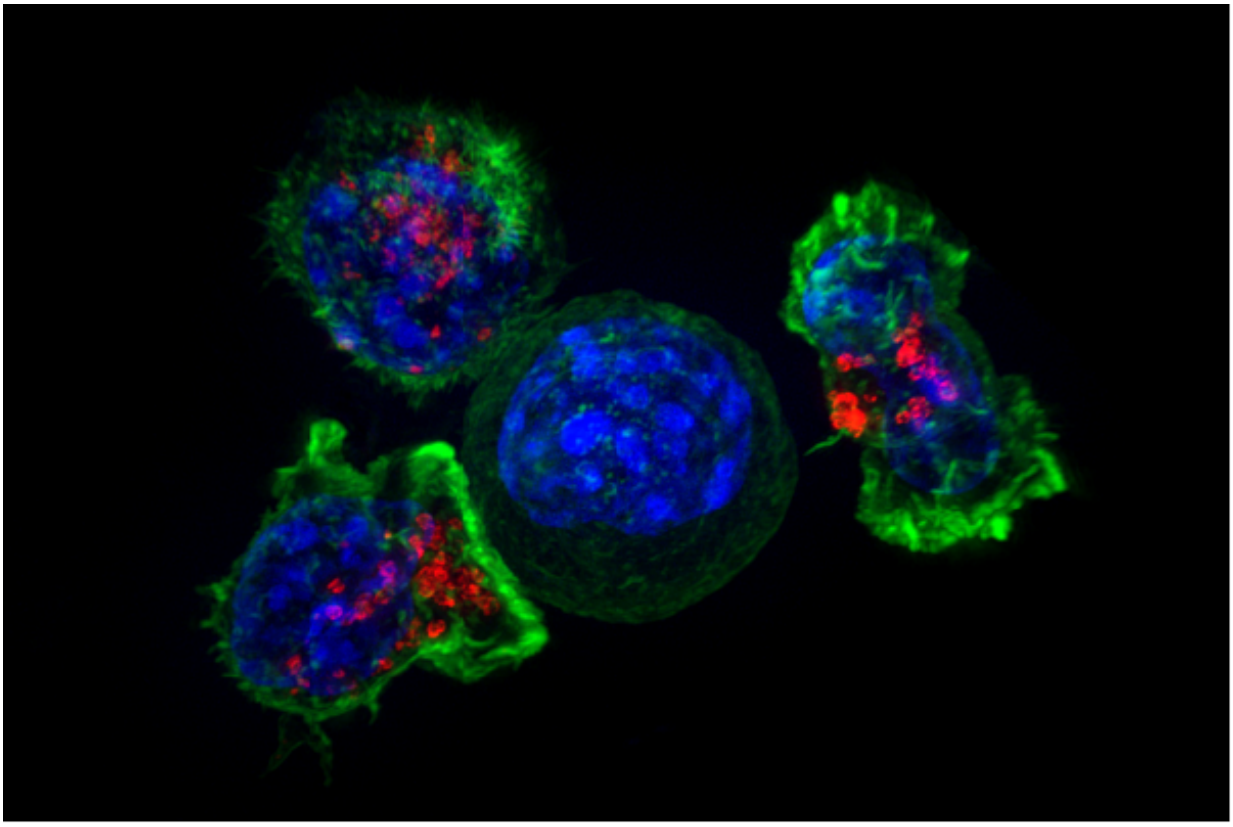
How cancer stem cells thrive when oxygen is scarce

March 28 2016



Killer T cells surround a cancer cell. Credit: NIH

Working with human breast cancer cells and mice, scientists at The Johns Hopkins University say new experiments explain how certain cancer stem cells thrive in low oxygen conditions. Proliferation of such

cells, which tend to resist chemotherapy and help tumors spread, are considered a major roadblock to successful cancer treatment.

The new research, suggesting that low-oxygen conditions spur growth through the same chain of biochemical events in both embryonic stem cells and breast cancer stem cells, could offer a path through that roadblock, the investigators say.

"There are still many questions left to answer but we now know that oxygen poor environments, like those often found in advanced human breast cancers serve as nurseries for the birth of cancer stem cells," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Medicine and a member of the Johns Hopkins Kimmel Cancer Center. "That gives us a few more possible targets for drugs that diminish their threat in human cancer."

