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A pair of proteins control the supply lines that feed cancer cells

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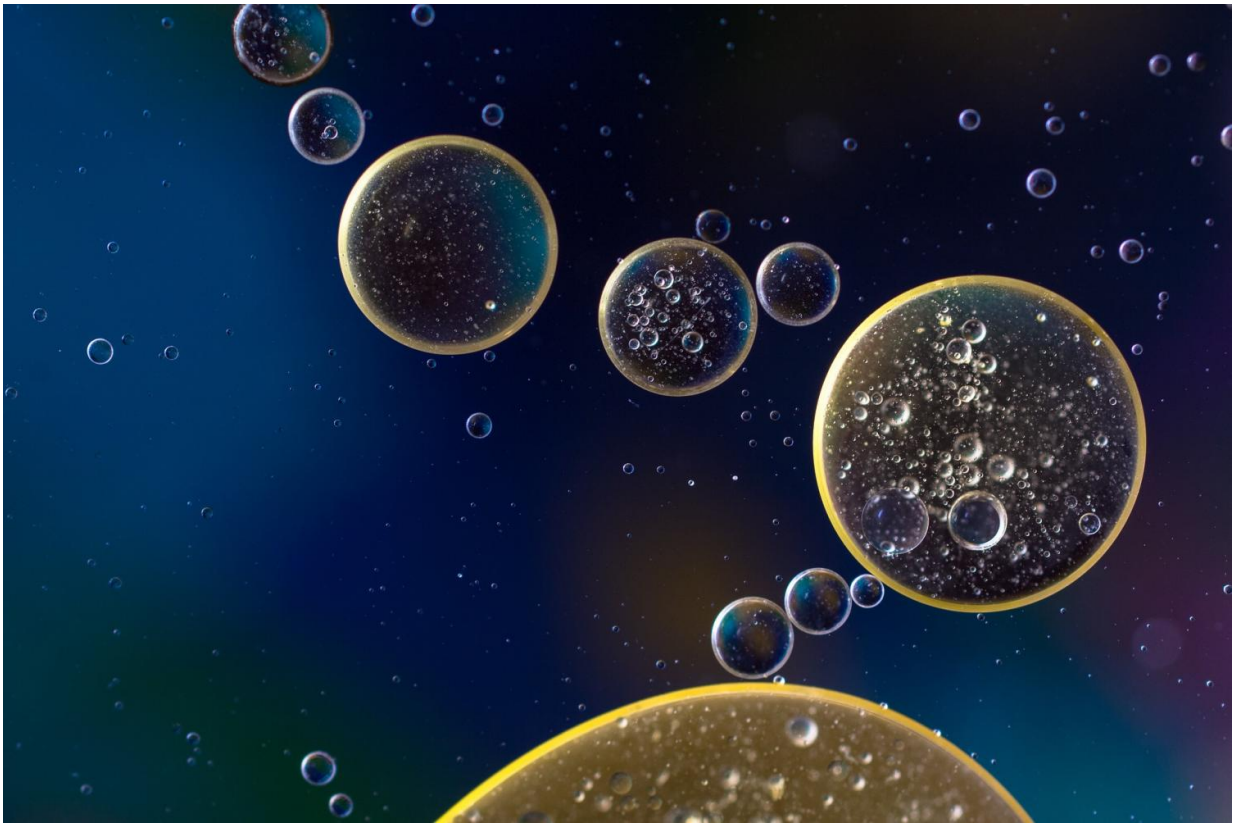

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In human cancer cell and mouse studies, researchers from Johns Hopkins Medicine have found that a set of proteins work in tandem to build supply lines that deliver oxygen and nutrients to tumors, enabling them

to survive and grow. The protein twosome, PADI4 and HIF-1, ramp up their activity under low-oxygen conditions that are typically found in a fast-growing tumor, allowing it to build new blood vessels that feed the cancer's growth.

The researchers say the discovery provides new avenues for developing anti-cancer therapies that interfere with blood vessel development.

A report describing the study was published online Aug. 27 in *Science Advances.*

"The discovery gives us an opportunity to find combinations of existing or new drugs that target these pathways to treat cancer and prevent drug resistance," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Genetic Medicine, Pediatrics, Oncology, Medicine, Radiation Oncology and Biological Chemistry at the Johns Hopkins University School of Medicine. Semenza also serves as director of the Vascular Program at the Johns Hopkins Institute for Cell Engineering.

Semenza shared the 2019 Nobel Prize in Physiology or Medicine for the discovery of how HIF-1 controls the ability of cells to adapt to low oxygen levels. His lab and others have found that HIF-1 (hypoxia-inducible factor 1) activates more than 5,000 genes under low-oxygen conditions. However, it was unclear precisely how HIF-1 turned on those genes to spur blood vessel growth.

Within the cell, DNA is negatively charged, which allows it to interact with positively charged proteins called histones. The DNA is wound like a spool of thread around the histones when it is not being used.

Specifically, Semenza says, PADI4 incites a reaction that causes the histones to lose their positive charge, allowing the DNA to unwind.

To explore the partnership between HIF-1 and PADI4, the researchers studied human breast and liver cancer cells grown in the laboratory. The researchers first interfered with the cells' ability to produce PADI4, and then exposed the cells to low oxygen conditions for 24 hours. By analyzing gene activity within these cells, the researchers found that 87% of the 1,300 genes turned on by HIF-1 in response to hypoxia were not turned on in cells lacking PADI4 protein.

The researchers then injected the cancer cells into the breast tissue of mice and tracked tumor growth. Tumors without PADI4 were five times smaller and developed five times fewer blood vessels compared with tumors formed from cells with normal levels of PADI4. This showed that in a living organism, elimination of PADI4 impaired the tumor's ability to grow.

The findings in mice, say the researchers, allow them to tie together studies from human cancers where higher HIF-1 activity in patients' primary tumor biopsies correlates with higher rates of mortality.

"The more we know about the cellular ecosystem of cancer, the better shot we have at controlling it," says Semenza.

More information: Yufeng Wang et al, Histone citrullination by PADI4 is required for HIF-dependent transcriptional responses to hypoxia and tumor vascularization, *Science Advances* (2021). DOI: 10.1126/sciadv.abe3771

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