MATHEMATICAL MODELING OF THE EFFECTS OF HER2 OVEREXPRESSION ON CELL PROLIFERATION AND CELL CYCLE IN BREAST CANCER

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ABSTRACT

The HER family of receptors (also known as type I receptor tyrosine kinase RTKs) plays a major role in promoting breast cancer cell proliferation and malignant growth. This receptor family is comprised of four homologous receptors: EGFR (ErbB1/EGFR/HER1), HER2 (erbB2/neu), HER3 (ErbB3), and HER3 (ErbB4). Overexpression of the HER2 receptor, due to the neu gene amplification, contributes to the development of human breast cancers. The carcinogenic effects of HER2 protein overexpression on cell growth and cell proliferation have been observed in a variety of experimental systems. These observations suggest that HER2 overexpression provides tumor cells with a growth advantage leading to a more aggressive phenotype.

Although these effects have been attributed to high levels of HER2-expression, there has been no quantitative (theoretical) linkages between HER2 expression levels and the proliferation rate of HER2-overexpressing cells. To investigate the effects of HER2 receptor overexpression on cell proliferation, we have developed two mathematical models that describe the proliferative behavior of HER2-overexpressing cells. In this thesis we address by means of mathematical models and numerical simulation the following major questions:

1. How does the cell proliferation rate depend on the number (expression level) of the HER2 receptor?

2. How do changes in the number of HER2 and EGFR receptors during the cell-cycle affect the cell proliferation rate?

The cell proliferation models enable us to simulate the proliferative behavior of the HER2-overexpressing cells with various HER2 and EGFR expression levels at various ligand concentrations. Both mathematical models predict a growth advantage associated with excess in cell surface HER2 receptors.

This thesis supports the view that overexpression of HER2 receptors contributes to the inappropriate proliferation of breast cancer cells.