Nanobombs might deliver agents that alter gene activity in cancer stem cells

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Researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) have developed nanoparticles that swell and burst when exposed to near-infrared laser light.

Such 'nanobombs' might overcome a biological barrier that has blocked development of agents that work by altering the activity—the expression—of genes in cancer cells. The agents might kill cancer cells outright or stall their growth.

The kinds of agents that change gene expression are generally forms of RNA (ribonucleic acid), and they are notoriously difficult to use as drugs. First, they are readily degraded when free in the bloodstream. In this study, packaging them in nanoparticles that target tumor cells solved that problem.

This study, published in the journal *Advanced Materials*, suggests that the nanobombs might also solve the second problem. When cancer cells take up ordinary nanoparticles, they often enclose them in small compartments called endosomes. This prevents the drug molecules from reaching their target, and they are soon degraded.

Along with the therapeutic agent, these nanoparticles contain a chemical that vaporizes, causing them to swell three times or more in size when exposed to near-infrared laser light. The endosomes burst, dispersing the RNA agent into the cell.

"A major challenge to using nanoparticles to deliver gene-regulating agents such as microRNAs is the inability of the nanoparticles to escape the compartments, the endosomes, that they are encased in when cells take up the particles," says principal investigator Xiaoming (Shawn) He, PhD, associate professor of Biomedical Engineering and member of the OSUCCC—James Translational Therapeutics Program.

"We believe we've overcome this challenge by developing nanoparticles that include ammonium bicarbonate, a small molecule that vaporizes when exposing the nanoparticles to near-infrared laser light, causing the nanoparticle and endosome to burst, releasing the therapeutic RNA," He explains.For their study, He and colleagues used human prostate-cancer cells and human prostate tumors in an animal model. The nanoparticles were equipped to target cancer stem-like cells (CSCs), which are cancer cells that have properties of stem cells. CSCs often resist therapy and are thought to play an important role in cancer development and recurrence.

The therapeutic agent in the nanoparticles was a form of microRNA called miR-34a. The researchers chose this molecule because it can lower the levels of a protein that is crucial for CSC survival and may be involved in chemotherapy and radiation therapy resistance.

The nanoparticles also encapsulate ammonium bicarbonate, which is a leavening agent sometimes used in baking. Near-infrared laser light, which induces vaporization of the ammonium bicarbonate, can penetrate tissue to a depth of one centimeter (nearly half an inch). For deeper tumors, the light would be delivered using minimally invasive surgery.

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The study's key technical findings include:

- Nanoparticles with ammonium bicarbonate enlarged more than three times when activated with near-infrared laser (from about 100 nm in diameter at body temperature to more than 300 nm at 43 degrees C. (110 degrees F). Endosomes measure 150-200 nm in diameter;
- The nanoparticles had great affinity for CSCs and very little for normal human adipose-derived stem cells;
- The miR-34a nanobombs significantly reduced tumor volume in an animal model that bore human prostate tumors.

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