

Acute myeloid leukemia (AML) is a cancer of bone marrow-derived blood cells, where leukemic blasts build up and block proper function and development of myeloid progenitors. Conventional therapy eliminates most bulk tumor cells but disease-initiating leukemic stem cells (LSCs) survive, leading to disease progression and relapse. LSCs are uniquely reliant on oxidative phosphorylation (OXPHOS). The key metabolic drivers of OXPHOS in LSCs from relapsed patients are amino acid and fatty acid metabolism. While we have previously described successful strategies for targeting amino acid metabolism the mechanisms that control fatty acid metabolism remain to be elucidated.

LSCs in relapsed/refractory patients display increased fatty acid metabolism, driving OXPHOS and LSC survival. We also show a strong correlation between fatty acid desaturase (FADS) expression and poor prognosis in AML. As unsaturated fatty acids are oxidized more rapidly than saturated, increased FADS activity fuels OXPHOS more than overall fatty acid metabolism. This suggests pharmacological targeting of fatty acid desaturation may offer a novel approach for LSC eradication in relapsed/refractory AML patients. We have also shown similar increases in fatty acid desaturation in cases of p53 loss in AML. Successful inhibition of OXPHOS is dependent on p53-driven apoptotic pathways, and p53 is a tight regulator of lipid metabolism. Therefore, a loss of p53 in AML may result in a loss of FADS inhibition and promotion of fatty acid desaturation.

We hypothesize that relapsed/refractory LSCs upregulate fatty acid desaturation through increased FADS activity to maintain OXPHOS as a mechanism for survival. Our goal is to determine the mechanism by which relapsed/refractory LSCs maintain OXPHOS through fatty acid oxidation. We also hypothesize that loss of p53 function in relapsed/refractory LSCs results in loss of inhibition of FADS, increasing fatty acid desaturation.