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Study reveals how cancer cells thrive in oxygen-starved tumors

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A new study identifies the molecular pathway that enables cancer cells to grow in areas of a tumor where oxygen levels are low, a condition called hypoxia.

The findings by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), might offer a new strategy for inhibiting tumor growth by developing agents that reverse this hypoxia-related pathway.

The study focuses on how cancer cells use the amino acid glutamine, the most common amino acid found free in the bloodstream. Under normal oxygen levels, healthy cells use glutamine largely to produce energy, with a small amount diverted to make fatty acids and lipids.

But when oxygen levels drop in areas of a growing tumor, the hypoxic conditions activate a gene called HIF1, initiating a pathway that shifts the use of glutamine away from energy production and to the synthesis of lipids needed for cell proliferation.

The findings were published in the journal *Cell Metabolism*.

"These results are particularly exciting because glutamine metabolism is a potential target for anticancer therapy," says principal investigator Nicholas Denko, PhD, MD, associate professor of radiation oncology at the OSUCCC – James.

"Tumor cells require glutamine to grow, so groups have been trying to identify drugs that block glutamine metabolism and inhibit tumor growth. However, drugs that completely block glutamine metabolism will have unwanted side effects because glutamine is also an important neurotransmitter," he says.

"We show that we can block the growth of model tumors by redirecting hypoxic glutamine metabolism to make it follow the normal-oxygen pathway. Such a therapeutic strategy should have few-if-any unwanted side effects, because normal tissue is oxygenated and already using glutamine in the normal manner," says Denko, who is a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

Denko and first author Ramon C. Sun, a postdoctoral researcher in radiation oncology, used several tumor-cell lines and an animal model for this study. Their key findings include:

- Hypoxia activates HIF1, leading to the breakdown of the enzyme called OGDH2, which is necessary for the typical use of glutamine to produce energy via the tricarboxylic acid, or Krebs cycle.
- When OGDH2 is lost, hypoxic cancer cells divert glutamine away from energy production and use it to generate citrate that is then used to produce the lipids needed for cell proliferation.
- Tumors with malignant cells that are forced to express a hypoxia-resistant form of OGDH2 grew significantly slower in an animal model than tumors with normal OGDH2, suggesting that reversing this hypoxic pathway might be an effective strategy for inhibiting tumor growth.

Provided by Ohio State University Medical Center