

Researchers find leukemia cells metabolize fat to avoid cell death

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Leukemia cells, like most cancers, are addicted to glucose to generate their energy, but new research shows for the first time that these cells also rely on fatty acid metabolism to grow and to evade cell death.

Inhibiting fatty acid oxidation makes leukemia cells vulnerable to drugs that force them to commit suicide, scientists from The University of Texas M. D. Anderson Cancer Center and The University of Texas Medical School at Houston report in the January edition of the Journal of Clinical Investigation.

"These findings translate to a potentially transformational approach to controlling leukemia and cancer <u>cell metabolism</u> by therapeutically targeting fatty acid oxidation," said co-senior author Michael Andreeff, M.D., Ph.D., professor in M. D. Anderson's Department of Stem Cell Transplantation and Cellular Therapy.

"Cancer metabolism has attracted renewed, cutting-edge research interest," Andreeff said. "Here we have first identified a metabolic target and our first in vivo results are promising, but there is much more work that needs to be done."

Andreeff and co-senior author Heinrich Taegtmeyer, M.D., D.Phil., professor in the University of Texas Medical School Division of Cardiovascular Medicine, are collaborating to develop drugs based on their research results.



"The leukemia cells' appetite for fat seems to be formidable," Taegtmeyer said. "More importantly, fat oxidation seems to promote leukemia cell survival. Conversely, shutting off fat oxidation makes the cells vulnerable to self-destruction. If these initial results hold up, inhibitors of fat oxidation may become a new way to treat leukemia patients."

In normal cells, the processing of fatty acids in the cell's powergenerating mitochondria leads to production of ATP, a molecule that serves as the major source of energy for the cell. The researchers showed that fatty acid oxidation in leukemia cell mitochondria drives cellular oxygen consumption and inhibits the activity of proteins that are vital to apoptosis, the programmed death of defective cells that begins in the mitochondria.

For energy generation, leukemia cells rely on glycolysis, the processing of a glucose molecule in the cellular cytoplasm that produces two molecules of ATP and two of pyruvate. Pyruvate, in turn, is converted to energy by the Krebs Cycle, a series of chemical reactions inside the mitochondria.

In a series of lab experiments, the researchers demonstrated that etomoxir, a drug used to treat heart failure, inhibits the growth of leukemia cells in culture in a dose-dependent manner. They also found that etomoxir sensitizes leukemia cells to drugs that cause apoptosis. The fatty acid synthase/lipase inhibitor orlistat also sensitized leukemia cells to programmed cell death.

Etomoxir treats heart failure by switching the heart's energy supply from fatty acids to pyruvate, which is more efficiently converted to energy by the mitochondria.

Mouse model experiments showed that combining etomoxir with the



apoptosis-inducing drug ABT-737 or with cytarabine, a frontline drug for acute myeloid leukemia, reduced the leukemia burden and increased median survival time by 33 percent and 67 percent respectively compared to control group mice.

Additionally, etomoxir was found to decrease the number of quiescent leukemia progenitor cells in half of blood samples taken from acute myeloid leukemia patients. These quiescent cells are important, the researchers note, because they are capable of initiating leukemia and are highly resistant to traditional chemotherapy.

"Our findings suggest that mitochondrial function and resistance to apoptosis in leukemia cells are intimately linked with the entry of fatty acids into mitochondria," said first author Ismael Samudio, M.D., a fellow in <u>Stem Cell Transplantation</u> and Cellular Therapy. "For many years it has been apparent that leukemia cells are addicted to glucose for the generation of cellular energy (ATP). Now our results suggest that <u>leukemia cells</u> are addicted to fatty acids for the function of the Krebs cycle and the prevention of cell death."

Provided by University of Texas M. D. Anderson Cancer Center

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