# Study of cancer cell metabolism yields new insights on leukemia

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University of Rochester Medical Center scientists have proposed a new reason why acute myeloid leukemia, one of the most aggressive cancers, is so difficult to cure: a subset of cells that drive the disease appear to have a much slower metabolism than most other tumors cells.

The slower metabolism protects leukemia cells in many important ways and allows them to survive better – but the team also found an experimental drug tailored to this unique metabolic status and has begun testing its ability to attack the disease, URMC researchers report in the Jan. 17, 2013, online edition of *Cell Stem Cell*.

As a result, the study's corresponding author, Craig T. Jordan, Ph.D., is working on forming a partnership with a drug-maker to conduct further testing in this arena. The compound under laboratory study has already been used in clinical trials.

"Targeting metabolism of leukemia stem cells is a unique approach that we believe has the potential to be broadly applied to several forms of leukemia," said Jordan, the Philip and Marilyn Wehrheim Professor at the James P. Wilmot Cancer Center at URMC. "An exciting part of our work is that because we've identified drugs that are being developed for clinical use, we hope there is significant potential to improve the care of leukemia patients relatively soon."

Lead investigator Eleni Lagadinou, M.D., Ph.D., a post-doctoral fellow in Jordan's laboratory, said that when the team discovered that the

metabolism of leukemia stem cells was so different from the rest of the tumor cells, they focused their efforts on exactly how that process works.

They found that leukemia stem cells generate all the energy they need in a cellular powerhouse called the mitochondrion, by way of a single process, known as oxidative phosphorylation. In contrast, other cancer cells and normal stem cells also rely on a second fuel source, known as glycolysis, to generate energy.

With this new information, researchers then explored the pathways involved in oxidative phophorylation, with an eye toward finding an Achilles' heel to stop the process. They discovered that an important gene, BCL-2, is elevated and central to leukemia stem cell energy production.

The team also knew that drugs to inhibit BCL-2 are in various stages of development in the pharmaceutical industry; Lagadinou and Jordan found two such compounds and tested them in human leukemia specimens. Their findings showed the drugs preferentially killed inactive and metabolically slower leukemia stem cells.

Leukemia is known for its ability to lie dormant for long periods, despite treatment, but then suddenly begin another assault.

"This treatment shows promise toward a dormant leukemic stem cell subpopulation that is relatively untouched by conventional drugs," Lagadinou said. "It's also important to note that normal cells were not harmed by the compounds, because they can use alternative pathways to generate energy."

Without the toxicity to healthy cells, researchers hope they can target the disease during periods of remission, when mopping up residual leukemia

is essential.

Leukemia is a blood cancer with four common types: acute myelogenous leukemia (AML), acute lymphoblastic (ALL), chronic myeloid leukemia (CML), and chronic lymphoblastic (CLL). AML is most common in adults and the most difficult to treat, in part because it affects immature cells. Nearly 50,000 new cases are diagnosed each year, with about half resulting in death.

Investigators have learned during the past decade that many therapies were not designed to kill the root of leukemia, the so called "leukemia stem cells," and therefore never truly eliminate the disease.

In fact, even the most modern cancer treatments were developed under the assumption that all cancer metabolism relies on glycolysis as a fuel source. This makes the URMC study – and the discovery that oxidative phosphorylation is the single fuel source for leukemia stem cells – all the more relevant for suggesting new and improved treatments, Jordan said.

He is a national leader in the investigation of leukemia stem cells and the search for currently available drugs that selectively target them.

Provided by University of Rochester Medical Center

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