Fatty acid metabolism and desaturation in the pathogenesis of leukemic stem cells in Acute Myeloid Leukemia

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Abstract

Ven/Aza targets de novo LSC metabolism...

Dysregulation of fatty acid desaturation in relapse

p53 controls FA metabolism and desaturation

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 oxidative phosphorylation (OXPHOS), metabolically 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. Unsataturated 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 p53 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 desaturation.

Conclusion: Relapsed/refractory AML upregulates 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.

Leukemic Blasts

Leukemic Stem Cells (LSCs)

p53

Traditional Chemotherapy

Energetic Pathways (OXPHOS)

Resistant LSCs

Survival

Ven/Aza targets de novo LSC metabolism...

... but relapse LSCs can metabolically compensate

Upon treatment with Ven/Aza, relapse LSCs are significantly more viable than de novo LSCs. Ven/Aza isn't affecting relapse LSCs in the same way as de novo LSCs. Upon depletion of AAs, relapse LSCs show increased levels of fatty acids. Addition of fatty acid translocase (CD36) inhibitor SSQ re-sensitizes relapse LSCs to Ven/Aza. Relapse LSCs may compensate for amino acid loss by upregulating fatty acid metabolism.

Dysregulation of fatty acid desaturation in relapse

p53 controls FA metabolism and desaturation

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

p53 knockout also results in increases in all intermediates of the mevalonate pathway, resulting from production of Acetyl-CoA from fatty acids.

Future Directions

- 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 prosurvive controlling function in the mechanism of survival for relapse LSC
- Explore metabolic progression from AML to AML

Methods

- Pharmacologic Inhibition
  - Venetoclax (Ven), 25 μM
  - Aza-2-deoxycytidine (Aza), 25 μM
- Full MS mode, 6000-125000 m/z
- Vanquish UHPLC
- Quadrupole time-of-flight mass spectrometer
- Full MS mode, 6000-100000 m/z, 1/25-10000 m/s

Full MS mode, 6000-100000 m/z, 1/25-10000 m/s