Imbalanced Folate Status Promotes Metabolic Stress, Cancer Stem Cell Phenotype, and Proteomic Signatures of Human Breast Cancer Cells

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Prescription of chemotherapeutic anti-folate drugs is the frontline treatment for breast cancer patients to induce folate-deficit cancer cytotoxicity. Alongside, folate supplements are used to reduce host toxicity. Few evidence has identified the exposure of cancer cells to low folate (LF) and high folate (HF) microenvironment can result in drug resistance and promote malignancy transformation, a cancer stem cell (CSC) phenotype. This study investigated whether imbalanced folate stress may promote CSC-mediated anchorage-independent tumorspheroid formation of breast cancer cells, the index of metastasis potential, and its underlying pathway. By western blot and flow cytometry analysis, cultivation of MCF-7 cells with LF and HF mediums promoted imbalanced folate metabolic stress, which coincided with increased expression of the pluripotent stemness markers (Sox2 and Nanog), stemness surface marker CD133, and epithelial to mesenchymal transition markers. Tumorspheroid assay revealed that both HF and LF exposure promoted self-renewal property of MCF-7 cells, evident by anchorage-indepdent tumorsphere formation. Quantitative proteomic analysis identified the changed complex signaling network signatures during transition of imbalanced folate cells to acquire CSC features in bioenergetics transformation, apoptotic and survival signaling, and upstream regulators of cellular migration and invasion. Our data for the first time demonstrated that imbalanced folate stress reprogrammed breast cancer cells into CSC to promote onco-spheroid formation with distinctive proteomic signatures of mediating their invasive and metastasis capability. The novel signatures could be used as therapeutic targets in the design of personalized nutrition-antifolate therapy for breast cancer.

Awards Won:

Fourth Award of $500