SLC25A1 Deletion Impairs Cellular Bioenergetics and Dysregulates Fatty Acid Metabolism in Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is the most common leukemia in adults; it has limited treatment options and often has a dismal prognosis. AML cells are characterized by dysregulated metabolic pathways and commonly upregulate the gene SLC25A1, which codes for the citrate-isocitrate carrier (CIC) protein that transports citrate across the mitochondrial membrane in exchange for malate. Citrate metabolism is crucial for many pathways including the citric acid cycle, glycolysis, and fatty acid synthesis. Along with CIC, CD36 is another fatty acid metabolism regulator that is dysregulated in AML. CD36 is a cell membrane surface receptor that transports long-chain fatty acids into the cell. The precise role of citrate and fatty acid metabolism is not yet explored in AML.We hypothesized that SLC25A1 knockout AML cells have lower respiratory capacities and dysregulated fatty acid metabolism in comparison to control cells. Using the CRISPR-Cas9 system, MOLM13 and Kasumi-1 cell lines stably expressing Cas9 were transfected with lentiviruses containing sgRNAs against non-essential DNA (sgROSA) or SLC25A1 (sgCIC1A and sgCIC2A). SLC25A1 knockout was confirmed using Western blotting. The Seahorse XF Cell Mito Stress Test was conducted to assess cellular respiration. Western blots were conducted on cell lysates to quantify the protein levels of fatty acid metabolism regulators. We found that SLC25A1 knockout cells have significantly lower glycolysis and oxidative phosphorylation. We demonstrated that SLC25A1 knockout led to increased levels of CD36. We concluded that blocking citrate transport leads to impaired mitochondrial respiration and glycolysis, as well as upregulation of the fatty acid transporter CD36 and potential increased net transport of fatty acids into the cytoplasm. This may be due to impaired fatty acid synthesis, which could increase fatty acid transport into the cell as a compensatory mechanism.