Discovery makes brain tumor cells more responsive to radiation

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Duke University Medical Center researchers have figured out how stem cells in the malignant brain cancer glioma may be better able to resist radiation therapy. And using a drug to block a particular signaling pathway in these cancer stem cells, they were able to kill many more glioma cells with radiation in a laboratory experiment.

The work builds off earlier research which showed that cancer stem cells resist the effects of radiation much better than other cancer cells.

The Duke team identified a known signaling pathway called Notch as the probable reason for the improved resistance. Notch also operates in normal stem cells, where it is important for cell-cell communication that controls cell growth and differentiation processes. The study was published in late November by *Stem Cells* journal.

"This is the first report that Notch signaling in tumor tissue is related to the failure of radiation treatments," said lead author Jialiang Wang, Ph.D., a research associate in the Duke Division of Surgery Sciences and the Duke Translational Research Institute. "This makes the Notch pathway an attractive drug target. The right drug may be able to stop the real bad guys, the glioma stem cells."

Stem cells in a cancer are the source of cancer cell proliferation, Wang said. Hundreds of cancer stem cells can quickly become a million tumor cells.

The Duke researchers, in collaboration with a team led by Dr. Jeremy Rich at Cleveland Clinic, used drugs called gamma-secretase inhibitors that target a key enzyme involved in Notch signaling pathway on gliomas in a lab dish. These inhibitors are being studied by other researchers for their ability to fight tumors in which Notch is abnormally activated, such as leukemia, breast and brain tumors.

"In our study, gamma-secretase inhibitors alone only moderately slowed down tumor cell growth," said senior author Dr. Bruce Sullenger, Duke Vice Chair for Research and Joseph W. and Dorothy W. Beard Professor of Surgery. "But when we looked at these molecules combined with radiation at clinically relevant doses, the combination caused massive cell death in the tumors and significantly reduced survival of glioma stem cells. These findings often correlate with better tumor control."

Wang said ongoing clinical trials are testing gamma-secretase inhibitors as stand-alone therapy for breast and brain tumors. "Our study suggests that Notch inhibition using these drugs would provide significant therapeutic benefits if combined with radiotherapy, and I hope that future research will study this combination therapy in this vulnerable patient population," Wang said. "More effective radiation may be attainable if we can stop Notch signaling in the tumor stem cells."

Source: Duke University Medical Center (news : web)