Targeted nanospheres find, penetrate, then fuel burning of melanoma

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Hollow gold nanospheres equipped with a targeting peptide find melanoma cells, penetrate them deeply, and then cook the tumor when bathed with near-infrared light, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center reported in the Feb. 1 issue of *Clinical Cancer Research*.

"Active targeting of nanoparticles to tumors is the holy grail of therapeutic nanotechnology for cancer. We're getting closer to that goal," said senior author Chun Li, Ph.D., professor in M. D. Anderson's Department of Experimental Diagnostic Imaging. When heated with lasers, the actively targeted hollow gold nanospheres did eight times more damage to melanoma tumors in mice than did the same nanospheres that gathered less directly in the tumors.

Lab and mouse model experiments demonstrated the first in vivo active targeting of gold nanostructures to tumors in conjunction with photothermal ablation - a minimally invasive treatment that uses heat generated through absorption of light to destroy target tissue. Tumors are burned with near-infrared light, which penetrates deeper into tissue than visible or ultraviolet light.

Photothermal ablation is used to treat some cancers by embedding optical fibers inside tumors to deliver near-infrared light. Its efficiency can be greatly improved when a light-absorbing material is applied to the tumor, Li said. Photothermal ablation has been explored for melanoma, but because it also hits healthy tissue, dose duration and volume have

been limited.

Lower light dose, great damage

With hollow gold nanospheres inside melanoma cells, photothermal ablation destroyed tumors in mice with a laser light dose that was 12 percent of the dose required when the nanospheres aren't applied, Li and colleagues report. Such a low dose is more likely to spare surrounding tissue.

Injected, untargeted nanoparticles accumulate in tumors because they are so small that they fit through the larger pores of abnormal blood vessels that nourish cancer, Li said. This "passive targeting" delivers a low dose of nanoparticles and concentrates them near the cell's vasculature.

The researchers packaged hollow, spherical gold nanospheres with a peptide - a small compound composed of amino acids - that binds to the melanocortin type 1 receptor, which is overly abundant in melanoma cells. They first treated melanoma cells in culture and later injected both targeted and untargeted nanospheres into mice with melanoma, then applied near-infrared light.

Fluorescent tagging of the targeted nanospheres showed that they were embedded in cultured melanoma cells, while hollow gold nanospheres without the targeting peptide were not. The targeted nanospheres were actively drawn into the cells through the cell membrane.

When the researchers beamed near-infrared light onto treated cultures, most cells with targeted nanospheres died, and almost all of those left were irreparably damaged. Only a small fraction of cells treated with untargeted nanospheres died. Cells treated only with near-infrared light or only with the nanospheres were undamaged.

An 8-fold increase in tumor destruction

In the mouse model, fluorescent tagging showed that the plain hollow gold nanospheres only accumulated near the tumor's blood vessels, while the targeted nanospheres were found throughout the tumor.

"There are many biological barriers to effective use of nanoparticles, with the liver and spleen being the most important," Li said. The body directs foreign particles and defective cells to those organs for destruction.

Most of the targeted nanospheres in the treated mice gathered in the tumor, with smaller amounts found in the liver and spleen. Most of the untargeted nanospheres gathered in the spleen, then in the liver and then the tumor, demonstrating the selectivity and importance of targeting.

In another group of mice, near-infrared light beamed into tumors with targeted nanospheres destroyed 66 percent of the tumors, but only destroyed 7.9 percent of tumors treated with untargeted nanospheres.

The researchers used F-18-labeled glucose to monitor tumor activity by observing how much glucose it metabolized. This action "lights up" the tumor for positron emission tomography (PET) imaging. Tumors treated with targeted shells largely went dark.

"Clinical implications of this approach are not limited to melanoma," Li said. "It's also a proof of principle that receptors common to other cancers can also be targeted by a peptide-guided hollow gold nanosphere. We've also shown that non-invasive PET can monitor early response to treatment."

The targeted nanospheres have a number of advantages, said Jin Zhang, Ph.D., professor in the University of California-Santa Cruz Department

of Chemistry and developer of the hollow nanospheres. Their size - small even for nanoparticles at 40-50 nanometers in diameter - and spherical shape allow for greater uptake and cellular penetration. They have strong, but narrow and tunable ability to absorb light across the visible and near-infrared spectrum, making them unique from other metal nanoparticles.

The hollow spheres are pure gold, which has a long history of safe medical use with few side-effects, Li said.

Source: University of Texas M. D. Anderson Cancer Center

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