

Molecular Mediators of Mammographic Density

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Background

Mammographic density (MD), created predominantly by increased stromal tissue, is a major risk factor for breast cancer, though little is known about the biological mechanisms mediating it. Tamoxifen prevents breast cancer in high-risk women via mechanisms that appear dependent on reduction of MD. Animal models suggest tamoxifen remodels the mammary stroma to a tumour-inhibitory phenotype.

Aims

This study aims to analyse the effect of tamoxifen on breast fibroblast function and identify pathways contributing to the density-associated risk.

Methods

Primary human breast fibroblasts from normal, high risk or breast cancer patients were treated with hydroxytamoxifen (4-OHTam, 100nM-5µM). Fibroblast function was analysed by measuring: proliferation, expression of stromal proteins fibronectin (FN), LOX and collagen 1; effects on TGF-β signalling and expression of the myofibroblast marker SMA. Genome wide analysis was performed using RNA-Seq.

Results

Fibroblasts from 25 patients were treated with 4-OHTam. All patients showed reduced proliferation with treatment. 62% of patients showed reduced FN expression. TGF-β-mediated upregulation of SMA and FN were consistently inhibited.

RNA-Seq analysis revealed downregulation of Wnt signaling, a pro-fibrogenic and pro-tumourigenic pathway, and modulation of many metabolic pathways, including components of the microsomal anti-oestrogen binding site (AEBS). Binding of tamoxifen to the AEBS inhibits ChEH activity promoting an anti-tumourigenic phenotype. The effects of tamoxifen on fibroblasts could be replicated using tesmilifene, a commercially available inhibitor of ChEH.

Conclusion

These data indicate that tamoxifen can directly remodel the stromal microenvironment, generating a less 'reactive' stroma. Thus, tamoxifen impacts on multiple pathways, many independent of the oestrogen receptor, to create a tumour-inhibitory microenvironment. This offers exciting potential for patient monitoring and alternative cancer prevention strategies.