Enabling nanoparticles to penetrate deeply in tumors

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Too often, researchers designing nanoparticles capable of delivering effective doses of anticancer agents to tumors must balance the need to choose a nanoparticle that is small enough to escape the leaky blood vessels that surround tumors but large enough to avoid rapid clearance from the blood stream via the kidneys. Balancing these two requirements usually results in using nanoparticles that are indeed small enough to accumulate in the vicinity of tumors, but that are really too large to penetrate deeply enough into tumors to have the maximum therapeutic effect.

Now, a large team of researchers from the Massachusetts Institute of Technology, Massachusetts General Hospital, and Harvard Medical School have developed a solution to this problem: multilayered, or multistage, nanoparticles that partially dissolve once they accumulate around tumors, leaving behind a payload of nanoparticles a mere one-tenth the size of the original delivery vehicle. The remaining 10-nanometer-diameter nanoparticles, loaded with anticancer drugs, can then diffuse deeply into a tumor's dense interior.

Dai Fukumura, Moungi Bawendi, and Rakesh Jain, all senior faculty members at their respective institutions, directed this study. The team published their results in the Proceedings of the National Academy of Sciences. Dr. Bawendi is also a member of the MIT-Harvard Center for Cancer Nanotechnology Excellence funded by the National Cancer Institute.

The key to the new nanoparticles is a gelatin material that can serve as a substrate for enzymes that are produced at high levels by tumors. Cancer cells use these enzymes to dissolve the extracellular matrix that surrounds organs, enabling these malignant cells to escape into the bloodstream and colonize sites distant from the primary tumor. The researchers took advantage of this enzyme by embedding tiny nanoparticles within the gelatin core of the larger nanoparticles that they designed to be injected into the blood stream.

For this set of experiments, the investigators loaded 100-nanometer the gelatin nanoparticles with 10-nanometer quantum dots. While quantum dots are not likely to be used to deliver drugs to tumors, these nanobeacons produce bright optical signals that can be easily monitored as they are released from the larger nanoparticles. Initial experiments using tumors growing in culture showed that the gelatin-degrading enzymes did their job and that the released quantum dots were able to diffuse farther and more efficiently than the 100 nanometer particles into the tumors. Subsequent experiments in tumor-bearing mice confirmed these in vitro findings, and as a result, the investigators are now planning to repeat these experiments using drug loaded 10-nanometer particles in place of the quantum dots they used in this study.

Another approach to getting nanoparticles deep into tumors is to disrupt a tumor's ability to form the dense extracellular matrix, made of the protein collagen, that keeps nanoparticles in the outer regions of a tumor. Dr. Jain's group at MIT and the Harvard Medical School have done just that, using the widely used high-blood pressure medication Losartan to inhibit collagen synthesis. The investigators also published the results of these studies in the *Proceedings of the National Academy of Sciences*.

Human clinical studies have shown that Losartan reduces the incidence of cardiac and renal fibrosis by reducing the synthesis of one particular

form of collagen, known as type I. Dr. Jain and his colleagues reasoned that this same inhibitory effect might lead to easier passage of nanoparticles into the deep recesses of a tumor. In fact, that is exactly the effect they observed at doses of the drug that were small enough to leave blood pressure unaffected. Tests showed that Doxil, the first approved nanoparticulate anticancer agent, was more effective at treating dense, fibrotic tumors, such as pancreatic tumors, growing in mice. Dr. Jain and his colleagues note in their paper that because long-term Losartan therapy has proven safe in humans, and because many anticancer agents raise blood pressure, administering Losartan with nanoparticles has the strong possibility of benefitting cancer patients.

The work on multistage nanoparticles, which is detailed in a paper titled, "Multistage nanoparticle delivery system for deep penetration into tumor tissue," was supported in part by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract of this paper is available at the journal's website.

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