Depletion of S-adenosylmethionine Synthesis Reduces Triple Negative Breast Cancer Cell Proliferation Independent of Oxidative Stress

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Triple-negative breast cancer (TNBC) is a type of aggressive breast cancer with a poor prognosis. TNBC is characterized by the lack of estrogen, progesterone, and human epidermal growth factor 2 (HER2) receptors, making hormonal or HER2-targeted therapies ineffective. Currently, methionine adenosyltransferase 2A (MAT2A) inhibitors are under clinical investigation for their efficacy as a potential therapeutic target in many cancer types, including TNBC. MAT2A is responsible for S-adenosylmethionine (SAM) production, which is the substrate for methylation reactions and is a precursor to the transsulfuration pathway. The transsulfuration pathway produces cysteine, which is the precursor to the major antioxidant glutathione (GSH). Data from the McBride Lab shows that treating TNBC cells with the MAT2A inhibitor AG270 causes a potent decrease in cell proliferation and decreased levels of SAM, transsulfuration pathway metabolites, and GSH, which indicates elevated oxidative stress. Thus, we aimed to investigate whether the cell death was caused by this oxidative stress induced by MAT2A inhibition. We performed add-back experiments in AG270-treated TNBC cells, supplementing cell culture media with different metabolites in the transsulfuration pathway, and reducing lipid oxidation with a ferroptosis inhibitor, and then measured cell proliferation with Sulforhodamine B assays. Restoring transsulfuration pathway metabolite levels and reducing lipid radical levels failed to rescue the anti-growth effects of AG270. We conclude that the anti-proliferative effect of MAT2A inhibition in TNBC cells is independent of disrupting the transsulfuration pathway to induce oxidative stress, and we look to confirm that it is due to SAM-mediated methylation in the future. Supported by NIH R25ES020721, NIH 1R35GM154956, and the New Jersey Health Foundation.