is differentially regulated by TGF-β1

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Aim: The significance of the tumor microenvironment in cancer progression is increasingly acknowledged. Reduced periductal decorin expression correlates with the presence of myxoid stroma in ductal carcinoma in situ (DCIS) of the breast, and both are significantly associated with an increased recurrence risk. Suppression of stromal decorin expression might contribute to the pathogenesis of myxoid stroma, as it plays an important role in collagen fibrillogenesis. Stromal changes may reflect the propensity of some DCIS lesions to progress to invasive cancer. We aimed to investigate the paracrine regulation of decorin expression and related extracellular matrix (ECM) proteins.

Methods: Immortalized cancer-associated fibroblasts (CAFs) were used as an in vitro model. Effects of cytokines on stromal protein expression were assessed by RT-PCR and Western blotting. Co-culture experiments were performed with conditioned medium (CM) of breast cancer cells (BCC). Immunohistochemistry was carried out on DCIS specimens. Adhesion assays were performed by seeding BCC on decorin and collagen coatings, and on CAF-derived matrices.

Results: TGF-β1 strongly enhanced the expression of biglycan, versican and type I collagen in CAFs, whereas it caused downregulation of decorin, lumican and fibromodulin. Despite the previously reported correlation between myxoid stroma and reduced stromal decorin expression, no statistically significant association was found between myxoid stroma and periductal biglycan or versican expression, although there was a tendency for the latter. Co-culture experiments showed that BCC-derived CM enhanced versican and biglycan expression, and caused downregulation of decorin expression in CAFs. Adhesion assays revealed that decorin coatings prevent adhesion of breast cancer cells. BCC, seeded on matrices derived from TGF-β1-treated CAFs, adhere in a highly organized manner along preformed ‘tracks’, as compared with the random adhesion pattern on matrices derived from untreated CAFs.

Conclusion: TGF-β1 seems a powerful modulator of the peritumoural extracellular matrix. In the breast, a decorin-depleted stroma enriched in versican might represent a DCIS-induced invasion-permissive ECM.

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