Targeting One-Carbon Metabolism in Triple Negative Breast Cancer Cells

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Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype and is characterized by its lack of estrogen, progesterone, and human epidermal growth factor (HER2) receptors, making hormonal and HER2-targeted therapies ineffective. One-carbon metabolism supports tumor proliferation by supplying carbon units for nucleotide synthesis. Tumors often rely heavily on specific one-carbon metabolism enzymes, such as serine hydroxymethyltransferase (SHMT) which correlate with increased tumor aggressiveness, higher metastatic potential, and poor overall patient survival. Based on this, we hypothesized that SHIN2, a small-molecule SHMT inhibitor, would reduce one-carbon unit production, leading to impaired nucleotide synthesis and reduced cell proliferation. SUM159 and MDA-MB-231 TNBC cell lines were treated with SHIN2 in the presence or absence of formate supplementation. Cell viability was quantified using sulforhodamine B (SRB) assays to evaluate SHMT dependence and the ability of formate to rescue SHIN2-induced growth inhibition. Liquid chromatography-mass spectroscopy (LC-MS) was additionally used to quantify metabolic changes with SHIN2 treatment and formate supplementation. Preliminary data shows that treating TNBC cell lines with SHIN2 causes a significant decrease in cell viability and formate supplementation rescues these effects, indicating an on-target drug response. LC-MS analysis further revealed significant glutathione depletion with SHIN2 treatment, suggesting future exploration of ferroptosis as promising therapeutic vulnerabilities in TNBC. Supported by NIH R25ES020721, NIH R35GM154956, and the New Jersey Health Foundation.