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Glucose regulated protein (GRP-78)-mediated selective phosphorylation of Akt on threonine 308 sensitizes breast cancer cells to tamoxifen-induced cytotoxicity.

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Breast cancer is the most prevalent cancer in women. Tamoxifen (TAM) has been used for several years as an effective drug for treating estrogen receptor positive breast tumors. However, resistance to TAM is a major challenge in treatment of breast cancer. Accumulating evidence has highlighted the role of Glucose-regulated protein (GRP)-78, the master regulator of the unfolded protein response, in chemoresistance. The present study aimed to decipher the function of GRP78 during response to TAM in breast cancer cells. Among a panel of drugs -paclitaxel, doxorubicin, 5-fluorouracil, UCN-01 and tamoxifen, only TAM induced apoptosis and up-regulated the expression of GRP78 in MCF-7 and MDA-MB-231 cell lines. Inhibition of GRP78 augmented apoptosis and overexpression rendered the cells resistant suggesting a decisive role for GRP78 in TAM-mediated cytotoxicity. Mechanistically, TAM selectively unregulated phosphorylation of Akt on Thr308 but not on Ser473, and silencing of GRP78 resulted in inhibition of Akt (Thr308) phosphorylation. GRP78 inhibition prevented TAM-induced phosphorylation of GSK3β, a downstream substrate of Akt implicating a role for GRP78 in TAM-induced Akt activation. Additionally, our study demonstrated a physical association of Akt and GRP78 that may be decisive for cell survival. The present study identifies a crucial role for GRP78 and Akt-mediated survival mechanism during TAM-induced response in breast cancer cells. The findings provide evidence for the protective function of GRP78 in stressed cells to promote drug resistance and suggest that a combination of compounds targeting GRP78 and anticancer drugs like TAM would be beneficial to overcome therapy resistance.

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A series study on brain metastasis for breast cancer

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Brain metastasis is the principle cause of death for breast cancer, we have conducted a series of studies on the occurrence, development, and treatment of breast cancer brain metastasis. Firstly, we analyze the clinical characteristics and prognostic factors of breast cancer patients with brain metastases, and found that WBRT+SRS is better than WBRT alone in multiple brain metastases, SRS alone can replace WBRT+SRS used in patients with less than three brain metastases. We also constructed a nomogram for predicting 1st and 2nd year overall survival, which exhibited good accuracy in predicting overall survival. Secondly, we investigated the risk and relapse of perihippocampal (PH) metastases in breast cancer, and found that hippocampal metastases were identified in 1.2% of metastases and 4.1% of patients. pH lesions comprised 3.5% of lesions in 11.1% of patients. The risks of PH metastasis recurrence were 4.6% for WBRT and 6.8% for sub-therapeutic irradiation in the pH region. Thirdly, we invested the characteristics of cystic BM in a large cohort of breast cancer patients and found patients with cystic metastasis were characterized by a larger metastasis volume, a shorter progression-free survival (PFS) following their first treatment for BM, and poor overall survival after BM ($p<0.05$). This study shows that cystic BM from breast cancer, a special morphological type of BM, had worse prognosis than the more commonly observed solid BM. Fourthly, we revealed that reirradiation is an effective and a safe treatment for patients with brain metastases from breast cancer. Patients with a high KPS score, stable extracranial metastasis and good response to reirradiation might be benefit from reirradiation, whereas patients with peritumoral edema, cystic brain metastasis and a low KPS score might not be appropriate candidates for reirradiation.

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