

Shedding light on 100-year-old cancer mystery

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Ze'ev Ronai, Ph.D., a professor in SBP's NCI-designated Cancer Center. Credit: Sanford Burnham Prebys Medical Discovery Institute (SBP)

For almost a century, scientists have observed a strange behavior in cancer cells: They prefer a less-efficient pathway to produce energy. While normal cells utilize aerobic glycolysis to use glucose to produce 36 energy-storing adenosine triphosphate (ATP) molecules, most cancer cells, despite the presence of oxygen, switch to anaerobic glycolysis, which only produces two ATPs.

Known as the Warburg effect, this process relies on a class of enzymes known as lactate dehydrogenase, with lactate dehydrogenase A (LDHA) being the most prominent player. Inhibiting LDHA could stop [cancer cells](#) from generating the energy they need to grow and survive, but little is known about how effective LDHA inhibition could be, largely due to the lack of pharmacological inhibitors that work in vivo.

Using genetic and pharmacological means, scientists at Sanford Burnham Prebys Medical Discovery Institute (SBP) were surprised to find that blocking LDHA had only a limited impact on [melanoma](#) cells, since they were able to redirect energy production. Their results identify an alternative growth pathway driven by a molecule called ATF4, revealing new potential targets for drug development. The study was published today in *EMBO Journal*.

"We set out to examine what actually happens to melanoma cells when LDHA is inhibited," says Gaurav Pathria, Ph.D., the first author of the paper and a senior postdoctoral associate in the laboratory of Ze'ev Ronai, Ph.D., a professor in its NCI-designated Cancer Center. "Our research identifies the ATF4-signaling pathway as one that prompts melanoma cells to gather [essential amino acids](#) needed to sustain tumor growth and survival in response to LDHA inhibition. We believe that targeting this pathway in combination with a LDHA-targeting drug may provide a promising treatment for melanoma."

Each year more than 9,000 Americans die of melanoma, a type of skin

[cancer](#). In the last decade, personalized treatments that target altered BRAF and MEK proteins—changes found in more than half of people with melanoma—have extended patient survival by months and even years. But cancer cells can adapt to therapy and outsmart these drugs, sending patients back into a state of illness after apparent recovery.

"Over the course of my career, melanoma has gone from a poorly treatable disease to a potentially beatable cancer, although in many cases, only for a limited time. Thus, our work isn't done," says Ronai, senior author of the paper. "Patients are quickly developing resistance to these medicines—in as little as a few months after starting treatment—creating a need for new and better targets and therapeutic modalities."

From ATP to amino acids

Several changes were seen in [melanoma cells](#) when LDHA was blocked. These cells switched from ATP-generating [aerobic glycolysis](#) to "eating" glutamine—an amino acid. The authors found that ATF4 drove this process, calling for more amino acids to be taken up by the cell. The increase in amino acids activated the master growth regulator, mTORC1, allowing cancer cells to keep growing. Blocking both LDHA and mTORC1 halted cell growth, indicating the therapeutic potential of targeting this pathway. In mapping the alternative route identified upon LDHA inhibition, the investigators point to additional targets that can be exploited, including glutamine metabolism and MAPK signaling, for which pharmacological inhibitors do exist.

"When we looked at tumor samples from patients with drug-resistant melanoma, we found strikingly similar results," says Ronai.

"ATF4-related metabolic signaling increased in the patient samples, indicating the cancer cells used the same ATF4-driven survival pathway to continue growing."

Adds Pathria, "This study also sheds light on the Warburg effect—the nearly 100-year-old mystery of why cancer cells prefer an inefficient pathway to fuel their growth. Our results indicate cancer cells crave amino acids, versus ATP. Perhaps these rapidly growing cells find the seemingly wasteful Warburg effect more efficient to gather protein building blocks—amino acids.

"These findings pave the way toward a better understanding of how restricting access to [amino acids](#) affects cancer [cells](#) at a molecular level," Ronai explains. "Results from this research could help uncover more cancer cell vulnerabilities and potential treatment targets."

More information: *EMBO Journal* (2018).
[embor.embopress.org/lookup/doi ... 15252/embj.201899735](https://embor.embopress.org/lookup/doi/10.1042/embj.201899735)

Provided by Sanford Burnham Prebys Medical Discovery Institute

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