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Molecular trigger for Cerebral Cavernous Malformation identified

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Researchers in Italy, Germany and the United States have identified a regulatory protein crucial for the development of Cerebral Cavernous Malformation – a severe and incurable disease mainly affecting the brain microvasculature. The results, which are published in *EMBO Molecular Medicine*, show that the KLF4 protein plays a central role in the development of CCM lesions.

Cerebral Cavernous Malformation (CCM) is caused by mutations in the CCM1, CCM2 or CCM3 genes, and is characterized by vascular lesions that can lead to cerebral haemorrhage. Previous research has shown that ablation of CCM1 in mice leads to CCM pathology via a mechanism called Endothelial-to-mesenchymal transition (EndMT). While considerable effort has gone into establishing that EndMT occurs and plays a role in a variety of pathologic conditions, its molecular triggers have not been well defined.

The scientists found that KLF4 – a zinc-finger transcription factor of the Kruppel-Like Factor family – is strongly upregulated in the lesions of CCM1 knockout mice.

"Our study demonstrates that the genetic inactivation of KLF4 blocks the development and progression of CCM lesions and prevents mouse mortality due to brain haemorrhage," says EMBO Member Elisabetta Dejana of the Italian FIRC Institute of Molecular Oncology and the University of Milan, the corresponding author of the study. KLF4 functions as one of the reprogramming "Yamanaka factors" in

pluripotent stem cell induction cocktails.

The CCM pathway is required in endothelial cells for normal cardiovascular development and to prevent postnatal vascular malformations. The malformations are usually located in the white matter (cortex) of the brain. CCM are present in up to 0.5% of the general population, and they account for a large proportion (8-15%) of all brain and spinal vascular malformations.

Presently, there are no pharmacological treatments to prevent development or reduce the size of existing CCMs. The study identifies novel potential pharmacological targets to prevent the progression of this disease.

The study was conducted by researchers of the Italian FIRC Institute of Molecular Oncology and the University of Milan, in collaboration with the Max Planck Institute for Molecular Medicine in Munster, Germany, University Hospitals Case Medical Center in Cleveland and University of Virginia, United States, and with the support of Telethon and the Italian Association for Cancer Research (AIRC).

More information: KLF4 is a key determinant in the development and progression of Cerebral Cavernous Malformations, embomolmed.embopress.org/cgi/d … 15252/emmm.201505433

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