

Interactions between breast cancer cells and their stromal component: An analysis of alterations in gene expression

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Abstract

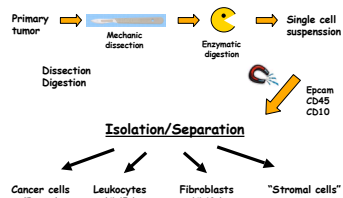
Background: Epithelial-stromal interactions are known to be important in normal mammary gland development and to play a role in breast carcinogenesis. The aim of this study was to explore the influence of breast tumor microenvironment on primary tumor growth, breast cancer sub-typing and prognosis.

Methods: Myo-fibroblast cells (CD10) were isolated and purified from breast tumor (N= 28) and normal (N=4) tissues. Gene expression analysis was performed using the Affymetrix GeneChip® Human Genome U133 Plus 2.0 arrays. Survival analysis was carried out using 12 publicly available microarray datasets including more than 1200 systemically untreated breast cancer patients.

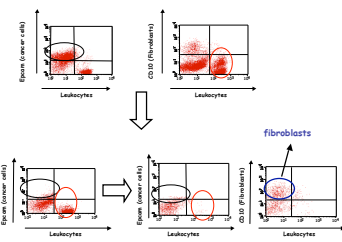
Results: Breast tumor myo-fibroblast stroma cells showed an altered gene expression patterns to the ones isolated from normal breast tissues. While some of the differentially expressed genes are found to be associated with extracellular matrix formation/degradation and angiogenesis, the function of several other genes remains largely unknown. Unsupervised hierarchical clustering analysis clustered breast tumor myo-fibroblast cells into subgroups recapitulating the molecular portraits of breast cancer based on ER, HER2 status and tumor differentiation. A stroma gene expression signature developed from myo-fibroblast cells isolated from normal versus BC tissues showed a statistically significant association with clinical outcome. Breast tumors with high expression levels of the stroma signature were significantly associated with worse prognosis (HR 1.95; CI 1.20-1.99; p=5.57 10⁻⁴). This association was only observed within the clinically high risk HER2+ subtypes. Interestingly, HER2+ tumors with high and low expression levels of the stroma signature showed 45% and 85% distant metastasis free survival at 5-year follow-up respectively (HR 2.53; CI 1.31-4.90; p=5.29 10⁻³).

Conclusions: Our results highlight the importance of tumor epithelial-stroma cell interactions in breast carcinogenesis and breast cancer sub-typing. Moreover, it shows the role of stroma cells in tumor dissemination particularly within the HER2+ subtype and provide basis for the development of novel therapeutic strategies.

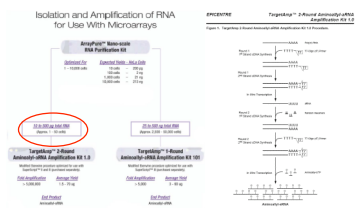
Experimental Protocol



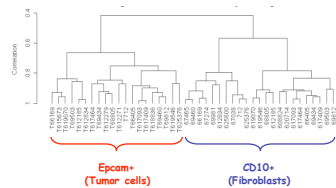
Purification of CD10 (fibroblasts) and Epcam+ (tumor) cells



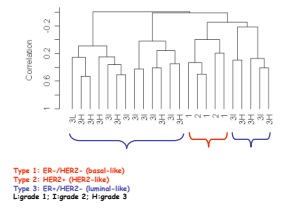
Amplification protocol



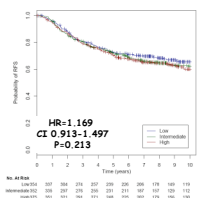
Unsupervised Analysis of CD10+ and Epcam+ cells



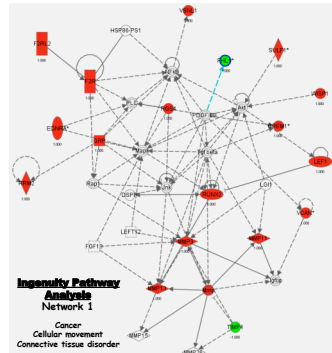
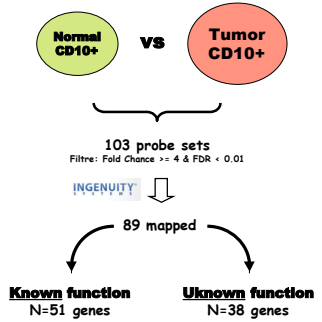
Differences in Gene Expression of CD10 (fibroblasts) According to Molecular Subtypes



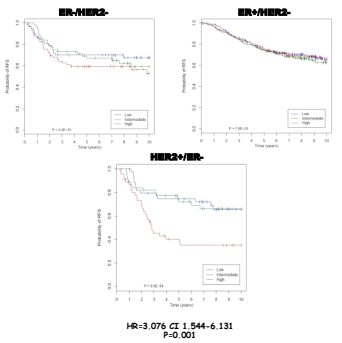
Clinical Relevance? All patients N≈1400 Systemically Untreated



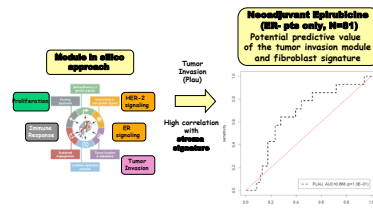
Tumor Fibroblast Signature CD10+ Tumor vs CD10+ Normal



Clinical Relevance? Molecular Subtypes



Tumor Fibroblast Signature Response to Therapy



Acknowledgments
FNRS, MEDIC Foundation, Breast Cancer Research Foundation (BCRF, Evelyn Lauder)