Cancer cells with a long breath: seeking the origin of brain tumors in children

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Medulloblastoma is one of the most common and most malignant brain tumours among children and teenagers. These tumours grow very rapidly, and fifty percent of patients in the long term die from the condition. The details of the processes that lead to the growth of these tumours have remained unknown until now.

In two studies, working together with international scientific teams, LMU medical scientist Dr. Ulrich Schüller has now successfully revealed certain molecular mechanisms that lead to the development of these cerebellar tumours. As reported in the current issue of the journal *Cancer Cell,* the researchers triggered genetic changes in cell populations in the brains of mice in order to provoke the growth of tumours. It turned out that medulloblastomas arose from only one type of cell – granule cells – and only if these were already fully committed. "Medulloblastomas are presently treated with nonspecific methods," states Schüller. "Our results could contribute to the development of targeted therapies, and thus improve the treatment of cerebellar tumours in children."

When children develop cancer, about every fifth tumour is a brain tumour – and every fifth of those in turn is a medulloblastoma. This common tumour occurs most of all in children under ten years of age, but also occurs in adults, albeit very infrequently. Up to now, medulloblastomas have only been treatable with the standard tools of cancer medicine: operation, radiotherapy and chemotherapy. Surgical interventions to treat this condition, like all operations on the brain, are particularly delicate, since it is difficult to remove the tumour completely without affecting healthy tissue. Because these cerebellar tumours scatter easily throughout the brain and even in the medullary canal, many cases result in metastases, that is the growth of secondary tumours, and not infrequently to a relapse of the original tumour – often even after successful conclusion of the treatment.

That is why patients and doctors are hoping for more targeted therapies that promise better therapeutic outcomes. "But for that to be possible, we first need to understand the principles of how the tumours develop," says Schüller. "If we know how a tumour arises at the molecular level, we can also develop specific therapies that actually treat the cause of that particular condition." Since it was still unknown from what type of cell and at what stage of development medulloblastomas arise, the researchers induced specific genetic changes in various cell populations in the brains of mice. This "conditional knock-out" method provoked changes in the so-called sonic hedgehog signalling pathway. Various processes in the development of nerve cells are controlled by this molecular signalling cascade. "Normally, the signalling pathway ensures a balance of growth and maturation of cells," says Schüller. "But if disrupted, it can lead to uncontrolled growth of cells – and thus the onset of cancer".

In another step, the research team investigated the effects of mutations on nerve cells in various stages of development. Multipotent progenitor cells have the ability – almost like stem cells – to develop into many different types of cell, while "unipotent" progenitor cells can only develop into one specific type of cell. "All of our studies have shown that medulloblastomas can only develop from granule cells and their progenitors," Schüller tells us. "Other cells on the other hand, such as the large Purkinje cells of the cerebellum, do not become tumourigenic. They don't seem bothered by these mutations at all." And there is yet another distinctive result that the researchers achieved: the genetic changes only triggered one specific type of tumour: the medulloblastoma. Other brain tumours such as astrocytomas or oligodendrogliomas did not occur, even though, normally, the genetically attacked multipotent progenitors could have just as easily developed into astrocytes or oligodendrocytes.

It was especially surprising that even mutations in

very early, immature cells triggered corresponding changes that only became tumourigenic if and when the cells had developed the characteristics of granule cells. The researchers were also surprised to find that the medulloblastomas appeared completely identical both morphologically and molecularly, no matter what stage of development they were triggered at. The researchers identified yet another factor in the development of medulloblastomas: the protein Olig2 has so far only been linked to the formation of glial cells in the brain, which primarily provide support for neurons. "But we also found Olig2 in progenitors of the granule cells of the cerebellum and in tumour cells," reports neuropathologist Schüller. "That means this protein also influences the formation and multiplication of cancer cells – which makes it clear once again just how closely normal and malignant development processes resemble one another. We hope our results will contribute to a targeted therapy for medulloblastomas. That will require further research, however, which we already have in the planning."

One of the funders of the studies was the German Cancer Aid, with whose assistance Schüller established one of two Max-Eder Young Investigator Groups at LMU.

Source: Ludwig-Maximilians-Universität München