Neoplasic transformation and modulation by extracellular matrix: the role of proteoglycans, EGF receptors and heparanase.

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The *c-erbB-2* gene is amplified in up to 30% of breast cancer tumors and its overexpression is correlated with a worse prognosis. A monoclonal antibody target to this antigen (Trastuzumab) has been recently introduced for the treatment of metastatic breast cancer patients whose primary tumors overexpress *c-erbB-2* gene and several studies have already shown encouraging clinical results. We are interested to select peptides that specifically inhibit ErbB2 activity. The peptide selection has been done using a phage display library that consists of 10^9 different random10-mer peptides expressed in the phage capsid and the peptide selected competes with Trastuzumab. It was also observed that trastuzumab increases heparan sulfate synthesis, showing a correlation between ErbB2 and heparan sulfate proteoglycan. Heparanase is an endo-beta-glucuronidase that degrades heparan sulfate proteoglycans and has been implicated in tumor development and metastasis. Semiquantitative RT-PCR analysis from mononuclear fraction of peripheral blood samples had demonstrated that breast cancer patients expressed significantly high levels of heparanase while healthy women did not express heparanase. We also found a decrease of heparanase expression after surgery ($p = 0.002$) and tamoxifen treatment ($p = 0.04$). However, there was an increase at heparanase expression with metastasis ($p = 0.027$). Seventy percent of lymphocytes from breast cancer patients were labeled with heparanase polyclonal antibody while only 10\% from healthy women. However, when healthy women lymphocytes were incubated with plasma obtained from breast cancer patients or with MCF-7 cells (human breast cancer cell line in culture), there was a three times increase in the heparanase expression. This data suggests that tumor cells and plasma from tumor bearing patients can stimulate lymphocytes to express heparanase.