Researchers find way to make tumor cells easier to destroy

May 6 2008

Tumors have a unique vulnerability that can be exploited to make them more sensitive to heat and radiation, researchers at Washington University School of Medicine in St. Louis report.

The Washington University radiation oncology researchers found that tumors have a built-in mechanism that protects them from heat (hyperthermia) damage and most likely decreases the benefit of hyperthermia and radiation as a combined therapy.

By interfering with that protection, the researchers have shown that tumor cells grown in culture can be made more sensitive to hyperthermia-enhanced radiation therapy. The findings are reported in the May 1, 2008 issue of *Cancer Research*.

Radiation therapy is a mainstay of cancer treatment but doesn't always completely control tumors. For several years, raising tumor temperature has been investigated as a radiation therapy enhancer with few adverse side effects.

"Past research has shown that hyperthermia is one of the most potent ways to increase cell-killing by radiation," says senior author Tej K. Pandita, Ph.D., associate professor of radiation oncology and of genetics and a researcher with the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital.

"But now we've found that heat also enhances the activity of an enzyme

called telomerase in cancer cells," he says. "Telomerase helps protect the cells from stress-induced damage and allows some of them to survive. We used compounds that inhibit telomerase and showed that cancer cells then become easier to destroy with hyperthermia and radiation used in combination."

Telomerase repairs the ends of chromosomes by maintaining stability of specialized cellular structures called telomeres after cells divide. Without telomerase the number of cell divisions is limited. Telomerase is not active in most normal human cells but is active in most cancer cells, which rely on telomerase to continue to proliferate.

In this study, Pandita's research group found that moderately turning up the heat also turns up the activity of telomerase in tumor cells. The researchers found that if they inactivated telomerase and then increased the temperature of tumor cells, more cells were killed by ionizing radiation. Because nearly all cancers have telomerase, drugs that turn off its activity could be useful against many cancers.

The researchers tested three compounds, and one, GRN163L, more strongly inhibited telomerase than the others. Many groups are studying GRN163L as an anticancer therapeutic, and it recently received clearance by the U.S. Food and Drug Administration to enter human phase I/II clinical testing in chronic lymphocytic leukemia. In some preliminary studies, GRN163L has been shown to be additive when used in combination with existing cancer drugs or radiation.

Next, Pandita and colleagues will test the effect of GRN163L on tumors in mice to see if it will enhance the cell-killing effect of hyperthermia and radiation. They are also working to develop chemicals that have heat-like effects to bypass the need to supply a physical heat source to tissue.

Citation: Agarwal M, Pandita S, Hunt CR, Gupta A, Yue X, Khan S,

Pandita RK, Prat D, Shay JW, Taylor JSA, Pandita TK. Inhibition of telomerase activity enhances hyperthermia-mediated radiosensitization. Cancer Research 2008;68: May 1, 2008.

Source: Washington University School of Medicine