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Lithium may help radiation target cancer, spare healthy tissue

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Vanderbilt-Ingram Cancer Center investigators have uncovered a mechanism that helps explain how lithium, a drug widely used to treat bipolar mood disorder, also protects the brain from damage that occurs during radiation treatments.

In the May 1 issue of the *Journal of Clinical Investigation*, Fen Xia, M.D., Ph.D., and colleagues show that lithium promotes DNA repair in healthy cells but not in brain tumor cells. The findings suggest that lithium treatment could offer a way to protect healthy brain tissue from damage that may occur during cranial radiation treatments.

Cranial irradiation is part of standard therapy for both primary and metastatic brain tumors. However, as with all treatment modalities, radiation often causes long-term side effects. In particular, neurological impairments - including lowered IQ, learning difficulties and memory loss - have been reported, especially in children treated for brain cancers. Radiation-induced damage to the healthy cells of the hippocampus, a brain structure crucial for learning and memory, is one likely source of these deficits.

These cognitive impairments have long-lasting effects on the quality of life for survivors, noted Xia, an assistant professor of Radiation Oncology and Cancer Biology.

"Because these patients can now survive longer and are being cured, alleviating long-term toxicity is becoming more important," she said.

Researchers have been searching for agents that could protect healthy brain tissue from radiation-induced damage. Previously, Vanderbilt-Ingram investigators - led by Dennis Hallahan, M.D., chair of Radiation Oncology and the Ingram Professor of Cancer Research - found that lithium treatment protects cultured hippocampal neurons from radiation-induced cell death and improves cognitive performance in irradiated mice.

But how lithium protects against radiation-induced damage is unclear.

Radiation kills tumor cells by damaging their DNA, but it can also attack the DNA of healthy cells. One of the most serious types of DNA damage is the chromosomal double-stranded break (DSB), in which both strands of the double helix are severed. Even a single unrepaired DSB can be lethal to a cell. Fortunately, the body has several different ways to repair DNA damage.

Xia, whose lab studies the mechanisms of DNA repair in normal cells and tumor cells, suspected that lithium might affect how DNA is repaired following radiation-induced damage.

Working with Eddy Yang, M.D., Ph.D., a resident in the Radiation Oncology department and an American Board of Radiology Holman Research Scholar, and postdoctoral research fellow Hong Wang, M.D., Ph.D., Xia and colleagues examined DNA repair in lithium-treated mouse hippocampal neurons exposed to radiation.

They found that lithium did not prevent the generation of DSBs but promoted a particular kind of DNA repair - called nonhomologous end-joining (NHEJ) repair - which is the predominant repair mechanism used by normal neurons. Xia and colleagues showed biochemical and genetic evidence that radiation-induced DSBs were repaired with greater efficiency in lithium-treated cells via the NHEJ pathway.

However, none of these effects were observed in malignant glioma (brain tumor) cells, presumably because cancer cells generally utilize a different DNA repair mechanism, Xia said.

The researchers confirmed these findings in mice treated with cranial radiation. The results suggest that lithium protects healthy hippocampal neurons by promoting NHEJ-mediated DNA repair - but that lithium offers no protective effect in the brain tumor cells tested.

Since some tumors are resistant to radiation, Xia hopes that lithium treatment could provide a way to increase the radiation dose to levels that will kill the tumor cells while protecting healthy brain tissue. The team is launching an investigation of the safety and feasibility of lithium treatment in patients with low-grade glioma or brain metastases from small cell lung cancer.

"Right now, the problem is that we cannot kill the tumor completely because normal tissue toxicity limits the dose," Xia said. "So if we can protect normal tissue, we can hopefully give a higher dose to the tumor."

Source: Vanderbilt University Medical Center (news : web)