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EMBARGOED until 4 p.m. Eastern Standard Time, Wednesday, January 3, to correspond with publication in the January 4 issue of *Nature*.

RESEARCHERS UNCOVER TRICK USED BY TUMOR SUPPRESSOR: FORCE TUMOR CELLS TO SELF-DESTRUCT

STANFORD — Researchers have known for roughly a decade that the protein p53 has something to do with controlling cancerous tumors — the question has been what.

Now researchers have at least a partial answer, based on research in mice.

Stanford researchers and colleagues have found that p53 works as an emergency brake on cancer development by killing cells that attempt to proliferate in oxygen-deficient regions of tumors. Cells with mutant forms of p53 have no such brake, and as a result they can survive low-oxygen conditions.

"P53 seems to work as a fail-safe for cells that find themselves in adverse conditions, such as the low-oxygen environment in tumor cells. It allows them to commit suicide," said Amato Giaccia, assistant professor of radiation oncology at Stanford University School of Medicine.

Giaccia and colleagues at Stanford, Massachusetts Institute of Technology, the University of Pennsylvania and Cold Spring Harbor, N.Y., describe their finding in the Thursday, Jan. 4 issue of *Nature*.

"Two sets of genes control tumor development: one set acts as accelerators, the other as brakes. The accelerators are the oncogenes. The brakes are tumor suppressor genes, like p53. What a tumor tries to do is lose the brakes and increase expression of oncogenes so it can keep growing without any restrictions," Giaccia said.

These mutant forms of p53 are plentiful in tumors of many types, including colorectal and ovarian cancers. This observation has led to thousands of genetic and biochemical studies of the protein.

Still, researchers were not able to figure out why mutant forms of the protein are so plentiful in cancer tissues — information that may be very useful for cancer therapy development.

(more — giaccia)

"The interesting thing about this finding is that it ascribes a very important role to low-oxygen conditions in determining the progression of a malignant tumor," Giaccia said.

Cells in tumors tend to be oxygen-poor, since blood vessels only minimally penetrate the dense cell masses.

"Since the success of radiotherapy and chemotherapy depends on chemical reactions involving oxygen inside cancer cells, it has previously been thought that the oxygen-deficient tumor microenvironment could play a role in the poor response of some tumors to radiotherapy and chemotherapy," Giaccia said.

But the finding that p53 is produced and causes cell death in low-oxygen conditions suggests another reason for some tumors' tenacity.

"Since cells capable of producing functional p53 commit suicide in low-oxygen conditions, the tumor microenvironment may select for cells with mutant forms of p53. This results in the proliferation of cancer cells that have lost their ability to eliminate themselves in response to adverse conditions, such as low oxygen," he said.

Cancer drugs that specifically attack cells low in oxygen might potentially overcome this problem, Giaccia said. Researchers at Stanford, led by radiation oncology professor Martin Brown, developed one such drug, called tirapazamine, which is undergoing clinical testing at Stanford and elsewhere.

Giaccia and colleagues made their finding that cells produce p53 in oxygen-poor conditions — including tumors — by analyzing mouse tumor cells in culture and *in vivo*.

Giaccia's collaborators were Stanford physics graduate student Thomas Graeber; Stanford biology undergraduate Cynthia Osmanian; Tyler Jacks, an assistant investigator of the Howard Hughes Medical Institute at the Massachusetts Institute of Technology; David Housman, professor of biology at MIT; Cameron J. Koch, a professor of radiation oncology at the University of Pennsylvania; and Scott Lowe, a researcher at Cold Spring Harbor Laboratory, New York.

Giaccia and colleagues at Stanford next plan to study whether low-oxygen conditions trigger p53 expression and cell death in human tumors.

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