Reducing Timp3 or vitronectin ameliorates disease manifestations in CADASIL mice.


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 (Notch3ECD) on the vessels. TIMP3 and vitronectin are two extracellular matrix proteins that abnormally accumulate in Notch3ECD-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 TgNotch3R169C 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 Notch3ECD 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 TgNotch3R169C and TgBAC-TIMP3 mice, and myogenic responses of brain arteries were likewise attenuated. These defects were rescued in TgNotch3R169C mice by haploinsufficiency of Timp3, although the number of white matter lesions was unaffected. In
contrast, haploinsufficiency or loss of vitronectin in TgNotch3R169C 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 Notch3ECD deposition in brain vessels.

**INTERPRETATION:** Elevated levels of TIMP3 and vitronectin, acting downstream of Notch3ECD deposition, play a role in CADASIL, producing divergent influences on early cerebral blood flow deficits and later white matter lesions. This article is protected by copyright. All rights reserved.


PMID: 26648042 [PubMed - as supplied by publisher]