

Attacking Cancer's Sweet Tooth Is Effective Strategy Against Tumors

This story has been adapted from a news release issued by Harvard Medical School.

An ancient avenue for producing cellular energy, the glycolytic pathway, could provide a surprisingly rich target for anti-cancer therapies. A team of Harvard Medical School (HMS) researchers knocked down one of the pathway's enzymes, LDHA, in a variety of fast-growing breast cancer cells, effectively shutting down glycolysis, and implanted the cells in mice.

Control animals carrying tumor cells with an intact glycolytic pathway did not survive beyond 10 weeks. In striking contrast, only two of the LDHA-deficient mice died, one at 16 weeks, another at just over 18 weeks. Eighty percent of the mice outlived the four month experiment. The findings by Valeria Fantin, Julie St-Pierre, and Philip Leder appear in the June Cancer Cell.

"This is an exciting contribution that reveals a surprising Achilles heel in cancer cells. It also adds to our sense of opportunity for new avenues of cancer therapeutics," said Stuart Schrieber, Morris Loeb professor and chair of the Department of Chemistry and Chemical Biology at Harvard University.

As a tumor grows, cells crowd one another and may be cut off from oxygen-carrying blood vessels--a distinct disadvantage since most cells require oxygen to produce the bulk of their energy-storing adenosine triphosphate (ATP). In the 1920s, Otto Warburg proposed that some cancer cells evolved the ability to switch over to an ancient, oxygen-free route, the glycolytic pathway. What is more, they continue to use this pathway even when access to oxygen is restored. Though the so-called Warburg effect has since been confirmed, the role played by glycolysis in cancer has been largely ignored. Few have attempted to attack specific points along the glycolytic pathway to gain a therapeutic effect.

"LDHA could be one weak point that we could attack but maybe, if we understand exactly all the steps involved, we could devise alternative strategies to attack the same pathway," said Fantin, who was an HMS research fellow in genetics when the study was performed. She is currently a research scientist at Merck & Co.

What may excite the growing band of researchers who are studying the Warburg effect, and cancer metabolism more generally, is the way the study resolves a long-standing debate about how and why cells switch to glycolysis in the first place. Warburg speculated that cancer cells change over to glycolysis, which occurs in the cytoplasm, because the mitochondria, where oxygen-dependent ATP synthesis occurs, are defective. But the mitochondria of cancer cells appear to be mostly intact, which led many researchers to minimize the importance of the glycolytic switch.

The mitochondria do display an intriguing difference, however. Normally, mitochondria turn glucose into ATP through the oxygen-dependent process of oxidative phosphorylation (OXPHOS). This results in the expulsion of protons, which lowers the mitochondria's membrane potential. Curiously, the mitochondria of cancer cells exhibit a high membrane potential. Researchers suspected that was because the cells have switched to an alternative means of producing ATP, namely glycolysis, but it was not clear if the glycolytic and mitochondrial pathways were connected in this fashion.

It appears the two pathways are reciprocally linked. Fantin and her colleagues found that by shutting down the glycolytic pathway (through the knock down of LDHA), they could lower the mitochondrial membrane potential of tumor cells. What is more, oxygen consumption increased in the knockdown cells, suggesting they were reverting to the mitochondrial OXPHOS pathway--a kind of Warburg effect in reverse.

"The findings provide us with an insight into a mechanism that had been suspected in the last six or seven decades," said Leder, John Emory Andrus professor and chair of the Department of Genetics at HMS. Knocking out the glycolytic pathway could deliver a big blow to tumor cells.

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What makes the prospect of anti-glycolytic therapies even more attractive is their potential safety.

Healthy cells meet 90 percent of their energy needs through OXPHOS. People who lack the LDHA enzyme appear to function normally though they cannot be pushed toward anaerobic exercise.

"They have muscle destruction because they lack an alternative route for producing energy," Fantin said. It is not clear whether they have a lower incidence of cancer.

Also appealing is the idea of combining anti-glycolytic therapies with anti-angiogenic ones.

"If you have a molecule that is very stable you could think about delivering it first, obliterating the glycolytic pathway," said Fantin. Angiogenesis inhibitors would wipe out blood vessels and the oxygen supply with it, leaving the cells with no way to cope. "There is definite potential to combining these things," she said

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