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Enhanced treatment of brain tumors

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Glioblastoma is regarded as the most malignant form of brain tumor. In many cases, neurosurgeons are not able to remove such tumors completely because of the risk of destroying too much brain tissue in the process. Moreover, it is often impossible to identify all the fine extensions by which the tumor spreads into surrounding healthy tissue. To at least slow down the growth of tumor cells that have remained in the head, almost all glioblastoma patients are treated by radiotherapy after surgery.

"Unfortunately, we can only delay cancerous growth in this way, but we cannot cure patients. The tumor cells, especially the cancer stem cells, are very resistant to radiation," says Prof. Dr. Dr. Peter Huber, who is head of the Clinical Cooperation Unit 'Radiation Oncology' at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ).

Studies conducted in recent years found that response to radiation therapy in various cancers is better when certain types of cellular growth factors are blocked at the same time. Glioblastoma cells often produce large amounts of a growth factor called TGF-β (transforming growth factor beta). High levels of TGF-β in these tumors are correlated with particularly aggressive growth and a poor prognosis. In addition, the factor seems to support the self-renewal capability of glioblastoma stem cells. "We therefore suspect that blocking TGF-β signaling pathways slows down the self-renewal of cancer stem cells and, thus, may improve radiation treatment outcomes," Peter Huber adds, explaining the background of the study now published.

In collaboration with colleagues from, among others, the Radiology Department of Heidelberg University Hospitals and a DKFZ department led by Prof. Dr. Ana Villalba, Huber's team investigated the effect of a combination of radiation treatment and a newly developed substance called LY2109761. This substance blocks the signals that are transmitted into cells by the TGF-β receptor. The investigators first studied glioblastoma cells in tissue samples taken during surgical removal of the tumors. Irradiation combined with adding the substance reduced the self-renewal capability of tumor stem cells and delayed their growth significantly better than radiation treatment alone.

The group transplanted human glioblastoma cells into the brains of mice and found that these animals, after receiving the combination therapy, survived longer than those animals treated by radiotherapy alone. Tissue studies showed that, under the combination therapy, tumors grew more slowly and less invasively and showed a lower density of newly formed blood vessels. "Paradoxically, radiation therapy can provoke aggressive growth behavior in surviving tumor cells. LY2109761 seems to prevent this fatal effect," says Huber, explaining how the drug seems to work.

Blocking of TGF-β signaling produced such promising results that researchers will now conduct a multicenter clinical trial to find out whether this mechanism may also slow down glioblastoma growth in patients more effectively than the current standard treatment. Led by Prof. Dr. Wolfgang Wick, who is head of a collaboration unit of DKFZ and the Neurology Department of Heidelberg University Hospitals, the combination therapy will be tested in Germany (Heidelberg), Spain, and the U.S.A.

More information: Mengxian Zhang, Susanne Kleber, Manuel Röhrich, Carmen Timke, Na Han, Jochen Tuettenberg, Ana Martin-Villalba, Jürgen Debus, Peter Peschke, Ute Wirkner, Michael Lahn and Peter E. Huber: Blockade of TGF-beta signaling by the TGFβR-I kinase

inhibitor LY2109761 enhances radiation response and prolongs survival in glioblastoma. Cancer Research 2011, DOI:10.1158/0008-5472.CAN-11-1212