Gene defect influences tumor development in childhood brain tumors

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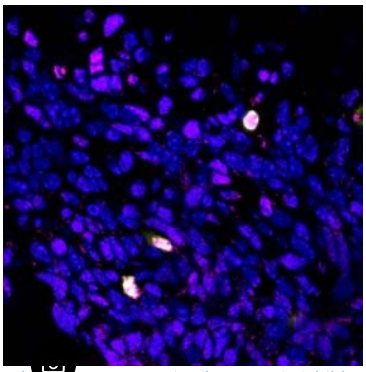
Medulloblastoma are the most common malignant brain tumors affecting children. The greatest danger is that the cancer cells can quickly spread to the surrounding tissues. Two genetic defects play a key role in the onset of these tumors, as scientists at the Hopp Children's Cancer Center Heidelberg (KiTZ), the German Cancer Research Center (DKFZ) and the National Institute of Neuroscience in Tokyo have discovered. The aim is for the findings to help scientists develop personalized treatment strategies for young patients.



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The picture shows the production of the protein BCOR (pink) in the brain cells of mice in which the gene Ptch1 is mutated. A particularly high amount of BCOR is produced in cells that are actively dividing (yellow).
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The "Hopp Children's Cancer Center Heidelberg" (KiTZ) is a joint institution of the German Cancer Research Center (DKFZ), Heidelberg University Hospital (UKHD) and Heidelberg University.

Medulloblastoma, malignant tumors in the cerebellum, account for only around one percent of all brain tumors in adults, but are the most common form of malignant brain tumor in children. The medulloblastoma spread from the cerebellum to the surrounding tissue and can also spread to other parts of the central nervous system via the cerebrospinal fluid. Because these tumors grow rapidly, physicians do not have much time to find a suitable treatment.

At the Hopp Children's Cancer Center Heidelberg (KiTZ), scientists are conducting intensive research into the onset of medulloblastoma in order to develop new therapy options. "The onset of malignant medulloblastoma cells has genetic causes and follows several stages," explains Lena Kutscher, a Junior Group Leader at the KiTZ and the DKFZ. "First, genetic mutations cause excessive proliferation of certain precursor nerve cells, and growths develop. If more mutations occur, they can turn into malignant tumor cells that spread into the surrounding tissue."

Together with colleagues from the National Institute of Neuroscience in Tokyo and from St. Jude Children's Hospital in the USA, the research team came across two key genetic drivers for the onset of medulloblastoma in the Sonic Hedgehog medulloblastoma subgroup (SHH). The BCOR gene is regarded as a tumor suppressor gene, and its protein product normally suppresses the uncontrolled division of cells with genetic defects, thereby preventing the onset of tumors. Earlier studies have shown that in eight percent of young SHH patients, BCOR is mutated or has been partially deleted from the genome. Boys are particularly affected by this mutation.

In combination with another gene defect, the loss of the Ptch1 receptor gene, the defective BCOR protein then becomes a key trigger for the onset of brain tumors in mice: mice that were unable to produce both proteins properly developed tumors in all cases. The researchers suspect that the cause is misregulation of the growth hormone Igf2. They found that, both in mice and in some human SHH tumors with defective BCOR protein, Igf2, a gene known to be associated with cancer, was particularly active.

"Our study uncovered a key signaling pathway for the onset of cancer – one that is caused by BCOR mutations in SHH medulloblastoma," says Daisuke Kawauchi, the last author of the paper, who was previously a group leader at the KiTZ and the DKFZ and is now a research group leader at the National Institute of Neuroscience in Tokyo. "These findings open up new opportunities to develop personalized treatment strategies for patients with and without these genetic mutations."

Original Publication:
L. M. Kutscher et al. Functional loss of a noncanonical BCOR– PRC1.1 complex accelerates SHH-driven medulloblastoma formation. In: Genes and Development (Online Publication 20. August 2020). DOI: 10.1101/gad.337584.120

An image for this press release is available for download at:
https://www.kitz-heidelberg.de/fileadmin/media/kitz/news/2020/Kutscher_preneoplastic_cells.png (http://https//www.kitz-heidelberg.de/fileadmin/media/kitz/news/2020/Kutscher_preneoplastic_cells.png)

Caption:
The picture shows the production of the protein BCOR (pink) in the brain cells of mice in which the gene

Ptch1 is mutated. A particularly high amount of BCOR is produced in cells that are actively dividing (yellow).

Note on use of images related to press releases

The Hopp Children's Cancer Center Heidelberg (KiTZ)

The „Hopp Children's Cancer Center Heidelberg" (KiTZ) is a joint institution of the German Cancer Research Center (DKFZ), Heidelberg University Hospital and Heidelberg University. As the National Center for Tumor Diseases (NCT), which focusses on adult oncology, the KiTZ is based on the US model of so-called "Comprehensive Cancer Centers" (CCC). As a therapy and research center for oncologic and hematologic diseases in children and adolescents, the KiTZ is committed to scientifically exploring the biology of childhood cancer and to closely linking promising research approaches with patient care– from diagnosis to treatment and aftercare. Children suffering from cancer, especially those with no established therapy options, are given an individual therapy plan in the KiTZ, which is created by interdisciplinary expert groups in so-called tumor boards. Many young patients can participate in clinical trials which ensures access to new therapy options. Thus, the KiTZ is a pioneering institution for transferring research knowledge from the laboratory to the clinic.
While the KiTZ focuses on pediatric oncology, the focus of the National Center for Tumor Diseases (NCT), founded in 2004, is adult oncology. Both facilities in Heidelberg are based on the US model of so-called "Comprehensive Cancer Centers" (CCC).

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ)

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institution in Germany. At DKFZ, more than 1,300 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful.
DKFZ's Cancer Information Service (KID) provides individual answers to all questions about cancer for patients, the general public, and health care professionals.
Jointly with partners from Heidelberg University Hospital, DKFZ runs the National Center for Tumor Diseases (NCT) located in Heidelberg and Dresden, and, also in Heidelberg, the Hopp Children's Cancer Center (KiTZ). In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center at the NCT and DKTK sites is an important contribution to the endeavor of translating promising approaches from cancer research into the clinic in order to improve the chances of cancer patients.
DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Heidelberg University Hospital and Medical Faculty

Internationally recognized patient care, research, and teaching
Heidelberg University Hospital is one of the largest and most prestigious medical centers in Germany. The Medical Faculty of Heidelberg University belongs to the internationally most renowned biomedical research institutions in Europe. Both institutions have the common goal of developing new therapies and implementing them rapidly for patients. With about 13,000 employees, training and qualification is an important issue. Every year, around 65,000 patients are treated on an inpatient basis, 56,000 cases on a day patient basis and more than 1,000,000 cases on an outpatient basis in more than 50 clinics and departments with almost 2,000 beds. Jointly with the German Cancer Research Center (DKFZ) and German Cancer Aid, Heidelberg University Hospital has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. Currently, about 3,700 future physicians are studying in Heidelberg; the reform Heidelberg Curriculum Medicinale (HeiCuMed) is one of the top medical training programs in Germany. www.klinikum.uni-heidelberg.de

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