National Institute of Biomedical Imaging and Bioengineering

Creating Biomedical Technologies to Improve Health

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Harnessing Plant Viruses for Cancer Imaging and Therapy

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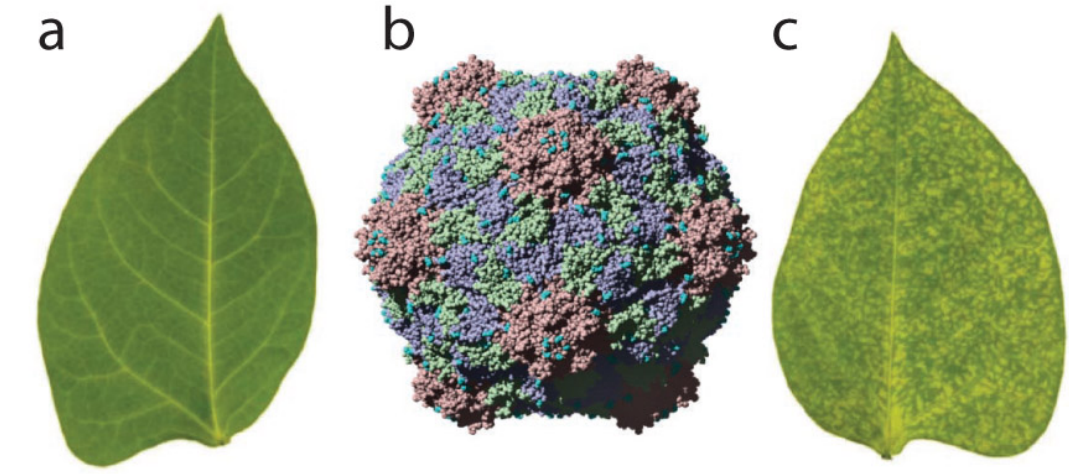
Prostate cancer is the most common cancer and the second leading cause of cancer-related death in men. Successful treatment of prostate cancer relies in part on its early and accurate detection. Conventional prostate imaging approaches including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are not sensitive enough to detect very small tumors in the prostate or signs that the disease has metastasized (spread). A new class of agents known as *viral nanoparticles* offers the opportunity to improve detection of small lumps of cancer cells.

Capitalizing on Mother Nature's Nanoengineering

Nicole F. Steinmetz, assistant professor of biomedical engineering at Case Western Reserve University School of Medicine, has developed a new prostate cancer imaging nanoparticle based on the cowpea mosaic virus (CPMV) that infects black-eyed peas. At a diameter of only 28 nm, CPMV is a natural nanoparticle. Steinmetz and her colleagues converted the intact CPMV into a "smart" nanoparticle equipped with bright fluorescent dyes for imaging and a chemical tag to help it find and latch onto prostate cancer cells.



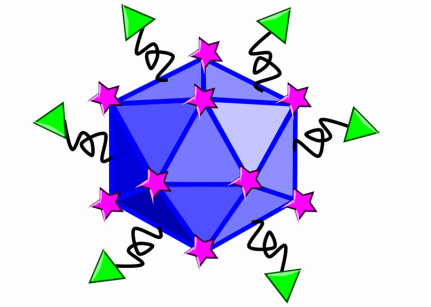
To obtain large quantities of plant-derived viral nanoparticles for research, scientists grow viruses in laboratory greenhouses. Leaves of black-eyed pea plants (a) are infected with the cowpea mosaic virus (b, computer-generated 3D model of the virus structure), which quickly starts multiplying and spreading throughout the plants, and in 7–10 days the leaves start showing signs of infection (c). Adapted by permission from Macmillan Publishers Ltd: Nature Protocols, 5(8):1406-17, copyright 2010.http://www.nature.com/nprot/journal/v5/n8/full/nprot.2010.103.html

Each viral nanoparticle can be decorated with over 100 dye molecules and targeting ligands (molecules that bind to receptors), leading to increased imaging sensitivity. The viral nanoparticles could be an invaluable tool for detecting prostate cancer that has spread to the bone. “Currently, this is done by bone scan, but the sensitivity is very poor and can only detect advanced metastatic disease,” says co-investigator John Lewis, associate professor at the University of Alberta in Canada and director of the Translational Prostate Research Group.

