Cancer Stem Cells Linked to Radiation Resistance

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Certain types of brain cancer cells, called cancer stem cells, help brain tumors to buffer themselves against radiation treatment by activating a "repair switch" that enables them to continue to grow unchecked, researchers at Duke University Medical Center have found.

The researchers also identified a method that appears to block the cells' ability to activate the repair switch following radiation treatment. This finding may lead to the development of therapies for overcoming radiation resistance in brain cancer as well as other types of cancer, the researchers said.

Working with animal and cell culture models, the researchers found that a specific cellular process called the "DNA damage checkpoint response" appears to enable cancer stem cells to survive exposure to radiation and to switch on a signal to automatically repair any damage caused to their DNA.

"In recent years, people have hypothesized that cancer stem cells are responsible for the resistance of malignant tumors to radiation treatment," said Jeremy Rich, M.D., senior investigator of the study and an associate professor of neurology at Duke. "We have shown, for the first time, that this is indeed the case."

The findings appear Oct. 18, 2006, in the advance online edition of the journal *Nature*. The research was supported by the National Institutes of Health and a number of philanthropic organizations.

The type of cancer that the researchers studied, glioblastoma, is highly resistant to radiation and other forms of treatment and is the most deadly form of brain cancer worldwide. Although aggressive treatments can destroy the majority of the cancerous cells, a small fraction of them remain and often regenerate into even larger masses of tumor cells.

Until recently, scientists knew little about what made these resistant cells different from those that succumb to radiation treatment. It was clear, however, that the cells shared characteristics similar to those of normally functioning nerve stem cells, Rich said.

In the current study, the researchers used glioblastoma tissue removed from patients during neurosurgery and created two separate models. For one model, the researchers extracted cells from the tissue and grew them in cultures in the laboratory. For the second model, they transplanted the glioblastoma tissue into the frontal lobes of the brains of mice.

The researchers first measured the number of glioma stem cells present in the original tissue and then administered set doses of ionizing radiation to the cell cultures and to the mice. In both cases, the researchers observed a roughly fourfold jump in the number of glioma stem cells present in the tumor tissue following radiation treatment.

Because ionizing radiation works primarily by causing permanent damage to the key genetic material of cells, DNA, the researchers hypothesized that the glioma stem cells survive and multiply by somehow fixing radiation-induced DNA damage better than the other cancer cells.

To test this, the researchers searched the tissue samples for specific proteins that are responsible for detecting DNA damage. Using cell samples taken from both study models, the team examined the DNA damage checkpoint response both before and after use of ionizing radiation treatments by testing for activation of the key proteins that detect DNA damage. The researchers wanted to know whether the cells, following exposure to radiation treatment, would repair the DNA damage by activating the checkpoint response or whether they would instead die.

The team found that after ionizing radiation, the DNA damage checkpoint proteins in glioma stem cells were more highly activated than in other cancer cells. This heightened activation, the researchers said, leads cancer stem cells to more effectively repair DNA damage and thus render the cells less likely to die as a result of the treatment.

In another set of experiments, the researchers treated both the test animals and the cell cultures with a drug, called debromohymenialdisine, which is known to inhibit the proteins involved in the activation process. They added the drug before and after radiation treatment and measured the number of surviving cancer stem cells.

They found that administering the drug before radiation did little to change the number of cancer stem cells, but giving the drug in conjunction with radiation appeared to halt the resistance of cancer stem cells to radiation. This finding, the researchers said, suggests that use of a checkpoint inhibitor during radiation ruins the cells' potential to repair themselves and increases the likelihood that the cells will die.

"Our findings show one pathway in cancer stem cells that promotes the radiation resistance of glioblastomas," said Rich. "Treatments that target DNA damage checkpoint response in cancer stem cells may overcome the radiation resistance and eventually allow us to help even greater numbers of cancer patients."

Source: Duke University