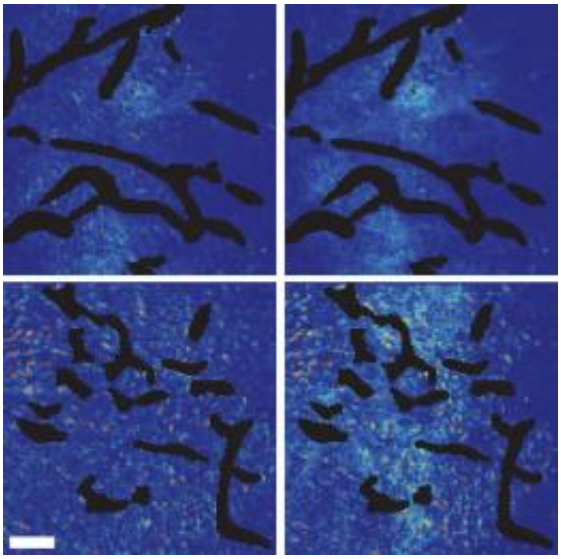
Normalizing tumor blood vessels improves delivery of only the smallest nanomedicines

April 9 2012



Top panels: control setups. Bottom panels: Mammary tumor tissue after normalization of blood vessels. Left: Few of the large nanoparticles are visible. Right: The smaller nanoparticles have penetrated well. Credit: Vikash Chauhan / Nature Nanotech.

Combining two strategies designed to improve the results of cancer treatment – antiangiogenesis drugs and nanomedicines – may only be successful if the smallest nanomedicines are used. A new study from Massachusetts General Hospital (MGH) researchers, appearing in *Nature Nanotechnology*, finds that normalizing blood vessels within tumors, which improves the delivery of standard chemotherapy drugs, can block the delivery of larger nanotherapy molecules.

"We found that vascular normalization only increases the delivery of the smallest nanomedicines to cancer cells," says Vikash P. Chauhan, of the Steele Laboratory of Tumor Biology in the MGH Radiation Oncology Department, lead author of the report. "We also showed that the smallest nanomedicines are inherently better than larger nanomedicines at penetrating tumors, suggesting that smaller nanomedicines may be ideal for cancer therapy."

Tumors need to generate their own blood supply to continue growing, but vessels supplying tumors tend to be disorganized, oversized and leaky. Not only does this prevent the delivery of chemotherapy drugs to cells not close to tumor vessels, but the leakage of plasma out of blood vessels increases pressure within the tumor, further reducing the ability of drugs to penetrate tumors. Treatment with drugs that inhibit angiogenesis – the process by which new vessels are generated – reduces some of these abnormalities, a process called vascular normalization that has been shown to improve treatment of some cancers with standard chemotherapy drugs.

Nanomedicines are actually designed to exploit tumor vessel abnormality. While the molecules of standard chemotherapy drugs are about one nanometer – a billionth of a meter – nanomedicine molecules are from 10 to 100 times larger, too large to penetrate the pores of blood vessels in normal tissues but small enough to pass through the oversized pores of tumor vessels. Since the size of nanomedicines should keep them out of normal tissues, they are prescribed to reduce the negative side effects of chemotherapy.

The current study was designed to investigate whether the use of antiangiogenesis drugs to normalize tumor vasculature would improve or impede delivery of nanomedicines to tumor cells. In studies using a mouse model of breast cancer, the investigators first confirmed that treatment with DC101, an antibody to a molecule essential to blood

vessel growth, temporarily decreased the diameter of enlarged tumor blood vessels. They then showed that this vascular normalization improved the penetration into tumors of 12-nanometer particles but not of 60- or 125-nanometer molecules.

A mathematical model prepared by the MGH team predicted that, while the abnormally large pores in the walls of tumor blood vessels lead to increased pressure within the tumor that impedes the entry of drugs, reducing pore size by antiangiogenesis treatment would relieve intratumor pressure, allowing the entry of those molecules that fit through the smaller pores. To test this prediction, they treated mice with implanted breast tumors either with DC101 and Doxil, a 100-nanometer version of the chemotherapy drug doxorubicin, or with DC101 and Abraxane, a 10-nanometer version of paclitaxel. Although treatment with both chemotherapeutics delayed tumor growth, vascular normalization with DC101 improved the effectiveness only of Abraxane and had no effect on Doxil treatment.

"A variety of anticancer nanomedicines are currently in use or in clinical trials," says Chauhan, who is a graduate student at the Harvard School of Engineering and Applied Sciences (SEAS). "Our findings suggest that combining smaller nanomedicines with antiangiogenic therapies may have a synergistic effect and that smaller nanomedicines should inherently penetrate tumors faster than larger nanomedicines, due to the physical principles that govern drug penetration. While it looks like future development of nanomedicines should focus on making them small – around 12 nanometers in size – we also need to investigate ways to improve delivery of the larger nanomedicines that are currently in use."

"Antiangiogenic agents are prescribed to a large number of cancer patients in combination with conventional therapeutics," explains Rakesh K. Jain, PhD, director of the Steele Lab and senior and corresponding

author of the Nature Nanotechnology report. "Our study provides guidelines on how to combine the antiangiogenic drugs with nanotherapeutics." Jain is Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School.

Provided by Massachusetts General Hospital