Heparan sulfate proteoglycan mediates resistence in breast cancer cells

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The monoclonal antibody trastuzumab is used in the treatment of HER2 positive breast cancer. Trastuzumab resistance has become a major focus in breast cancer research, but so far there are no reliable markers to explain the resistant mechanisms. Extracellular matrix molecules can be directly involved in cancer development. In order to assess a possible relationship between trastuzumab resistance and such essential components of extracellular matrix, glycosaminoglycans (GAG) profile and the expression of HER2, proteoglycans and heparanase was evaluated in different breast cancer cells, as well as a non-tumor lineage. Stable transfection using heparanase cDNA triggered tratuzumab resistance in the MCF-7 cell line. The profile of GAG and disaccharides were significantly different comparing the breast cancer cell lineages. Breast cancer cell lines responsive to tratuzumab present higher amounts of HER2, syndecan-1 and heparan sulfate (HS) on the cell surface, but low levels of secreted HS. Moreover, HS shedding was significantly increased in the resistant cells. FRET analysis proved interaction between tratuzumab and HS. There is a correlation between heparanase expression, GAG and proteoglycan synthesis which can possibly explain different patterns of tumorigenesis. The data propose that trastuzumab effect is modulated by cell surface HS. Furthermore, high levels of HS shedding are able to block the antibody action. Therefore, HS synthesis and shedding determine breast cancer cell susceptibility to trastuzumab.