A preclinical mouse model of CADASIL to dissect the early-stage disease mechanisms

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CADASIL is a genetic paradigm of cerebral small vessel disease caused by NOTCH3 mutations. The vast majority of mutations lead to the gain or loss of a cysteine residue in the extracellular domain of NOTCH3 (Notch3ECD) that stereotypically lead to the extracellular deposition of Notch3ECD on the vessels. In all mouse models expressing a mutant NOTCH3 with a cysteine mutation that have been analyzed to date, vascular Notch3ECD deposition has emerged as the earliest pathological feature. An important, as yet unresolved, question is whether and how Notch3ECD deposition causes the disease. TgNotch3R169C mice, which overexpress a mutated NOTCH3 receptor under the control of the endogenous cis-regulatory elements, exhibit Notch3ECD deposition in the cerebral vessel as early as 1 month of age. Mutant mice further develop a profound impairment of cerebrovascular reactivity from 6 months of age and progressive cerebral white matter lesions from 12 months of age. We recently reported that TIMP3 and vitronectin, which are two extracellular matrix proteins, abnormally accumulate in Notch3ECD-containing deposits on brain vessels of patients with CADASIL and TgNotch3R169C mice. Using genetic-interaction approaches in TgNotch3R169C mice, our results provide evidence that excess levels of TIMP3 and vitronectin contribute to compromised cerebrovascular reactivity and white matter lesions respectively, and that Notch3ECD deposition is at the top of the pathogenic cascade. In summary, our study identifies a new early-stage disease mechanism in CADASIL—accumulation of TIMP3 and vitronectin—that provides a first missing link between Notch3ECD deposition and disease manifestations.