For the past decade, scientists have been exploring viruses as a natural alternative to manmade nanoparticles for imaging, drug delivery, vaccination, and design of electronic devices. Plant-based viral nanoparticles have several advantages over synthetic nanomaterials—they are biodegradable and harmless to humans, have a defined structure with anchor points for attaching dyes and targeting tags, and can be modified through genetic engineering. “These nanoparticles are in the human food chain. We know that they are highly biocompatible,” says Lewis, and unlike other nanoparticles, “they don’t require any dangerous chemicals.”

From Black-Eyed Pea to “Smart” Nanoparticle

Another major advantage of plant-derived viral nanoparticles is that production is relatively cheap. “We start out from dirt and sunlight, and it’s very scalable,” says Steinmetz. Just ten days after sowing in the laboratory greenhouse, leaves of young black-eyed pea plants are infected with the virus. First, leaves are coated with an abrasive powder, and then a liquid containing viruses is applied to the leaf surface. When the leaves are gently rubbed, the powder wounds the leaf surface, allowing the virus to penetrate and infect the plant. The virus multiplies quickly and spreads throughout the plant. Ten days after infection, leaves are harvested and viral nanoparticles are extracted. With as few as 50 plants, researchers can produce 100 mgs of CPMV, enough nanomaterial for hundreds of imaging experiments. The surface of the natural nanoparticles is decorated with various chemical appendages—fluorescent dyes, stabilizing chemicals, and targeting molecules. For example, polyethylene glycol (PEG) is incorporated to extend the nanoparticle’s persistence in the bloodstream. A molecule called bombesin is added to enable nanoparticles to find prostate cancer cells, which have high levels of a protein that binds bombesin.



To turn the cowpea mosaic virus (blue) into a nanoparticle for prostate cancer imaging, researchers attach different molecules—the fluorescent dye (pink stars) for visualization, polyethylene glycol (black squiggly lines) for stability, and bombesin (green triangle) for latching onto tumor cells.

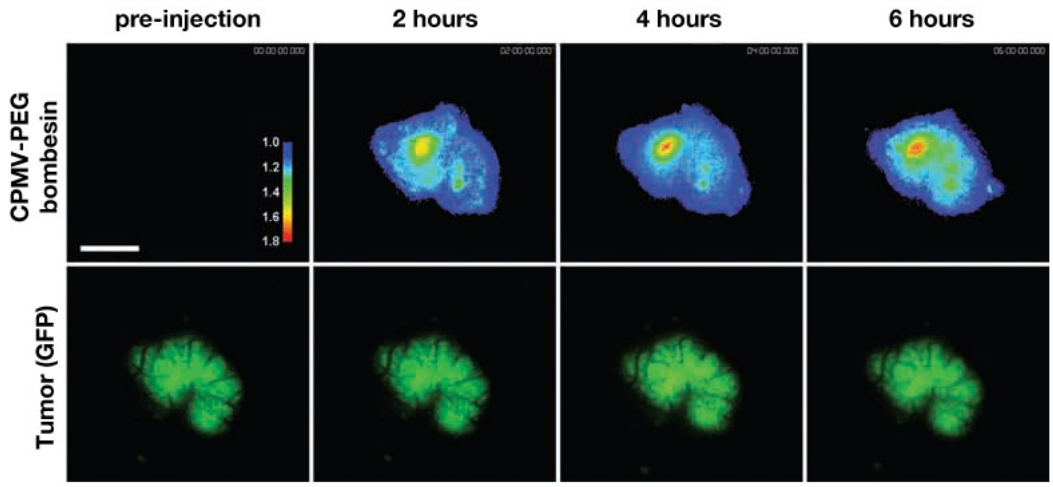
The researchers use so-called “click chemistry” to attach bombesin and PEG to the nanoparticle. This relatively new approach to chemical synthesis minimizes the number of steps involved and “allows us to use the minimal amount of material,” explains Steinmetz. The nanoparticles’ performance as an imaging agent was validated using an established model for visualizing tumor growth with fluorescence imaging: a chicken embryo. The embryos are small enough to fit under a microscope and their thin skin allows fluorescent light to pass through. To verify that the viral nanoparticles could home in on human prostate cancer cells in vivo, the researchers implanted chicken embryos with human prostate cancer cells. When the implanted cells formed tumors, the embryos were injected with fluorescently-labeled nanoparticles. Using a specialized instrument for real-time fluorescence microscopy in live animals, the researchers visualized and measured the uptake of viral nanoparticles. They found that the targeted nanoparticles accumulated and were retained in tumors, warranting further development of viral nanoparticles for tumor imaging and treatment.

