GERMAN CANCER RESEARCH CENTER
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Defective intercellular connections cause hydrocephalus

A defective gene leads to changes in the cellular layer between cerebrospinal fluid and brain nervous tissue, thus causing a buildup of fluid in the brain. This link, which scientists from the German Cancer Research Center in Heidelberg have now discovered, is the first known mechanism underlying genetic hydrocephalus.

About one in 2,000 babies are born with hydrocephalus, a condition in which cerebrospinal fluid (CSF) cannot flow towards the spinal column and builds up instead in the cavities (ventricles) of the brain. This causes the head to swell like a balloon and puts pressure on the brain. Various neurological symptoms can occur as a result including headache, vomiting, impaired vision, loss of coordination, seizures and cognitive difficulties. There are various causes of hydrocephalus. In some cases the condition is caused by a genetic abnormality.

The research team led by Andreas Fischer from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg already discovered in 2013 that a defect in a gene called Mpdz causes hydrocephalus in mice. In the same year, scientists from Saudi Arabia identified its human counterpart as a genetic cause of hydrocephalus in humans.

Now Fischer and his team have been able to uncover the mechanism underlying this genetic defect. The scientists observed in newborn mice with defective Mpdz that the ependyma, a cellular layer separating the brain nervous tissue from the CSF, is severely damaged. In order to maintain this vital dividing line, cells of a different type, called astroglia, fill in and ensure that the dividing tissue layer remains stable. However, this has a high price: Scar tissue develops in the ependyma leading to blockage of the so-called aqueduct, a channel connecting two ventricles of the brain, thus blocking the flow of cerebrospinal fluid.

“Evidence suggests that loss of the Mpdz gene reduces the stability of so-called tight junctions between adjacent ependymal cells, explains Anja Feldner, who is the first author of the study. The gene product of Mpdz controls molecules that play a crucial role for the stability of tight junctions. In fact, experiments in the Petri dish have shown that these junctions are impaired between ependymal cells with defective Mpdz. “This means we have uncovered a crucial mechanism that underlies the onset of genetic hydrocephalus,” Fischer commented.

Anja Feldner, M. Gordian Adam, Fabian Tetzlaff, Iris Moll, Dorde Komljenovic, Felix Sahm, Tobias Bäuerle, Hiroshi Ishikawa, Horst Schroten, Thomas Korff, Ilse Hofmann, Hartwig Wolburg, Andreas von Deimling and Andreas Fischer: Loss of Mpdz impairs ependymal cell integrity leading to perinatal-onset hydrocephalus in mice. EMBO Molecular Medicine, 2017, DOI: 10.15252/emmm.201606430

An image for this press release is available at:
http://www.dkfz.de/de/presse/pressemitteilungen/2017/bilder/Feldner-Mpdz.jpg
Caption: Scanning electron microscopy image of impaired ependymal cell layer within a brain ventricle following loss of Mpdz gene.

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 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. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (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 is an important contribution to improving 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.

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