Sneaking Spies into a Cell’s Nucleus

Duke University

DURHAM, N.C. – Duke University bioengineers have not only figured out a way to sneak molecular spies through the walls of individual cells, they can now slip them into the command center -- or nucleus -- of those cells, where they can report back important information or drop off payloads.

Using silver nanoparticles cloaked in a protein from the HIV virus that has an uncanny ability to penetrate human cells, the scientists have demonstrated that they can enter the inner workings of the nucleus and detect subtle light signals from the “spy.”

In order for these nano-spies to be effective, they not only need to get through the cell’s first line of defense -- the cell wall -- they must be able to enter the nucleus.

The ultimate goal is to be able to spot the earliest possible moment when the genetic material within a cell begins to turn abnormal, leading to a host of disorders, especially cancer.

The finding also shows how drugs or other payloads might be delivered directly into the nucleus.

“This new method of getting into and detecting exactly what is going on in the nucleus of cell has distinct advantages over current methods,” said Molly Gregas, a graduate student in the laboratory of Tuan Vo-Dinh, R. Eugene and Susie E. Goodson Distinguished Professor of Biomedical Engineering, professor of chemistry and director of The Fitzpatrick Institute for Photonics at Duke’s Pratt School of Engineering.

“The ability to place these nanoparticles into a cell’s nucleus and gather information using light has potential implications for the selective treatment of disease,” Gregas said. “We envision that this approach will also help basic scientists as they try to better understand what occurs within a cell’s nucleus.”

The Duke researchers reported their findings in a series of papers, culminating in the latest issue of Nanomedicine, which was published online. The research was supported by the National Institutes of Health.

The researchers coupled miniscule particles of silver, a metal that is not rejected by cells and is an efficient reflector of light, with a small portion of the HIV protein responsible for its highly efficient ability to enter a cell and its nucleus. In this case, the researchers harnessed only the ability of HIV to sneak past cellular defenses, while stripping away its ability to take over the cell’s genetic machinery and cause disease.

"This combination takes advantage of the smallness of the nanoparticle and the 'delivery instructions' of the HIV protein," Gregas explained. "Once we can get that nanoparticle into the nucleus, we have many options. We can for example deliver some sort of payload and then observe its effects within the nucleus."

That's where a four-decades-old optical technique known as surface-enhanced Raman scattering (SERS) comes into play. It is used here as a sensitive imaging technique to demonstrate that the nanoparticles and their payloads successfully entered the nucleus.

When light, usually from a laser, is shined on a sample, the target molecule vibrates and scatters back its own unique light, often referred to as the Raman scatter. However, this Raman response is extremely weak. When the target molecule is coupled with a metal nanoparticle, the Raman response is greatly enhanced by the SERS effect -- often by more than a million times, Vo-Dinh said.

In the early 1980s, while at the Oak Ridge National Laboratory in Tennessee, Vo-Dinh and colleagues were among the first to demonstrate that SERS could be put into practical use to detect chemicals, including carcinogens, environmental pollutants and early markers of disease. At Duke, Vo-Dinh is pushing the boundaries of SERS technology for biomedical detection and molecular imaging.

"Our ultimate goal is to develop a nanoscale delivery system that can drop off its payload – in this case nanoparticles with other agents attached -- into a cell to enhance the effectiveness of a drug treatment," Vo-Dinh said. "Theoretically, we could 'load up' these nanoparticles with many things we are interested in -- for example a nanoprobe for a cancer gene -- and get it into a cell's nucleus. This would provide us a warning signal of the disease at its earliest stage, thus allowing faster and more effective treatment."

The current experiments were conducted with living cells in the laboratory. New experiments are focusing on using this approach in animal models to determine how it works in a complex living system.

Other Duke engineering members of the research team include Fei Yan, Jonathan Scaffidi, Hsin-Neng Wang and Benoit Lauly. Victoria Seewaldt of Duke's Comprehensive Cancer Center also participated in the research.

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