Radiologist and molecular imaging specialist Jan Grimm

Summary

Memorial Sloan Kettering researchers are investigating the use of tiny particles that behave like sponges to take in drugs and deliver them to tumors.

Memorial Sloan Kettering researchers have shown that tiny particles can be manipulated to act like sponges, taking in drugs and ferrying them to tumors. The minuscule objects hold on to their cargo with weak electric bonds, which give way as they draw near cancer cells.

The research, conducted in the laboratory of radiologist and molecular imaging specialist Jan Grimm, suggests that these spongelike nanoparticles, which the scientists dubbed nanophores, could deliver chemotherapy and other drugs more efficiently than current methods by ensuring they

accumulate at the tumor site.

The researchers employed a particle called ferumoxytol, a drug already used clinically to treat patients with iron deficiency. Cancer drugs loaded onto ferumoxytol are held by the particle until the nanophore senses a slight drop in pH level, which signals a rise in acidity — one of the hallmarks of cancer cells.

“Having the tumor microenvironment and the cancer cells’ unique metabolism trigger the drug’s release is one thing that makes this approach novel,” says Charalambos Kaittanis, the study’s first author. “Until now, researchers have used nanoparticles that release the drug only when they are taken up by the cancer cells, or when the cells secrete certain enzymes. Nobody had tested whether the drug release could be caused by the tumor’s mildly acidic conditions.”

Another novelty of the method is that it allows the monitoring of drug delivery directly in a living organism. The use of magnetic resonance imaging (MRI) enables researchers to detect and measure the amount of drug loaded into the nanophore, as well as to confirm when it is released upon reaching its target.

The research was reported online March 4 in *Nature Communications*.

A Better Transporter

Although a variety of nanoparticles have been investigated as drug transporters, ferumoxytol offers some critical advantages. It already has been proven safe for use in humans, and unlike many nanoparticles, it does not need to be linked chemically to the drug it is carrying — a process that can alter a drug’s properties and reduce its effectiveness. In addition, ferumoxytol allows unambiguous proof that the drug is actually delivered.

“Although others have used MRI to visualize drug release, it was done somewhat indirectly using an imaging agent that was loaded onto the nanoparticle along with the drug,” Dr. Grimm says. “So what you were seeing was the imaging agent being released, and you had to assume the drug was going with it. You never knew for certain that the drug was not still trapped inside the nanoparticle.”

The researchers loaded the ferumoxytol nanophores with two chemotherapy drugs and tested them on human prostate cancer cells, both in a lab dish and in mice. Using MRI, they confirmed that the drugs were delivered to the target cells more efficiently when loaded onto ferumoxytol than if they were given on their own. In the animals, the drug-loaded nanophores shrank tumors markedly while the free drug just slowed their growth.

“We wanted to see if these particles could deliver two drugs simultaneously so they could be used for combination therapy, which has been shown to prevent resistance and maximize response,” Dr. Grimm says. “This approach mainly has proved effective in the treatment of prostate cancer, but it is increasingly considered for other cancers as well.”

The researchers repeated their experiments with human breast cancer cells implanted in mice — although a single drug was loaded in this case — with the same promising result.

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Noninvasive Imaging Potential

The nanophore method also could be used to improve noninvasive imaging of tissues, including lymph nodes that cancer often spreads to from a tumor. In January, Dr. Grimm’s laboratory reported in *Nature Communications* that ferumoxytol loaded with a radioactive tracer could show the location of lymph nodes where prostate cancer first spread in a mouse model for the disease. When imaged with positron emission tomography combined with MRI, the particles showed these nodes in great detail.

“This information could help surgeons who are sampling nodes or removing them completely — the imaging could pick up nodes they might otherwise have missed,” Dr. Grimm says.

The researchers believe ferumoxytol’s well-established safety profile in humans could speed its transition into clinical use.

“We’re at the beginning stages, but there’s great potential because of our ability to put multiple drugs in one nanophore,” Dr. Kaittanis says. “By learning more about the biology of the cancers, we think we can optimize the therapy by adjusting how much of each drug is delivered and tailoring it for individual patients.”

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