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UCSD Discovery Opens New Avenues For Design Of Anti-Tumor Medications

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The response of blood vessels to low oxygen levels may be the Achilles' heel of a developing tumor, according to a study led by University of California, San Diego biologists.

The study, published in the November 15 issue of the journal *Cancer Cell*, is the first to examine how blood vessels respond to the low oxygen conditions that result from the presence of a growing tumor. Previous work by the UCSD group and others has shown that tumors, which need a blood supply to provide oxygen and nutrients, release chemical signals that summon the blood vessels to grow toward them.

However, these latest findings show that the blood vessels themselves are actively responding to oxygen levels, not just to the signals sent by the tumor. According to the researchers, developing drugs that interfere with the blood vessels' response to low oxygen may be a potent anti-tumor strategy.

"We show that the blood vessels' response to lack of oxygen is just as important as the response of cancer cells to lack of oxygen," said Randall Johnson, a professor of biology at UCSD who headed the research team. "We identified a gene that turns on in the cells lining blood vessels when they are not getting enough oxygen and showed that without this gene the blood vessels cannot grow to nourish the developing tumor. Drugs that interfere with this gene, or another gene involved in the blood vessels' response, should block tumor growth."

The researchers showed that the gene, HIF-1alpha, is normally turned off in endothelial cells-the cells lining blood vessels. But when the endothelial cells are exposed to low oxygen conditions, such as those generated when a tumor is using up the oxygen supply, the gene becomes activated. By switching on other genes, HIF-1alpha causes the endothelial cells to proliferate and migrate.

In mice lacking HIF-1alpha in endothelial cells, blood vessels failed to grow to the tumors. Without blood vessels, the tumors were starved of oxygen and nutrients, resulting in tumors were smaller in size than in normal mice and had dead tissue at their centers.

To date, most efforts to develop angiogenesis inhibitors-drugs to prevent growth of blood vessels- have focused on inhibiting the signals sent out by the tumor in response to low oxygen. These latest findings suggest that targeting the endothelial cells' response to low oxygen is a viable alternative strategy to the development of angiogenesis inhibitors. Furthermore, the researchers point out that it may be easier to design effective treatments that target the endothelial cells rather than the tumor cells.

"Cancer cells mutate frequently," says Nan Tang, a graduate student working with Johnson and the first author on the paper. "This means that it is common for these cells to develop resistance to drugs. On the other hand, the endothelial cells are normal cells and would be much less likely to develop drug resistance."

"The endothelial cells are also in direct contact with the blood, simplifying the delivery of drugs," adds Tang.

Because HIF-1alpha is usually turned off in endothelial cells, and the mice lacking the gene in blood vessels were healthy and had normal lifespans, the researchers think that inhibiting the blood vessels' response to low oxygen should be relatively safe. One caveat is that interfering with blood vessels' response to low oxygen may also inhibit wound healing, as was observed in the mice lacking HIF-1alpha. According to the researchers, further work will be needed before their discovery can be applied to actually design new anti-tumor drugs.

"Since the response of the blood vessels to low oxygen likely involves multiple genes and chemical signals, we still need to tease apart the steps involved in the response," says Johnson. "It will also be important to understand how the signals sent out by the tumor, to stimulate the endothelial cells to grow toward it, differ from the signals that the endothelial cells themselves use to stimulate their own proliferation."

The coauthors on the paper, in addition to Johnson and Tang, are Lianchun Wang and Jeffrey Esko from UCSD's Department of Cellular and Molecular Medicine, Frank J. Giordano and Yan Huang from Yale University School of Medicine and Hans-Peter Gerber and Napoleone Ferrara from Genentech, Inc. The study was supported by the National Institute of Environmental Health Sciences, Pfizer and the University of California Biotechnology Strategic Targets for Alliances in Research Program.

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