Cancer stem cells arise from tissue stem cells

The Tlx transcription factor induces the transformation of neural stem cells into new nerve cells in the adult brain. Scientists at the German Cancer Research Centre in Heidelberg showed that the overproduction of Tlx and the silencing of the p53 tumour suppressor gene in mice stimulates the development of malignant brain tumours (glioblastomas) from brain stem cells.

In contrast to common tumours such as lung carcinoma, mamma carcinoma or colorectal carcinoma, glioblastoma is a relatively rare tumour, affecting only around 3,000 people a year in Germany. However, it is the most common brain tumour and the most malignant of human brain cancers due to its rapid infiltrating growth. Glioblastomas develop predominantly in the cerebrum, in particular in what is known as the subventricular zone, a tissue layer touching one of the two brain chambers of the cerebrum. It is known that neural stem cells reside in the subventricular zone in the adult mammalian brain. These stem cells continually generate new neurons.

Neural stem cells require Tlx

Prof. Dr. Günther Schütz
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Scientists at the German Cancer Research Centre (DKFZ) in the departments of Professor Dr. Günther Schütz and Professor Dr. Peter Lichter have shown in mice that the brain stem cells of the subventricular zone are characterised by a specific protein known as Tlx. Tlx is encoded by the gene NR2E1, which is homologous to the "tailless" gene that was first discovered in Drosophila.

Prof. Dr. Peter Lichter
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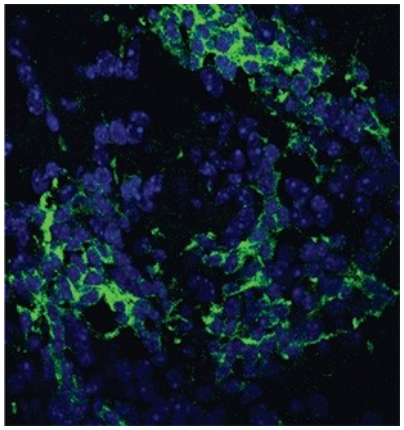
The gene product belongs to the "orphan nuclear receptors" protein family. The proteins are referred to as orphans because these DNA-binding receptors do not seem to require ligands to exert their proper function. No specific ligands have so far been identified.

Tlx is a transcription factor that controls the expression of genes that are necessary for differentiation. Switching off the Tlx gene in the brain of adult mice led to the complete loss of neurogenesis (i.e. the generation of new nerve cells) in the subventricular zone. It was no longer possible to detect 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.

Tlx overexpression induces the formation of brain tumours

Instead of switching off Tlx, the researchers tested the opposite case. They induced the brain stem cells to increase the production of Tlx. This led to an increase

of cell division activity in the subventricular zone. Moreover, the stem cells left their stem cell niche in the neural glial tissue and started forming glioblastoma-like tissue lesions. These findings were obtained by Schütz's and Lichter's teams in cooperation with the team of Professor Dr. Guido Reifenberger from the Institute of Neuropathology at the University of Düsseldorf.



Mice overexpressing Tlx develop glioma-initiating lesions

In another experiment, the researchers additionally switched off the tumour suppressor protein p53, a key regulator of cell growth, and 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 (angiogenesis) in the brain. This enabled the Tlx-positive glioblastoma cells to migrate into more distant brain areas and generate the typical coral-like growth of glioblastoma. This is typical for this type of tumour and makes effective therapy extraordinarily difficult, if not completely impossible.

In a press release published by the DFKZ (No. 13 of 1st April 2010), Schütz summarised the researchers' findings as follows: "We recognise brain stem cells specifically by their Tlx production. If we boost the Tlx production, 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 tumour cells."

These exciting findings do not seem to be restricted to mice. Lichter and Reifenberger discovered in the tumour tissue of glioblastoma patients that the Tlx gene is often present in multiple copies, thus leading to the production of more Tlx protein. Apparently, human brain tumour stem cells also depend on Tlx. This opens up the possibility of attempting to develop therapies that are very specifically directed against Tlx-producing cells. Mice whose brain stem cells overproduce Tlx are therefore an ideal model system for investigations into glioblastoma pathogenesis and for the development of effective therapies to combat this malignant brain tumour.

Glioblastoma

Glioblastoma is the most common and most aggressive type of primary brain tumour in the group of gliomas or astrocytomas. Glioblastomas are neuroepithelial tumours that develop from glial cells or astrozytes, which are the nurse and support cells of brain neurons.

These tumours are characterised by the expression of "glial fibrillary acidic protein" (GFAP), a specific cytoskeleton protein that enables the differentiation of glioblastomas from brain metastases of different origin in cases of doubt. Glioblastomas occur mainly in elderly adults (more frequently in men than in women). They are extremely rare in children. High doses of ionising irradiation have been shown to be a major risk factor; otherwise little is so far known about the causes of the formation of glioblastomas.

Due to its rapid, aggressive growth, disease symptoms develop relatively rapidly within a few weeks or months after diagnosis. Common symptoms include prevailing unusual headaches, often combined with paralysis and speech and vision disorders. Epileptic seizures and personality changes, apathy and slower movements are symptoms of a progressive brain tumour.

It is very difficult to treat glioblastoma. Although neurosurgical operations can remove the major tumour mass, surgery can nevertheless not permanently halt the progression of the disease. Complicating factors include the infiltration of healthy brain tissue by individual, widely spread tumour cells that cannot be fully destroyed using chemotherapy and irradiation. Standard glioblastoma therapy involves surgery followed by irradiation and chemotherapy in order to prolong the medium survival by a few months and also ease the symptoms. The five-year survival rate is below two per cent. Despite bad prognosis, there are nevertheless some patients that are in relatively good health and are able to live with glioblastoma for many years.

Publications:

Liu HK, Belz T, Bock D, Takacs A, Wu H, Lichter P, Chai M, Schütz G: The nuclear receptor tailless is required for neurogenesis in the adult subventricular zone. Genes & Development 22: 2473-2478 (2008).

Liu HK, Wang Y, Belz T, Bock D, Takacs A, Radlwimmer B, Barbus S, Reifenberger G, Lichter P, Schütz G: The nuclear receptor tailless induces long term neural stem cell expansion and brain tumor initiation. Genes & Development 24: 647-652 (2010).

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