A summary of the findings was published online March 21 in the *Proceedings of the National Academy of Sciences*.

Semenza says scientists have long known that low oxygen environments affect tumor growth, but, in the case of advanced tumors, there was a paradox. "Aggressive cancers contain regions where the cancer cells are starved for oxygen and die off, yet patients with these tumors generally have the worst outcome. Our new findings tell us that low oxygen conditions actually encourage certain cancer stem cells to multiply through the same mechanism used by embryonic stem cells."

All stem cells are immature cells known for their ability to multiply indefinitely and give rise to progenitor cells that mature into specific cell types that populate the body's tissues during embryonic development. They also replenish tissues throughout the life of an organism. But stem cells found in tumors use those same attributes and twist them to maintain and enhance the survival of cancers. According to Semenza,

"Chemotherapy may kill more than 99 percent of the cancer cells in a tumor but fail to kill a small population of cancer stem cells that are responsible for subsequent cancer relapse and metastasis."

"The search has been intense to find these cells' Achilles' heel. If we could get cancer stem cells to abandon their stem cell state, they would no longer have the power to keep repopulating tumors," says Semenza, who also directs the Vascular Biology Research Program at the Institute for Cell Engineering.

Aiding their new research, Semenza says, was the knowledge that whereas the air we breathe is 21 percent oxygen, oxygen levels average around 9 percent in healthy human breast tissue but only 1.4 percent in breast tumors. Recent studies showed that low oxygen conditions increase levels of a family of proteins known as HIFs, or hypoxia-inducible factors, that turn on hundreds of genes, including one called NANOG that instructs cells to become stem cells.

Studies of embryonic stem cells revealed that NANOG protein levels can be lowered by a chemical process known as methylation, which involves putting a methyl group chemical tag on a protein's messenger RNA (mRNA) precursor. Semenza says methylation leads to the destruction of NANOG's mRNA so that no protein is made, which in turn causes the embryonic stem cells to abandon their stem cell state and mature into different cell types.

To see whether cancer stem cell renewal involves a chain of events similar to that used by embryonic stem cells, and whether the process was affected by oxygen levels, Semenza and graduate student Chuanzhao Zhang focused their studies on two human breast cancer cell lines that responded to low oxygen by ramping up production of the protein ALKBH5, which removes methyl groups from mRNAs. (Breast cancer is categorized and treated based on the presence or absence of three

hormone receptors displayed on the outer membranes of cells. One human cell line they studied displays the receptors for estrogen and progesterone, and one, known as triple negative, displays none.)

Zeroing in on NANOG, the scientists found that low oxygen conditions increased NANOG's mRNA levels through the action of HIF proteins, which turned on the gene for ALKBH5, which decreased the methylation and subsequent destruction of NANOG's mRNA. When they prevented the cells from making ALKBH5, NANOG levels and the number of cancer stem cells decreased. When the researchers manipulated the cell's genetics to increase levels of ALKBH5 without exposing them to low oxygen, they found this also decreased methylation of NANOG mRNA and increased the numbers of breast cancer stem cells.

Finally, using live mice, the scientists injected 1,000 triple-negative breast cancer cells into their mammary fat pads, where the mouse version of breast cancer forms. Unaltered cells created tumors in all seven mice injected with such cells, but when cells missing ALKBH5 were used, they caused tumors in only 43 percent (six out of 14) of mice. "That confirmed for us that ALKBH5 helps preserve cancer stem cells and their tumor-forming abilities," Semenza says.

Semenza says his team will continue its mouse studies to see if metastasis—the spread of cancer from the original tumor—is affected by the low oxygen/ALKBH5/NANOG relationship too. The researchers also want to see what other proteins and mRNAs are involved in the relationship, and why some cancer cell lines they tested did not show the same increased ALKBH5 levels in response to low oxygen levels.

More information: Chuanzhao Zhang et al. Hypoxia induces the breast cancer stem cell phenotype by HIF-dependent and ALKBH5-mediated m A-demethylation of NANOG mRNA ,

MedicalXpress

Proceedings of the National Academy of Sciences (2016). DOI: 10.1073/pnas.1602883113

Provided by Johns Hopkins University School of Medicine

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