

Brain Tumors: Tissue Stem Cell Turning into Tumor Stem Cell – Scientists discover key molecule for cancer initiation

Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now shown for the first time that malignant brain tumors arise directly from brain stem cells. In the adult brain, the Tlx protein is responsible for generating new neurons from tissue stem cells. Overproduction of Tlx in mice stimulates the development of malignant brain tumors from brain stem cells. Tlx also plays an important role in glioblastoma, the most malignant of human brain cancers. Therefore, the discovery of Tlx might provide the first target for a specific therapy against deadly glioblastoma.

The “cradle” of new neurons in the adult brain is well known. It is what is called the subventricular zone, a tissue structure lining the lateral ventricles. This is where neural or brain stem cells reside, which are responsible for generating new neurons if needed. For many years now, the subventricular zone has been suspected to be the origin of specific malignant brain tumors called gliomas, the most deadly type of which is glioblastoma.

Scientists from the divisions of Professor Dr. Günther Schütz and Professor Dr. Peter Lichter at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have recently shown in mouse brains that brain stem cells in the subventricular zone are characterized by a specific molecule: Protein Tlx, a transcription factor, which stimulates the activity of various genes. In the adult animal, Tlx is expressed exclusively in brain stem cells. When the scientists switched off Tlx, there were no more detectable stem cells in the brain and the formation of new neurons ceased. Functioning of the stem cells thus appears to depend on the presence of this protein.

In their recent study, the teams headed by Günther Schütz and Peter Lichter, jointly with Professor Dr. Guido Reifenberger of Düsseldorf University, have now tested the opposite case: What happens if the production of Tlx is increased? Using a molecular-biological trick, the investigators induced an overproduction of Tlx by the brain stem cells of mice. As a result, cell division activity in the subventricular zone increased, the cells left their habitual environment called stem cell niche, and started forming glioblastoma-like tissue lesions. In another experiment in which the researchers additionally switched off the p53 protein as an important cancer brake, invasively growing glioblastomas arose from the cancer precursors.

Moreover, the scientists discovered that stem cells with increased Tlx production stimulate the formation of new vessels. This enables the cells to migrate into distant brain regions and, thus, to generate the typical coral-like growth of glioblastoma.

“We recognize brain stem cells specifically by their Tlx production. If we boost it, the tissue stem cell turns into a cancer stem cell from which malignant glioblastomas arise. Therefore, we are now able, for the first time, to hold brain stem cells directly responsible for the formation of brain tumor stem cells,” Günther Schütz explains.

The researchers expect to be able to develop new therapies to treat glioblastoma on the basis of these results from fundamental cell biology research. Tlx seems to play its fatal role not only in mouse brains. Studying tumor tissue from glioblastoma patients, Lichter and Reifenberger discovered that the Tlx gene is often present in multiple copies and, thus, more Tlx protein is produced. “Apparently, human brain tumor stem cells also depend on Tlx.

Therefore, we can now try to develop therapies that are directed very specifically against Tlx producing cells," said Schütz describing the next steps. The mice whose brain stem cells overproduce Tlx are an ideal model system for such investigations.

Hai-Kun Liu, Ying Wang, Thorsten Belz, Dagmar Bock, Andrea Takacs, Bernhard Radlwimmer, Sebastian Barbus, Guido Reifenberger, Peter Lichter and Günther Schütz: The nuclear receptor tailless induces long term neural stem cell expansion and brain tumor initiation. *Genes & Development*, April 1, 2010

A picture for this press release is available on the Internet at:

http://www.dkfz.de/de/presse/pressemitteilungen/2010/images/DCX_308.jpg

Figure caption: Mice overexpressing Tlx develop glioma initiating lesions

Photography: Haikun Liu, German Cancer Research Center

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,000 staff members, including 850 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Württemberg (10%).

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