Metabolic Reprogramming Underlies Differential Effects of Folate Depletion in Nonmetastatic and Metastatic Claudin-low Breast Cancer

Cells undergo metabolic reprogramming during oncogenic transformation and cancer progression. Proliferating cells exhibit a high demand of carbon for biosynthesis, and the folate one-carbon cycle plays an important role in providing the necessary structural intermediates. Aberrant folate metabolism has been implicated in the development of several cancer types, though underlying mechanisms remain unclear. Our lab previously showed that a folate-restricted diet increased growth and invasion of orthotopically transplanted invasive mesenchymal nonmetastatic murine caudin-low breast cancer cells (M-Wnt) in vivo. In contrast, it decreased growth and lung metastases of transplanted metaM-Wnt cells, a metastatic subclone of the M-Wnt tumor. The current study set out to explore the metabolic reprogramming of the two cell lines underlying the differential response to folate withdrawal. The nonmetastatic and metastatic cells differ in several metabolic pathways, including energetics and autophagy. To examine the effect of long-term folate depletion (LFD) on M-Wnt and metaM-Wnt cell metabolism in vitro, the two cell lines were grown in standard or folate-depleted media for 14 days. Both M-Wnt and metaM-Wnt cells exhibited more autophagy and oxidative stress following LFD. However, following LFD, metaM-Wnt cells showed decreased viability and increased apoptosis. These results suggest that cells underwent metabolic reprogramming in response to nutrient stress. Nonmetastatic M-Wnt cells were able to adapt to nutrient starvation through reprogramming glutathione metabolism and upregulating autophagy. In contrast, metastatic cells were less adaptable, and thus folate restriction prevented growth of these cells.