New metabolic profile in patients with acute myeloid leukemia

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Acute myeloid leukemia (AML) is a pathology with a high genetic, clinical and metabolic heterogeneity which hinders the success of the currently available therapeutic treatments. Specifically, the FLT3 internal gene duplications (FLT3-ITD+) represent the most prevalent mutations in AML patients and are associated with high relapse rates in those affected.

The new study defines a new specific metabolic profile related to the patients with the FLT3-ITD+ phenotype. To get the results, the team applied innovative techniques of metabolomics, proteomics and stable isotope-resolved metabolomics (SIRM). The team found that leukemic cells in patients with these mutations present high levels of the succinate-CoA Ligases enzymes and a high activity of the chain of mitochondrial electron transport complex II which provides energy to the cell metabolism.

Moreover, "the study shows for the first time that this subtype of leukemic cells uses the lactate as a substrate for mitochondrial respiration. Therefore, this profile of cancer cells could be sensitive to the simultaneous pharmacological inhibition of complex II of the respiratory chain and lactate transporter," notes Professor Marta Cascante, from the Department of Biochemistry and Molecular Biomedicine of the UB.

In all cells, the main substrates of the mitochondrial respiration chain are pyruvate (from glucose) and other carbohydrates and amino acids that lead to pyruvate, apart from ketone bodies, glutamine and fatty acids. "However, in general, lactate had not been described to date as a substrate of mitochondrial respiration in tumor cells," adds Marta Cascante, also ICREA Academic researcher.

Customized medicine depending on the identified mutations

Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia
As stated in the study, the chain of mitochondrial respiration in these leukemic cells could be inhibited pharmacologically if we combine synergistically the complex II inhibitors (specifically, TTFA and 3-NPA compounds) with those from the MCT1 lactate transporter (CHC and AZD3965).

This better knowledge of the metabolic profile of a patient's leukemic cells could lead to new and potential possibilities in the design of specific-type combined therapies according to the mutations identified at the genetic level. "Customized medicine, which aims to establish specific therapies for each patient according to the phenotype of their tumor, implies having the best knowledge of each patient's tumor in order to be able to offer them the best therapeutic option for their specific tumor," concludes researcher Marta Cascante.

**More information:** Ay?egül Erdem et al, Inhibition of the succinyl dehydrogenase complex in acute myeloid leukemia leads to a lactate-fuelled respiratory metabolic vulnerability, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-29639-0](https://doi.org/10.1038/s41467-022-29639-0)

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