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Clot-Mimicking Nanoparticles Attack Tumors

A collaborative, multidisciplinary team of researchers has created nanoparticles that act much like a developing clot to target tumors. These nanoparticles seek out and bind to the blood vessels surrounding tumors and then attract more nanoparticles to the tumor target. Using this system, the team demonstrated that the homing nanoparticle could be used to deliver a "payload" of an imaging compound, and in the process act as a clotting agent, obstructing as much as 20 percent of the tumor blood vessels.

These findings, published in the *Proceedings of the National Academy of Sciences*, come from a research team led by Erkki Ruoslahti, M.D., Ph.D., of the Burnham Institute for Medical Research at the University of California, Santa Barbara, Michael Sailor, Ph.D., of the University of California, San Diego, and Sangeeta Bhatia, Ph.D., of the Massachusetts Institute of Technology. All three team leaders are investigators with Centers for Cancer Nanotechnology Excellence, funded by the National Cancer Institute Alliance for Nanotechnology in Cancer.

Using a screening technique developed previously in Ruoslahti's laboratory, the group identified a peptide that homed to the blood vessels, or vasculature, inside breast cancer tumors growing in mice. The peptide was comprised of five amino acids: Cysteine-Arginine-Glutamic acid-Lysine-Alanine, abbreviated CREKA.

The researchers then demonstrated that the CREKA peptide recognizes clotted blood, which is present in the lining of tumor vessels but not in vessels of normal tissues. They used a special mouse strain that lacks fibrinogen, the main protein component of blood clots, to show this: tumors growing in these fibrinogen-deficient mice did not attract the CREKA peptide, whereas the peptide was detected in the tumors of a control group of normal littermates.

Having confirmed clotted blood as the binding site for CREKA, the team constructed nanoparticles from superparamagnetic amino dextran-coated iron oxide (SPIO); such particles are used in the clinic to enhance magnetic resonance imaging (MRI) scans. The investigators coupled the CREKA peptide with the SPIO particles to give the particles a tumor-homing function. The researchers also added a fluorescent molecule to the nanoparticle.

Initially, CREKA-SPIO's tumor-homing ability was impeded by a natural defense response, which activates the reticuloendothelial system (RES) – white blood cells working in concert with the liver and spleen comprise a protective screening network in mice (and humans). The investigators devised "decoy" molecules of liposomes coated with nickel, which diverted the RES response that would have otherwise been directed toward CREKA-SPIO. The use of decoy molecules extended the half-life of CREKA-SPIO in circulating blood five-fold, which greatly increased the nanoparticle's ability to home to tumors.

The CREKA-SPIO that accumulated in the tumor enhanced blood clotting in tumor vessels, creating additional binding sites for the nanoparticles. This "self amplification" of the

nanoparticles' tumor-homing properties greatly enhanced the investigators' ability to image the tumors. It also contributed to blocking as much as 20 percent of the blood vessels in the tumor. While occluding 20 percent of tumor vessels was not sufficient to reduce the rate of tumor growth, it is a promising target for future studies.

"Having identified the principle of self-amplification, we are now optimizing the process, hoping to obtain a more complete shut-down of blood flow into the tumor to strangle it," says Ruoslahti. "We are also in the process of adding a drug delivery function to the particles. These two approaches are synergistic; the more particles we bring into the tumor, the greater the obstruction of the blood flow and more of the drug is delivered into the tumor."

This work is detailed in a paper titled, "Biomimetic amplification of nanoparticle homing to tumors." Investigators from Berlex, Inc., and Anticancer, Inc., also participated in this study. This paper was published online in advance of print publication. An abstract is available at the journal's website.
View abstract.