

Study sheds light on angiogenesis inhibitors, points to limitations, solutions

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A new generation of cancer drugs designed to starve tumors of their blood supply - called "angiogenesis inhibitors"--succeeds at first, but then promotes more invasive cancer growth—sometimes with a higher incidence of metastases, according to a new study in animals. The research clarifies similar findings in other animal studies and is consistent with some early evidence from a small number of clinical trials with cancer patients.

"People have thought that angiogenesis-inhibiting therapy should hinder metastasis, but these studies show this is not necessarily the case," says Gabriele Bergers, PhD, co-author of a paper reporting the study in the March 3, 2009 issue of the journal *Cancer Cell*. Bergers is an associate professor of neurosurgery and anatomy at the University of California, San Francisco (UCSF).

The scientists urge new studies to determine if the drugs affect tumors in patients as they do in their mouse models of human cancers. They call for preclinical and clinical trials combining angiogenesis-inhibiting drugs with ones targeting the capability for invasion and metastasis. Some treatment strategies already in clinical trials that pair angiogenesis inhibitor drugs with chemotherapy, for example, might gain the first drug's early benefit without triggering subsequent invasion or metastasis, they note.

"The ability of angiogenesis inhibitors to starve tumors rather than poison them has been a true breakthrough," says Douglas Hanahan, PhD,

professor of biochemistry and biophysics at UCSF and co-senior author on the paper. "But they are not likely to be a one-stop fix. No cancer drug has yet been found to cure most forms of human cancer. Therapies beat it back, but almost inevitably the cancer develops some form of resistance."

Hanahan and Bergers are both scientists at the UCSF Helen Diller Family Comprehensive Cancer Center.

The other co-senior author of the paper is Oriol Casanovas, PhD , a group leader at the Catalan Institute of Oncology-IDIBELL, in Spain.

In addition to their call for more studies of angiogenesis inhibitors' effects, the researchers encourage more research to identify the mechanisms underlying cancer's resurgence after initial success with the angiogenesis inhibitors. They suspect that the increased invasion and/or metastasis is the tumor's response to starvation induced by the drugs.

"A well vascularized tumor is well fed and happy," Hanahan says. "It has no driving force to become more invasive. We hypothesize from the mouse models that if you cut off the tumor's blood supply this drives the cancer to become more invasive—more metastatic— as it seeks more oxygen and nutrients."

The *Cancer Cell* paper extends earlier findings reported by Casanova, Hanahan and Bergers in 2005 and 2008 (Casanovas O. et al. *Cancer Cell* 2005; Du R. et al. *Cancer Cell* 2008), and it appears along with one by another research team from Robert Kerbel and colleagues at the University of Toronto, also reporting evidence of increased metastasis in mice treated with anti-angiogenesis drugs. In August, 2008, Bergers and Hanahan reviewed all of the recent research addressing resistance to angiogenesis inhibitor therapy in the journal *Nature Reviews Cancer*.

The scientists tested the effects of the anti-angiogenic drug sunitinib (manufactured as Sutent) in mouse models of both pancreatic neuroendocrine cancer and glioblastoma, the most common type of primary brain tumor. In both cancers, they found that treated tumors shrank or stabilized but did not disappear during the first weeks of treatment. But after this initial benefit, they detected an adaptive response by the tumor. The glioblastomas increased invasion into adjacent normal tissue. The pancreatic tumors also became more invasive and, in addition, metastasized to the liver.

"Our animal studies are consistent with some clinical results that human glioblastomas adapt to the angiogenesis-inhibiting drugs," Bergers says. "Scientists have reported results from a clinical trial in which a subset of patients developed tumor recurrence at many sites during the course of treatment with bevacizumab, an angiogenesis inhibitor. The recurrence was measured by MRI imaging."

"While anti-angiogenesis drugs are in general not proving to be an enduring success, this does not mean they aren't valuable therapies," she adds. "There is growing evidence that the drugs improve the quality of life, or even provide increased survival - typically of a few months for glioblastoma patients. The drugs also can reduce edema in brain tumors and in some instances restore memory and speech."

A tumor's resistance to angiogenesis inhibitors differs from resistance to chemotherapy drugs, Bergers explains. The targets of anti-angiogenic therapy are normal cells that form the tubes of blood vessels, known as endothelial cells. Despite the fact that the drugs are still effective against these cells, resistance develops because the tumor finds additional pathways to circumvent the drug's inhibitory effect. One evasive tumor strategy involves tapping growth factors in the body other than VEGF for the new blood vessel growth they need. If the tumor can't rebuild its vasculature to a sufficient level, it can adopt another strategy—to spread

and become invasive.

In contrast, tumor cells resist chemotherapy by cell-intrinsic mechanisms such as mutating the gene targeted by the drug, or changing how the tumor takes up or expels the drug.

One class of anti-angiogenesis drugs works by blocking the action of an essential protein known as vascular endothelial growth factor, or VEGF, which normally stimulates new blood vessel growth. The strategy of starving tumors by depriving them of nutrients and oxygen in blood was first proposed in the early 1970s by the late Dr. Judah Folkman at Harvard Medical School. The idea took more than two decades to gain traction in the research and clinical oncology communities, but it gained acceptance as new research confirmed its promise. Clinical trials are now the focus of great interest and hope.

Clinical trials with anti-VEGF drugs have had mixed results. One trial, using the anti-VEGF drug bevacizumab in metastatic breast cancer failed, and a recent trial, also in breast cancer did not increase survival, Hanahan and Bergers say. The sobering results from animal studies may explain why.

Source: University of California - San Francisco

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