Single gene defect causes brain tumor

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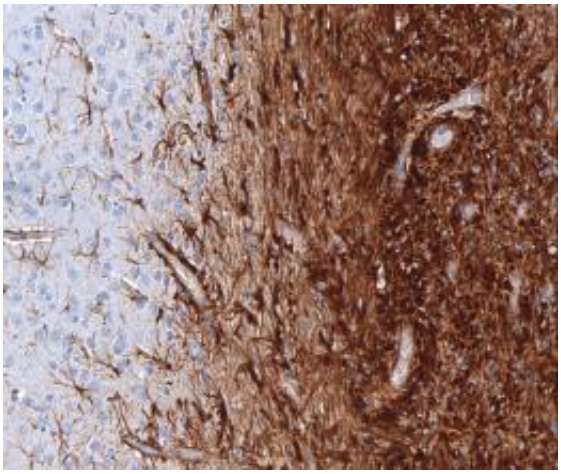

Tissue section of a mouse brain with a pilocytic astrocytoma. The brown staining indicates astrocytes. Source: Jan Gronych, Deutsches Krebsforschungszentrum

Pilocytic astrocytoma, the most common brain tumor in children, is usually slow-growing and benign. However, surgeons often cannot completely remove the diffusely growing tumor. This means that patients need further treatment in order to destroy remaining tumor tissue. Chemotherapy or radiation therapy can lead to severe side-effects and have only little effect on these slowly growing tumors. Affected children therefore urgently need new, targeted therapies.

A typical genetic defect in these brain tumors is already known: "From our own research we know that there is a defect in the BRAF gene in the great majority of pilocytic astrocytomas," says Professor Dr. Peter Lichter of the German Cancer Research Center. This defect causes a

cellular signaling pathway, which in healthy cells is active only in case of acute need, to be permanently activated.

Jan Gronych from Lichter's department has now studied, jointly with colleagues of Heidelberg University Hospitals, the actual relevance of the BRAF defect for carcinogenesis. To this end, the investigators packed a defective BRAF gene into a virus and thus introduced it into neuronal precursor cells of mice. In 91 percent of animals thus treated, tumors developed around the injection site. These tumors corresponded to pilocytic astrocytoma in terms of their biology, growth characteristics and tissue structure.

Cells of these tumors all showed the typical symptom of a defective BRAF gene: a permanently activated MAP kinase enzyme. "This proves that a single gene defect is really sufficient to cause pilocytic astrocytoma," said Lichter, summarizing the results.

A permanently active MAP kinase constantly transmits growth signals in cancer cells, while it is also their Achilles' heel: In recent years, a number of drugs have been developed which inhibit the enzyme activity of kinases very specifically and, thus, can impede cancer growth. The Heidelberg researchers have shown that brain cells which are driven to permanent abnormal cell division by a defective BRAF gene slowed down growth after treatment with kinase inhibitor sorafenib.

"Up to now, we did not have a suitable model system for testing newly developed drugs against pilocytic astrocytoma," says Peter Lichter. "The BRAF mice open up the possibility to test new kinase inhibitors or other drugs specifically for their effectiveness against pilocytic astrocytoma."

More information: Jan Gronych, Andrey Korshunov, Josephine Bageritz, Till Milde, Manfred Jugold, Dolores Hambardzumyan, Marc Remke, Christian Hartmann, Hendrik Witt, David T.W. Jones, Olaf

Witt, Sabine Heiland, Martin Bendszus, Eric C. Holland, Stefan Pfister and Peter Lichter: An activated mutant BRAF kinase domain is sufficient to induce pilocytic astrocytoma in mice. *The Journal of Clinical Investigations*, 2011, DOI: 10.1172/JCI44656
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