# Defective signaling pathway leads to vascular malformations in the brain

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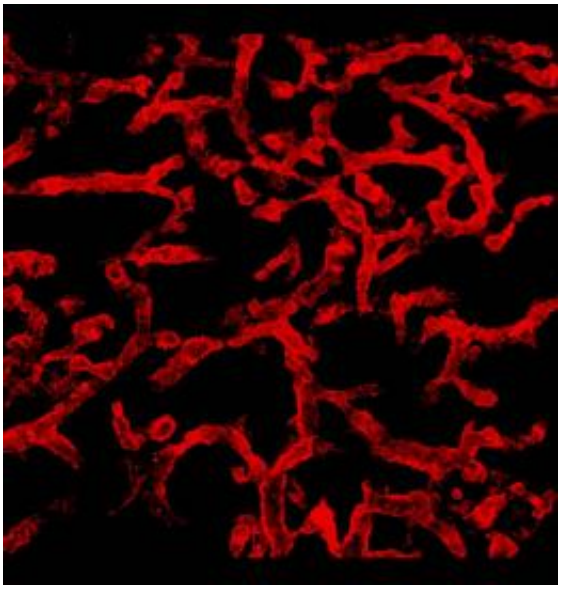

Human blood vessel in an experimental mouse model: Turning off the CCM1 gene leads to the typical, disorganized appearance.

A disrupted signaling pathway in endothelial cells, which line the insides of blood vessels, leads to cavernomas, vascular malformations in the brain which are often dangerous. This has been published by a research team of the Medical Faculty Mannheim of Heidelberg University and the German Cancer Research Center. The investigators have found the cause of one of the most common human malformations and point out that cavernomas might be treated by drugs which inhibit vascular growth.

Benign vascular malformations known as cavernomas can occur in many tissues of the body. These abnormalities are characterized by enlarged, instable and unstructured blood vessels. Cavernomas of medical relevance are primarily those of the brain, which develop approximately in one out of two hundred people. In the brain, such growths often remain unnoticed and are typically found by chance in MRI scans. If they grow larger, they often cause unspecific symptoms such as headaches or dizziness. There is a growing danger of cerebral hemorrhage from these vascular growths, which can lead to seizures, neurological failures and even stroke. Therefore, cavernomas causing symptoms are surgically removed from the brain, if possible.

In the joint department of Vascular Biology and Tumor Metastasis of Mannheim Medical Faculty of Heidelberg University and DKFZ, researchers are investigating how blood vessels and lymphatic vessels are newly formed in tumor diseases. "Our latest findings suggest that - like in tumors - excessive and uncontrolled vascular growth leads to the development of cavernomas," said Dr. Andreas Fischer, who leads the current study.

It was already known that the disease develops when the CCM1 gene is inactive in endothelial cells, which line all blood vessels. However, it was still unclear why this leads to the characteristic malformations. The research team has now identified, jointly with colleagues from Essen and Greifswald, the central signaling pathways in endothelial cells which are affected if the CCM1 gene is missing. For best possible simulation of the disease occurring in humans, the investigators transplanted human endothelial cells with disabled CCM1 gene into mice. The transplanted cells subsequently grew into the typical vascular malformations. Thus, it was possible to perform experiments with human vascular malformations in the mouse model. Therefore, the results obtained can well be transferred to the human disease situation so that it was even possible, for example, to perform drug tests.

In their first approach, the researchers tested the anticancer drug sorafenib, which inhibits the formation of new blood vessels (angiogenesis). In the transplanted mice, the substance led to massive reduction of the vascular growth. "We will now investigate whether we can treat brain cavernomas without surgery using a drug from cancer medicine," said Dr. Andreas Fischer describing the project's future goals.

**More information:** Wüstehube J, Bartol A, Liebler SS, Brütsch R, Zhu Y, Felbor U, Sure U, Augustin HG, Fischer A: Cerebral cavernous malformation protein CCM1 inhibits sprouting angiogenesis by activating DELTA-NOTCH signaling. Proc. Natl. Acad. Sci. USA; early online edition, June 21, 2010 DOI: 10.1073/pnas.1000132107

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