Cancer drugs may build and not tear down blood vessels

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Scientists have thought that one way to foil a tumor from generating blood vessels to feed its growth – a process called angiogenesis – was by creating drugs aimed at stopping a key vessel growth-promoting protein. But now the opposite seems to be true.

Researchers at the Moores Cancer Center at the University of California, San Diego (UCSD) in La Jolla have found evidence that blocking that protein target, called VEGF, or vascular endothelial growth factor, doesn't really halt the process at all. Instead, cutting levels of VEGF in a tumor actually props up existing blood vessels, making them stronger and more normal, and in some cases the tumors larger. But as a result, the tumor is more vulnerable to the effects of chemotherapy drugs.

In a paper appearing online November 9, 2008 in the journal *Nature*, David Cheresh, Ph.D., professor and vice chair of pathology at the UC San Diego School of Medicine and the Moores UCSD Cancer Center and his co-workers mimicked the action of anti-angiogenesis drugs by genetically reducing VEGF levels in mouse tumors and inflammatory cells in various cancers, including pancreatic cancer. They also used drugs to inhibit VEGF receptor activity. In every case, blood vessels were made normal again.

The researchers say the findings provide an explanation for recent evidence showing that anti-angiogenesis drugs such as Avastin can be much more effective when combined with chemotherapy. The results may lead to better treatment strategies for a variety of cancers.

"We've discovered that when anti-angiogenesis drugs are used to lower the level of VEGF within a tumor, it's not so much a reduction in the endothelial cells and losing blood vessels as it is an activation of the tumor blood vessels supporting cells," said Cheresh. "This enables vessels to mature, providing a conduit for better drug delivery to the tumor. While the tumors initially get larger, they are significantly more sensitive to chemotherapeutic drugs."

As a result, Cheresh said, the findings may provide a new strategy for treating cancer. "It means that chemotherapy could be timed appropriately. We could first stabilize the blood vessels, and then come in with chemotherapy drugs that are able to treat the cancer."

Co-author Randall Johnson, Ph.D., professor of biology at UCSD, Cheresh and their colleagues showed in a related paper in the same journal that tumors were more susceptible to drugs after inflammatory cells lost the ability to express VEGF.

"These two papers define a new mechanism of action for VEGF and for anti-angiogenesis drugs," Cheresh said. "It appears that the drugs, in shutting down VEGF activity, are actively maturing blood vessels, causing them to become stable and more normal, as opposed to reducing blood vessels."

VEGF normally promotes the growth of endothelial cells, which in turn helps build new blood vessels in tumors. But tumor blood vessels are built poorly and do a terrible job of carrying blood and oxygen – and drugs. Cutting VEGF levels in the tumor in turn increases the activity of cells called pericytes that surround the blood vessels, stabilizing them and making them more susceptible to chemotherapy, Cheresh explained.

Cheresh's group found that receptors for VEGF and another growth-promoting protein, PDGF, form a complex that turns off PDGF and the

activity of the blood vessel-support cells. Tumors make too much VEGF in their haste to form blood vessels, which turns on the receptor complex. "When you take away the VEGF, you 'take the foot off of the brake,'" he said, allowing the pericytes to go to work, maturing blood vessels. The same mechanism is at work during wound repair.

Cheresh said that the results show that the host response to the cancer – whether or not it is making blood vessel-maturing cells, for example – is critical in terms of susceptibility to therapy. "It's not just about the therapy, but also what the host does in response to the cancer that makes a difference whether a tumor lives or dies, and if it's susceptible to a drug or not. We can change the host response to the cancer, which is otherwise resistant, and make the vessels more mature, temporarily increasing blood flow to the cancer. We're sensitizing the cancer."

The type of solid tumor should not matter, since the mechanism isn't specific to a particular kind of tumor, he noted. That the quality of the tumor's blood vessels could dictate the patient's response to chemotherapy could be one reason that two patients with similar cancers respond differently to the same therapy.

Cheresh believes that some drug regimens may need to be reexamined. "We have to test available regimens and perhaps restructure the way that we give drugs," he said. "We may be giving the right drugs, but we may not be giving them in the right order. We're just beginning to understand how it works."

Source: University of California - San Diego