Medical Xpress

Researchers pinpoint key gene mutations, new mechanisms that cause brain bleeding and dementia

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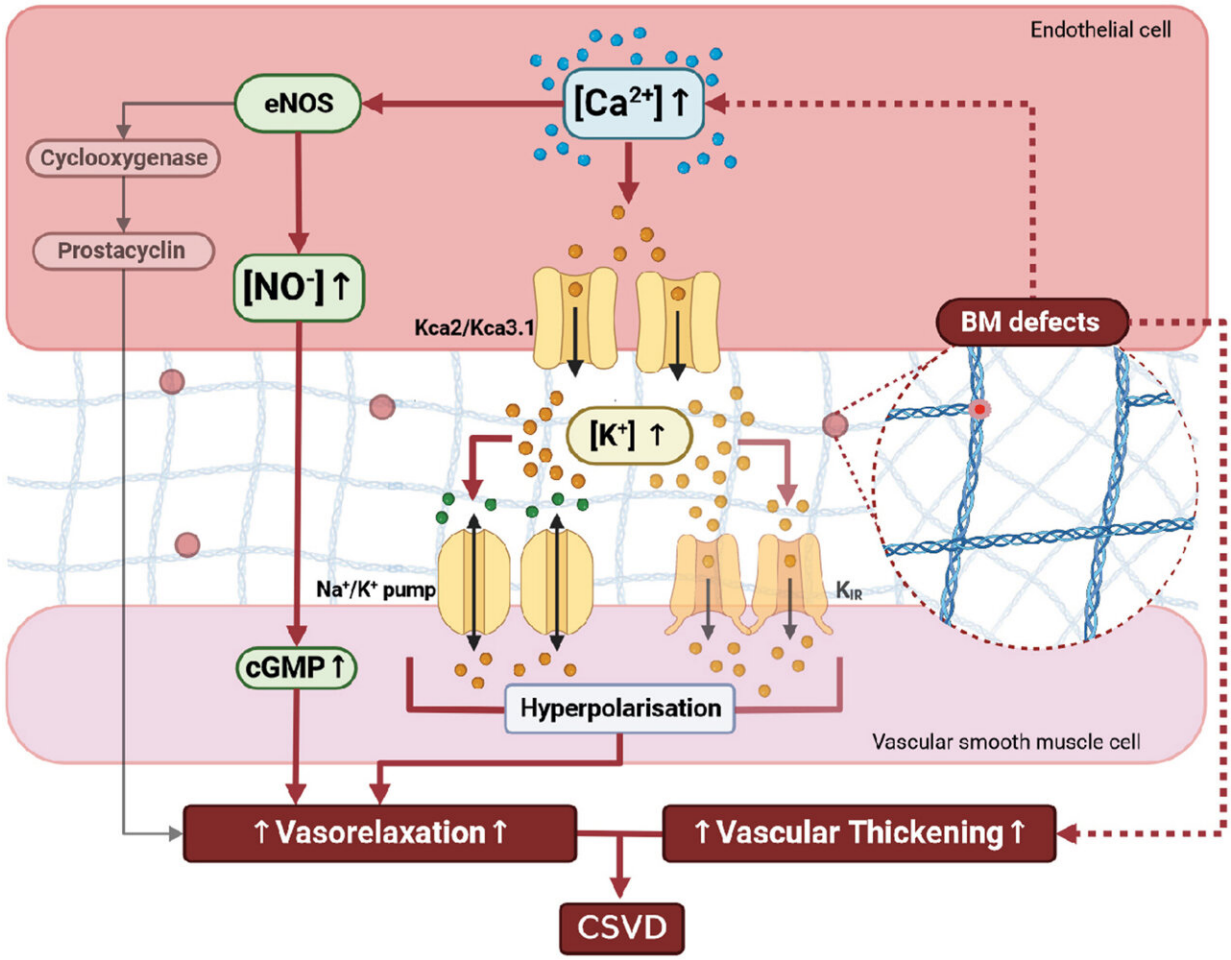

Mechanisms of COL4A1/COL4A2 variants in CSVD. Credit: *eBioMedicine* (2024). DOI: 10.1016/j.ebiom.2024.105315

Scientists have revealed new insights into the mechanisms behind cerebral small vessel disease, a condition that affects the smaller blood vessels in the brain and causes approximately half of all dementia cases.

The latest study, which is led by the University of Glasgow and published in *eBioMedicine*, has unlocked insights into the mechanisms behind some of the causes of cerebral small vessel disease by studying COL4A1/COL4A2, the genes responsible for the production of the collagen IV protein, which is crucial for vascular health.

Cerebral small vessel disease (CSVD) is a common, chronic vascular disease, with age one of the main risk factors. CSVD is an umbrella term for a variety of conditions resulting from damage to small blood vessels in the brain. This damage can cause internal bleeding, including strokes, and also lead to dementia. There are currently no specific treatments for CSVD.

In this study, through work in mice, the research team were able to show that mutations of the COL4A1/COL4A2 genes caused lower collagen IV levels in the non-cellular part of the walls of blood vessels. This in turn negatively impacted the regulation of how blood vessels widen, which is important for controlling blood flow.

The team were then able to show that this collagen reduction was a key driving factor in the onset of CSVD, and that these changes in blood vessel function were present at a very early stage of the disease, before significant disease symptoms were visible.

Following on from the investigation in mice, analysis of human brain samples confirmed that lower collagen IV levels in blood vessels also occurred in people with CSVD. Researchers suggest these findings highlight a potential new therapeutic target to combat strokes and dementias.

Professor Tom Van Agtmael, professor of matrix biology and disease at the University of Glasgow's School of Cardiovascular & Metabolic Health, and lead author of the study, said, "There was a real surprise that lower collagen IV levels cause CSVD and that this protein not only provides structural support to blood vessels, but also influences how vessels regulate their diameter.

"As these changes in collagen IV levels and blood vessel function occur well before any visible signs of the disease, including brain bleeding, this indicates that a window of opportunity exists during which the development of CSVD may be modified.

"This is only the beginning but, increasing our knowledge of how CSVD and brain bleeding develops will form a platform for the development of urgently needed treatments."

More information: Sarah McNeilly et al, Collagen IV deficiency causes hypertrophic remodeling and endothelium-dependent hyperpolarization in small vessel disease with intracerebral hemorrhage, *eBioMedicine* (2024). DOI: 10.1016/j.ebiom.2024.105315

Provided by University of Glasgow