

IDENTIFICATION OF SIGNALING NETWORKS INVOLVED IN BREAST CANCER METASTASIS TO THE BRAIN USING PROTEOMIC APPROACHES

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Brain is a common site of breast cancer metastasis, associated with significant neurologic morbidity, decreased quality of life, and greatly shortened survival. Development of new preventive and therapeutic strategies for controlling and treating breast cancer brain metastasis would benefit from in-depth knowledge of the molecular mechanisms underpinning breast cancer spread to the brain. We used proteomic analysis, 2D-DIGE (Differential in Gel Electrophoresis) followed by LC-tandem and Quadrupole Time-of-Flight (Q-TOF) Mass Spectrometry to identify the proteins differentially expressed in brain-targeting breast carcinoma cells (MB231-Br) compared with the parental breast cancer cell line from which it was developed (MB-231). Based on these analyses, we identified 12 proteins exhibiting greater than 2-fold ($p < 0.05$) difference in expression between these two cell lines. Recently, a list of 19 proteins differentially expressed in brain-targeting 435-Br1 cells compared with parental MDA-MB-435 cells was identified by another group using a similar approach (Martin et al., *J Proteome Res.* 2008 7:908-920). Between the two sets (MB-231-based identified by our group and MB-435-based reported by Martin et al.) only 2 proteins, HSPA8 and vimentin, were the same. Remarkably, however, as revealed by the Ingenuity pathways analysis, both sets of proteins converged on the same major signaling network involving NF κ B, TP53 and HSP70 pathways. These results demonstrate that different cancer cell lines may exploit distinct avenues to achieve the same goal, i.e. activate signaling networks required for organ-specific colonization of the brain. Creating new treatment paradigms targeting these signaling networks, rather than single proteins, offers a new and exciting approach in the treatment of brain metastases.