Nanoshells aid in killing breast tumors

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Using tiny gold "nanoshells" to deliver just a little heat to breast tumor cells already treated with radiation boosts the killing potential of the treatment - not just shrinking the tumor but killing the cancer stem cells, said researchers at The Methodist Hospital, Baylor College of Medicine and The University of Texas M. D. Anderson Cancer Center in a report for *Science Translational Medicine*.

In studies of tumor cells grown in the laboratory and of mice with the most aggressive mouse and human tumors, the researchers found that radiation plus gold nanoshells heated with a near-infrared laser not only shrank the tumors but dramatically decreased the population of cancer stem cells, said Rachel Atkinson, the Baylor graduate student who is first author of the report. Her mentors are Dr. Jeffrey Rosen, professor of molecular and cellular biology and a member of the NCI-designated Dan L. Duncan Cancer Center and Dr. Jenny C. Chang, a former BCM professor who is now director of the Methodist Cancer Center. Both are senior authors of the report.

Atkinson said, "I stumbled on this when I was a first-year graduate student. I was working with radiation and cancer stem cells, which are resistant to chemotherapy and radiation therapy. I had treated my cells with radiation and left them over the weekend. When I returned on Monday, I was disappointed because my cancer stem cells were dead and the normal cells were fine."

She opened the incubator and her glasses fogged, giving her a clue that the temperature had gone up over the weekend. That was the clue that

heat plus radiation appeared to be effective against the stubborn stem cells.

She followed it up with different kinds of tumor cells and was about to publish her data when she learned of a group at M.D. Anderson that used nanoshells to deliver hyperthermia and to sensitize tumors to radiation therapy. These original studies had demonstrated hyperthermia delivered through nanoshells increases perfusion of tumors with oxygen and also focally disrupts the blood supply to tumors, both of which enhance the effectiveness of radiation. They decided to collaborate to determine what effect heat delivered by the nanoshells would have in highly resistant tumors in mice.

Atkinson chose two aggressive breast tumors that represent one of the worst breast cancer types -triple negative breast cancer, which lacks crucial receptors that can make it targetable with specific drugs. She also worked with mice that had human tumors of the same type.

When she treated the tumors with radiation alone, the tumors would shrink, but a large percentage of the cells left behind were cancer stem cells, which could regrow the tumor. Adding just a little heat - from 37 degree C (98.6 degrees F) to 42 degrees C (107.6 degrees F) - via the nanoshells reduced the population of stem cells dramatically.

"The cancer stem cells were more sensitive to the combination treatment than the bulk of the tumor. This the exact opposite response we see with radiation only," she said.
When Atkinson transplanted cells from the treated tumors into mice, she found that tumors were less aggressive and appeared (phenotype) more differentiated then tumors treated with radiation only. When she looked at the tumors that grew after transplantation, she found that the undifferentiated tumors had changed, becoming more differentiated with the formation of ducts and lumens typical of breast architecture.

"The advantage of the nanoshells is that you are not heating the whole mouse," said Rosen. Earlier studies of the effect of heat on cancer have used whole body heating, which can have serious side effects. In this case, the gold nanoshells, which are 100-nanometer silica spheres with gold shells, invade the tumor through the leaky blood vessels that provide it nourishment. (A nanometer is one-billionth of a meter.) They used a special near-infrared laser to heat the nanoshells for about 20 minutes.

"We were focusing on the cancer stem cells, not just the shrinking of the tumor. Decreasing the size of the tumor is not a good endpoint. You can shrink the tumor with drugs or radiation, but it does not kill the stem cells," said Rosen, who is a pioneer in the field. "What Rachel showed using mouse models and xenografts is leading to clinical trials in patients."

"These findings may have tremendous clinical implications. The use of gold nanoshells with heating and radiation could eliminate cancer stem cells as well as the bulk of the tumor, which may improve survival in women with breast cancer," said Chang.

Atkinson also found that with the addition of hyperthermia the cancer cells could not repair the damage done to their DNA and most of them died. The heat also prevented the cells from increasing levels of most of the heat shock proteins, she said. The only heat shock protein that increased may explain why some of the stem cells progressed to a more differentiated state.

An editor's summary in the journal noted: "Although gold nanoshells still require further testing, hyperthermia treatments are already in clinical trials, and ionizing radiation is a staple of cancer therapy. This suggests that the dual hyperthermia-radiation cancer therapy of Atkinson et al. should be amenable to a clinical setting."

More information: Read a copy of the full report: stm.sciencemag.org/content/2/55/55ra79.abstract

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