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Researchers target cancer's ability to survive at low oxygen levels

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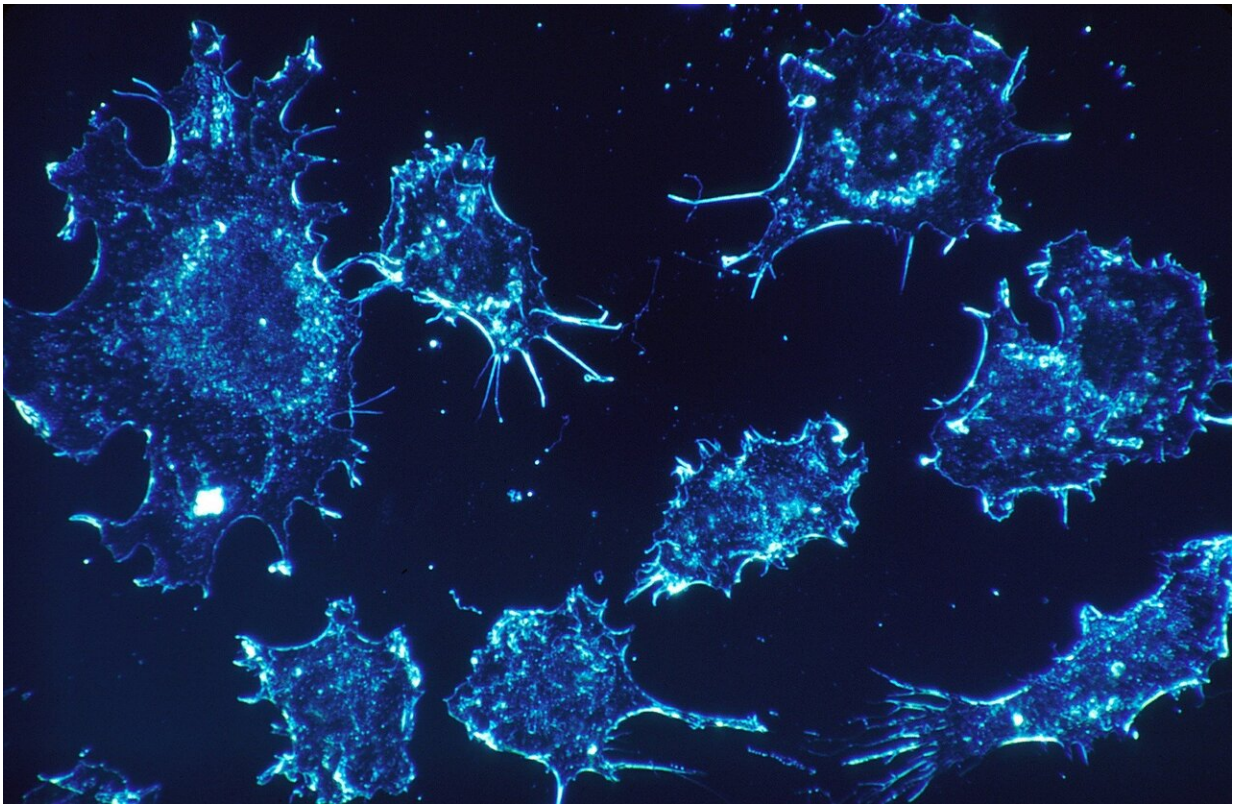

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Researchers at the Francis Crick Institute have shed light on how cancer cells survive in the first few hours after being cut off from a supply of oxygen.

Published in *The EMBO Journal*, this finding could one day help to prevent cancer from becoming resistant to therapy.

A major use of oxygen by cells is for energy production. When oxygen supplies are low, most cells can survive because they adapt, by changing which proteins they make, to produce energy through different processes than in normal oxygen levels. This is coordinated by a protein called HIF1α, which turns on the activity of genes.

Although HIF1α levels increase as soon as the oxygen supply decreases, it takes around 24 hours for the relevant genes to produce proteins, leaving cells exposed to a period of low oxygen without an obvious mechanism for maintaining energy production.

By studying how cancer cells use nutrients, the researchers found that, within three hours of the cells being deprived of oxygen, a process called glycolysis (breaking down glucose to make energy) increases.

HIF1α has been known to drive increased glycolysis when cells are chronically exposed to low oxygen. However, when the researchers genetically modified the cells to stop making HIF1α and deprived them of oxygen, glycolysis still increased, suggesting that other factors supported this increase in the immediate aftermath of oxygen deprivation.

The rate of glycolysis is controlled by the levels of NAD^+, a small molecule that is found in cells and is necessary for the process. The team discovered that two enzymes, LDHA and GOT1, must work together to make enough NAD^+ for glycolysis to increase.

LDHA and GOT1 exist in normal oxygen conditions, so this work highlights that they act as reserves for a state of low oxygen. This means a cell living in normal oxygen is already primed: it doesn't need to make

anything new and is always ready to deal with a sudden decrease of oxygen levels in its environment.

Intriguingly, the authors found that GOT1 activity also helps HIF1α accumulate, through a mechanism for which Crick Clinical Director Peter Ratcliffe was awarded the Nobel Prize in Physiology or Medicine in 2019. So, in addition to supporting glycolysis in the short term, GOT1 can also impact the long-term adaptation of cells to oxygen limitation by ensuring robust HIF1α activity.

Cancer treatment potential

As treatment-resistant cancer cells are likely to be deep within a tumor without access to a blood supply, and therefore oxygen, the research suggests that inhibiting LDHA and GOT1 could target these hard-to-reach cancer cells by stopping their ability to produce energy.

The team tested this idea by blocking the action of LDHA and GOT1 and found that inhibiting both enzymes together was more effective at killing cancer cells in low oxygen than in normal oxygen levels, or by targeting either enzyme alone.

This highlights LDHA and GOT1 as promising targets for treatment, especially because cells with a normal oxygen supply—including non-cancerous cells—shouldn't be affected as they don't need these enzymes to the same extent.

Dimitrios Anastasiou, Group Leader of the Cancer Metabolism Laboratory at the Crick, said, "A major problem in cancer therapy is how to target cancer cells specifically, while avoiding damage to healthy cells. Researchers often look at this problem by studying how cells adapt to chronic stress, but instead, we've looked at the acute needs of cells due to a changing environment. Our research highlights a vulnerability

for cancer cells in the first few hours of becoming cut off from oxygen."

Fiona Grimm, former Ph.D. student at the Crick, and first author, said, "We can think about this as a classic problem of supply and demand: in low oxygen conditions, there's more demand for LDHA and GOT1 than in normal oxygen conditions. By blocking these enzymes in oxygen-deprived cells where they are needed most, we can hopefully target these cells before they adapt to low oxygen and become hard to reach or resistant to therapy."

More information: Grimm, F. et al. Metabolic priming by multiple enzyme systems supports glycolysis, HIF1α stabilisation and cell survival in early hypoxia., *The EMBO Journal* (2024). DOI: 10.1038/s44318-024-00065-w

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