Fatty acid metabolism and desaturation in the pathogenesis of leukemic stem cells in acute myeloid leukemia

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Abstract

Background: Acute myeloid leukemia (AML) is a cancer of bone marrow-derived blood cells, where leukemic blasts build up and block function and development of myeloid progenitors. Conventional therapy eliminates bulk tumor cells but leukemic stem cells (LSCs) survive, leading to disease progression and relapse. LSCs uniquely rely on an oxidative phosphorylation (OXPHOS) metabolism driven by amino acid and fatty acid metabolism.

Aim: We have successfully targeted amino acid metabolism in LSCs, but the mechanisms controlling fatty acid metabolism are yet unknown. Our primary objective is to understand how fatty acids fuel OXPHOS in LSCs.

Results and Discussion: LSCs in relapsed/refractory patients display increased fatty acid metabolism, driving OXPHOS and LSC survival. Unsaturated fatty acids are oxidized more rapidly than saturated, so increased fatty acid desaturation (FADS) activity fuels OXPHOS more than overall fatty acid metabolism. Similar increases in fatty acid desaturation occur in cases of p53 loss in AML. Successful inhibition of OXPHOS is dependent on p33-driven apoptotic pathways, and p33 is a tight regulator of lipid metabolism. Therefore, loss of p53 function in AML may result in loss of FADS inhibition and promotion of fatty acid metabolism.

Conclusion: Relapsed/refractory LSCs upregulate fatty acid desaturation through increased FADS activity to maintain OXPHOS as a mechanism for survival. Additionally, loss of p53 function in AML may result in loss of inhibition of FADS1, increasing fatty acid desaturation. As unsaturated fatty acids are oxidized more quickly than saturated, this may allow relapse LSCs to compensate for a loss of amino acids resulting from Ven/aza.

p53 controls FA metabolism and desaturation

p53 knockout in an AML cell line results in increased unsaturated fatty acids, including docosapentaenoic acid (22:5) and docosahexaenoic acid (22:6). Loss of p53 increases unsaturated fatty acids, similar to the relapsed AML phenotype.

Methods

- Determine the effects of Ven/aza on lipid desaturation and fatty acid metabolism
- Perform p53 knockdown in primary patient LSCs to confirm aberrant lipid desaturation
- Genetically and pharmacologically inhibit FADS in the context of p53 loss
- Further explore the role of p53 and the proteins controlling its function in the mediation of survival for relapse LSCs
- Explore metabolic progression from MDS to AML

Future Directions

Further study of the role of p53 and the proteins controlling its function in the mediation of survival for relapse LSCs

Explore metabolic progression from MDS to AML