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TK1 as a Biomarker of Chemosensitivity and Metastatic Potential in Breast Tumors

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Eric Olsen and Kim O’Neill, Microbiology and Molecular Biology

Introduction

Breast cancer is the most common form of cancer in women, accounting for 23% of total cancer cases and 14% of cancer deaths. Breast carcinoma is not a simple disease. It is comprised of many different biological forms with distinct phenotypes and prognoses. Hormone receptor expression, such as ER, PR, and HER2, along with more universal clinical manifestations like pathological stage, grade, and lymph node invasion are often used for patient prognosis. The heterogeneous nature of breast tumors makes prognosis and response to therapies difficult to determine, and further research is needed to classify breast tumors and their response to traditional therapies.

This study documents the potential of Thymidine Kinase 1 (TK1) to be utilized as a marker of malignant potential and sensitivity to chemotherapies in breast cancers. TK1 is an enzyme active during the S phase of the cell cycle that contributes to DNA synthesis, and is thought to contribute to a high proliferative potential in cancerous cells.

Methodology

Four publicly available datasets were utilized for analysis of gene expression and clinical markers of disease progression, which allowed for a better understanding of how the expression of TK1 correlated to the severity of each individual’s disease. Other statistical analyses were utilized to estimate overall survival time in patient populations.

Assays were also performed in cultured cells. For in vitro assays, cells were cultured in standard cell culture media supplemented with fetal bovine serum. To investigate the effects of TK1 on the behavior of cultured cancer cells, we manipulated the expression of this protein through RNA knockdown. TK1 mRNA-targeting drugs were introduced into the cell through Lipofectamine, a reagent that creates holes in the cell membrane. This subsequently decreased the levels of TK1 in cells, which were compared with a control group of cells. For assays utilizing chemotherapeutics, 5-fluorouracil (5-FU), a common drug used in breast cancer patients, was used. All experiments were done using MDA-MB-231 cells, a triple-negative breast cancer cell line.

Results

Clinical dataset analysis indicated a correlation between high TK1 expression and poor outcomes, including a higher incidence of metastasis and lymph node invasion. Additionally, survival analysis suggested that TK1 expression loses its prognostic capability when patients were treated with chemotherapy—in patients treated with chemotherapy, high TK1 expression did not correlate to poor outcomes. This suggests that tumors high in TK1 respond more favorably to chemotherapy. In vitro analysis also indicated that low TK1 levels correlated with less malignant cells. A reduction in TK1 protein levels was accompanied by reduced growth rate of cancer cells, as well as a reduced capacity to migrate.
Chemotherapeutics were found to be more effective in cells high in TK1 than in cancer cells in which TK1 levels had been diminished.

Discussion

Multiple datasets exhibited a significant correlation between TK1 expression in breast cancer and metastatic event at 3 years, lymphatic invasion, and cancer grade. TK1 knockdown caused a significant inhibition of proliferative and migratory capacity in breast cancer cells, while melanoma cells that had metastasized to the breast exhibited neither of these differences. This suggests that the effect of TK1 in mediating metastatic potential may be limited to primary breast tumors, as well as breast tumors that metastasize to other locations. Significant differences in cell growth in the presence 5-FU were seen in aggressive breast cells but not in metastatic melanoma cells, again indicating TK1 as a mediator of chemotherapeutic response only in breast cancer cells. Our results suggests a role for TK1 in mediating the effects of treatment with chemotherapy as well as the metastatic potential of breast cancer cells. Additionally, TK1 is implicated as an effective prognostic marker of chemosensitivity in breast cancers.

Conclusion

Personalized medicine is the idea that genomic analysis can be utilized to prescribe specific treatments to patients based on their genetic makeup. It has the potential to revolutionize the way cancer patients are prescribed medicines. While these data show potential for the utilization of TK1 expression data in personalized cancer treatment—indicating that cancers with high TK1 expression respond well to chemotherapeutic drugs—further testing is needed to verify current results. Our experiments were done in one high-TK1-expressing breast cancer cell line, MDA-MB-231, but thorough testing would include multiple other cell lines. Experiments should eventually be done in mice to verify the effects of chemotherapeutics on cancer cells in a living system, as in vivo results can sometimes vary greatly from in vitro results.

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