Abstract

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Reducing Timp3 or vitronectin ameliorates disease manifestations in CADASIL mice.

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Abstract

OBJECTIVE: CADASIL is a genetic paradigm of cerebral small vessel disease caused by NOTCH3 mutations that stereotypically lead to the extracellular deposition of NOTCH3 ectodomain (Notch3^{ECD}) on the vessels. TIMP3 and vitronectin are two extracellular matrix proteins that abnormally accumulate in Notch3^{ECD} -containing deposits on brain vessels of mice and patients with CADASIL. Herein, we investigated whether increased levels of TIMP3 and vitronectin are responsible for aspects of CADASIL disease phenotypes.

METHODS: Timp3 and vitronectin expression were genetically reduced in TgNotch3^{R169C} mice, a well-established preclinical model of CADASIL. A mouse overexpressing human TIMP3 (TgBAC-TIMP3) was developed. Disease-related phenotypes, including cerebral blood flow deficits, white matter lesions and Notch3^{ECD} deposition, were evaluated between 6 and 20 months of age.

RESULTS: Cerebral blood flow responses to neural activity (functional hyperemia), topical application of vasodilators, and decreases in blood pressure (CBF autoregulation) were similarly reduced in TgNotch3^{R169C} and TgBAC-TIMP3 mice, and myogenic responses of brain arteries were likewise attenuated. These defects were rescued in TgNotch3^{R169C} mice by haploinsufficiency of Timp3, although the number of white matter lesions was unaffected. In

contrast, haploinsufficiency or loss of vitronectin in TgNotch3^{R169C} mice ameliorated white matter lesions, although cerebral blood flow responses were unchanged. Amelioration of cerebrovascular reactivity or white matter lesions in these mice was not associated with reduced Notch3^{ECD} deposition in brain vessels.

INTERPRETATION: Elevated levels of TIMP3 and vitronectin, acting downstream of Notch3^{ECD} deposition, play a role in CADASIL, producing divergent influences on early cerebral blood flow deficits and later white matter lesions.

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