Tracking tumor-targeting nanoparticles in the body

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Though targeted nanoparticle-based imaging agents and therapeutics for diagnosing and treating cancer are making their way to and through the clinical trials process, researchers still do not have a good understanding of how nanoparticles reach tumors and how they then bind to and enter the targeted tumor. To overcome that knowledge deficit, two teams of investigators, both part of the Alliance for Nanotechnology in Cancer have undertaken studies aiming to track nanoparticles as they move through living animals.

In one study, a team of investigators at Stanford University used quantum dots to study how nanoparticles travel through tumor blood vessels in living test subjects, bind to molecular targets on the surface of those blood vessels, and then travel out of the blood stream and into the tumor itself. Sanjiv Sam Gambhir, co-director of one of nine National Cancer Institute (NCI) Centers of Cancer Nanotechnology Excellence, led this study. He and his colleagues published their findings in the journal *Small*. In a second study, published in the journal *ACS Nano*, Alliance investigators Dong Shin, Mostafa El-Sayed, and Shuming Nie of Emory University and the Georgia Institute of Technology used targeted gold nanocrystals to study both active and passive targeting of tumors.

In the Stanford study, Dr. Gambhir and his collaborators exploited the capabilities of intravital microscopy, a technique that enables researchers to see brightly fluorescent markers through a living animal's skin in real time. In this series of experiments, the Stanford team examined

nanoparticle trafficking in mice in which a variety of different types of tumors were allowed to grow in the animals' ears. For the fluorescent marker, the investigators used a near-infrared emitting quantum dot linked to RGD, a molecule known to bind tightly to a protein found on the surface of blood vessels surrounding tumors.

To their surprise, the researchers found that regardless of the type of tumor studied, nanoparticle binding only occurred when aggregates of particles - not single particles - were able to tether themselves to multiple, discreet sites within a tumor. The researchers were not able to detect any significant binding when they repeated these experiments using quantum dots lacking the RGD targeting molecule. The investigators also found that binding rates and binding patterns were consistent across all tumor types, a reassuring finding given the natural heterogeneity that characterizes human cancers.

While binding ability appears to be independent of tumor type, the same cannot be said for extravasation, i.e., the transit of a nanoparticle out of the blood stream and into a tumor. The researchers noted in their paper that it is likely that nanoparticle shape and size will play a critical role in determining how a given nanoparticle will extravasate into each particular type of tumor.

Meanwhile, the Emory-Georgia Tech team used rod-shaped gold nanocrystals linked to tumor-targeting peptides to explore the delivery mechanisms that enable nanoparticles to accumulate in tumors. The investigators used gold nanoparticles so that they could quantify the number of nanoparticles reaching tumors and other tissues. Gold does not occur naturally in mammals, so any gold detected in a given tumor or tissue using the highly sensitive and accurate technique known as elemental mass spectrometry would had to have come from gold nanoparticles.

To conduct their experiments, the investigators created three formulations by attaching one of three tumor-targeting molecules to the surface of the gold nanorods. They then injected the nanoparticles into animals bearing implanted human tumors, allowed the nanoparticles to circulate through the body, and measured the amount of gold that accumulated in the implanted tumors and other tissues. The researchers also repeated this experiment using untargeted gold nanoparticles. The results were surprising in that the targeting molecules only marginally increased the amount of gold that accumulated in tumors.

The investigators concluded that gold nanoparticles designed to be used in photothermal anticancer therapy should be injected directly into tumors rather than via intravenous administration in order to achieve the greatest concentration of gold in tumors. They also noted in their paper that these experiments suggest that target binding is not the rate limiting step for nanoparticle delivery, but rather that transport out of the blood stream and into tumors is the major barrier to nanoparticle accumulation in tumors.

More information: An abstract of the paper "Dynamic Visualization of RGD-Quantum Dot Binding to Tumor Neovasculature and Extravasation in Multiple Living Mouse Models Using Intravital Microscopy," is available at the journal's website. doi:10.1002/smll.201001022 . An abstract of the paper "A Reexamination of Active and Passive Tumor Targeting by Using Rod-Shaped Gold Nanocrystals and Covalently Targeted Peptide Ligands," is available at the journal's website as well. doi:10.1021/nn102055s

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