Nano-sized 'factories' churn out proteins

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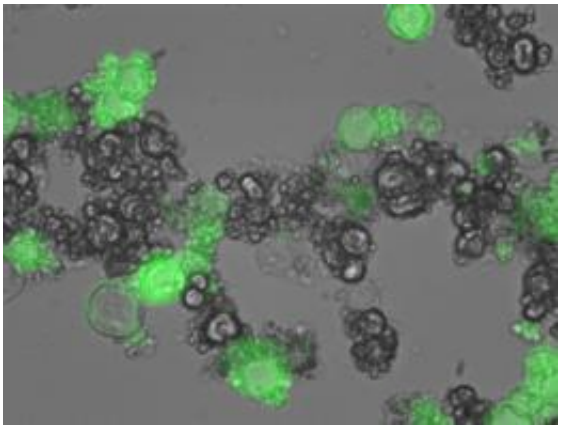

MIT researchers designed these particles that can produce proteins when ultraviolet light is shone on them. In this case, the protein is green fluorescent protein. Image: Avi Schroeder

Drugs made of protein have shown promise in treating cancer, but they are difficult to deliver because the body usually breaks down proteins before they reach their destination.

To get around that obstacle, a team of MIT researchers has developed a new type of nanoparticle that can synthesize proteins on demand. Once these “protein-factory” particles reach their targets, the researchers can turn on protein synthesis by shining ultraviolet light on them.

The particles could be used to deliver small proteins that kill cancer cells, and eventually larger proteins such as antibodies that trigger the

immune system to destroy tumors, says Avi Schroeder, a postdoc in MIT's David H. Koch Institute for Integrative Cancer Research and lead author of a paper appearing in the journal *Nano Letters*.

"This is the first proof of concept that you can actually synthesize new compounds from inert starting materials inside the body," says Schroeder, who works in the labs of Robert Langer, MIT's David H. Koch Institute Professor, and Daniel Anderson, an associate professor of health sciences and technology and chemical engineering.

Langer and Anderson are also authors of the paper, along with former Koch Institute postdocs Michael Goldberg, Christian Kastrup andChristopher Levins

Mimicking nature

The researchers came up with the idea for protein-building particles when trying to think of new ways to attack metastatic tumors — those that spread from the original cancer site to other parts of the body. Such metastases cause 90 percent of cancer deaths.

They decided to mimic the protein-manufacturing strategy found in nature. Cells store their protein-building instructions in DNA, which is then copied into messenger RNA. That mRNA carries protein blueprints to cell structures called ribosomes, which read the mRNA and translate it into amino acid sequences. Amino acids are strung together to form proteins.

"We wanted to use machinery that has already proven to be very effective. Ribosomes are used in nature, and they were perfected by nature over billions of years to be the best machine that can produce protein," Schroeder says.

The researchers designed the new nanoparticles to self-assemble from a mixture that includes lipids — which form the particles' outer shells — plus a mixture of ribosomes, amino acids and the enzymes needed for protein synthesis. Also included in the mixture are DNA sequences for the desired proteins.

The DNA is trapped by a chemical compound called DMNPE, which reversibly binds to it. This compound releases the DNA when exposed to ultraviolet light.

"You want to be able to trigger it so the system turns on only when you want it to work," Schroeder says. "When the particles are hit by light, the DNA is released from a caging compound and then can enter the cycle of producing the protein."

Programmable factories

In this study, particles were programmed to produce either green fluorescent protein (GFP) or luciferase, both of which are easily detected. Tests in mice showed that the particles were successfully prompted to produce protein when UV light shone on them.

Waiting until the particles reach their destination before activating them could help prevent side effects from a particularly toxic drug, says James Heath, a professor of chemistry at the California Institute of Technology. However, more testing must be done to demonstrate that the particles would reach their intended destination in humans, and that they can be used to produce therapeutic proteins, he says.

"There are lots of details left to be worked out for this to be aviable therapeutic approach, but it is a really terrific and innovative concept, and it certainly gets one's imagination going," says Heath, who was not part of the research team.

The researchers are now working on particles that can synthesize potential cancer drugs. Some of these proteins are toxic to both cancerous and healthy cells — but using this delivery method, protein production could be turned on only in the tumor, avoiding side effects in healthy cells.

The team is also working on new ways to activate the nanoparticles. Possible approaches include production triggered by acidity level or other biological conditions specific to certain body regions or cells.

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