Developing Viral Nanoparticles for Cancer Imaging and Treatment

This research is one of the first attempts to use a plant-derived viral nanoparticle for cancer imaging. “My goal is to move plant viruses for cancer imaging and treatment into the clinic,” says Steinmetz. Although plant-derived viral particles cannot infect humans, the viral genetic material must be removed prior to clinical use in order to protect the environment. Fluorescent dyes are not suitable for human use because tissues absorb the light signal, so the dyes would have to be replaced by other agents, like radioisotopes used in bone scans. “These nanoparticles have been formulated with either gadolinium [an MRI dye] or iron oxide, so we have an opportunity to do MRI as well,” says Lewis. His lab also is developing a number of radionuclide imaging agents, some based on viral nanoparticles, some on other nanoparticles.

Experiments are in progress to determine how long the nanoparticles survive in cancer cells and to define their potential side effects. Steinmetz is exploring various viral particle shapes to see which one is ideal for targeting and penetrating tumors. She is also collaborating with Ruth Keri, associate professor of pharmacology at Case Western, to develop nanoparticle formulations for breast cancer imaging and therapy. Meanwhile, Lewis is exploring alternatives to bombesin for directing nanoparticles to prostate cancer cells.

As a long-term goal, both researchers wish to develop viral nanoparticles for delivering drugs directly to the tumor, which would decrease toxic side effects of therapy to the rest of the body. This approach would be very valuable in the slow-growing prostate cancer, where the side effects of conventional chemotherapy generally outweigh the benefit.



To test how well the cowpea mosaic virus (CPMV) nanoparticle performed in imaging of prostate tumors, researchers injected chicken embryos bearing human prostate tumors with CPMV nanoparticles containing polyethylene glycol (PEG), bombesin, and a fluorescent dye. Within the first hour after injection, targeted nanoparticles accumulated in the tumor and surrounding vasculature (stroma). In the second hour, the signal in the stroma decreased, while the signal in the tumor remained high. In the top strip, color change from blue to red depicts progressively higher accumulation of nanoparticles in the tumor. To assess how nanoparticle signal is distributed in the tumor, researchers imaged whole tumors (bottom strip). The tumors glow green from the presence of green fluorescence protein (GFP) in prostate cancer cells. Adapted by permission from John Wiley and Sons: Small, 7(12):1664-72, copyright 2011.http://onlinelibrary.wiley.com/doi/10.1002/smll.201000435/abstract

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Steinmetz NF, Ablack AL, Hickey JL, Ablack J, Manocha B, Mymryk JS, Luyt LG, Lewis JD. Intravital imaging of human prostate cancer using viral nanoparticles targeted to gastrin-releasing peptide receptors. Small. 2011 Jun 20;7(12):1664-72.

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