New transgenic rat model may enable better understanding of amyloid buildup in cerebral blood vessels

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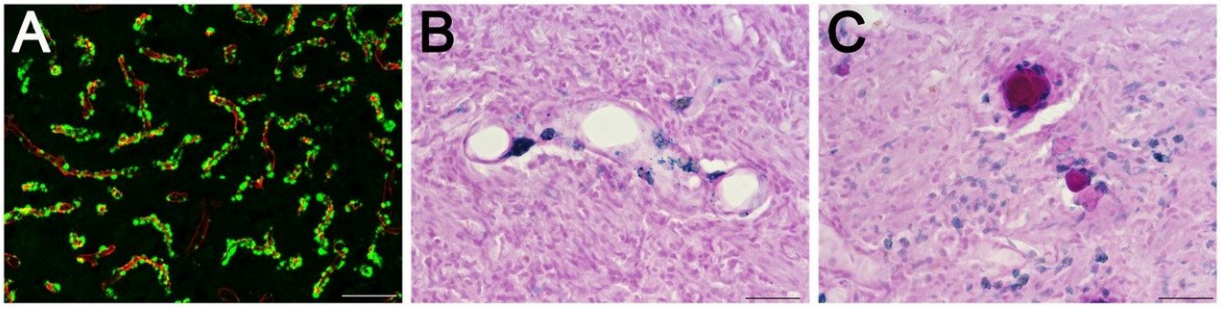

rTg-DI transgenic rats develop severe capillary/microvascular fibrillar amyloid accumulation accompanied by numerous microbleeds and occluded microvessels that were observed in areas of microbleeds. In (A), brain tissue from a twelve-month-old rTg-DI rat was stained for fibrillar amyloid using thioflavin-S (green) and immunolabeled for collagen type IV to identify cerebral microvessels (red); extensive microvascular amyloid is seen. Staining with hemosiderin (blue) and counterstaining with pararosanline (pink) was used to identify microhemorrhages (B) and occluded microvessels (C) in the thalamic region. Scale bars = 50 μm. Credit: The *American Journal of Pathology*

In a report in The *American Journal of Pathology* investigators describe the generation of a successful novel transgenic rat model that accumulates amyloid specifically in brain blood vessels and strongly mimics many of the associated detrimental changes that are observed in

humans—a condition known as cerebral amyloid angiopathy (CAA), which is also commonly observed in Alzheimer disease.

Accumulation of β-amyloid in brain tissue is considered a hallmark pathological finding of Alzheimer disease. Less well known is that β-amyloid deposits are also found in small blood vessels of the brain, the condition known as CAA, which is also associated with impaired cognition and dementia. The lack of reliable preclinical animal models has limited our understanding of CAA.

Transgenic rats mimic many of the characteristics of human pathology, including amyloid deposits in small blood vessels in the brain, capillary structural changes, neuroinflammation, and microhemorrhages. "The transgenic rats, known as rTg-DI, develop progressive accumulation of brain blood vessel amyloid-associated inflammation, small bleeds, and occluded vessels in the brain and exhibit cognitive impairments," explained William E. Van Nostrand, Ph.D., of the George and Anne Ryan Institute for Neuroscience, Department of Biomedical and Pharmaceutical Sciences, of the University of Rhode Island, Kingston, RI, USA. "Although rats are still far from a perfect model to investigate CAA, the new model described here more completely mimics the pathological changes observed in the human brain and offers a better opportunity to test potential therapeutic interventions and develop useful biomarkers for this condition."

Transgenic rats have had foreign DNA inserted into their genome. In this case, human amyloid precursor protein DNA was introduced into the rats' DNA, rendering their offspring transgenic (having both human and rat DNA). The transferred DNA contained mutations that originated from patients with CAA, so that the rats would produce low levels of human mutant amyloid β peptides in their brains.

The investigators showed that human amyloid-β precursor protein was

evident in neurons throughout the cortex, hippocampus, and thalamus of the rats. As the rats aged from three to 12 months, there was a progressive accumulation of the mutant amyloid-β peptides in the rat brains. At 12 months, fibrillar amyloid covered nearly 45 percent of capillaries in the thalamus, 70 percent of capillaries in the hippocampus, and 30 percent of capillaries in the cortex. Most of the peptides were of the shorter Aβ40 form, the type of amyloid that is found in human CAA.

The investigators observed that early-onset and progressive accumulation of cerebral microvascular fibrillar amyloid was accompanied by early-onset and sustained behavioral deficits in the transgenic rats. They performed more slowly on a behavioral test that measured the time taken to explore novel objects in an open field. "That the early-onset development of microvascular CAA and associated neuroinflammation coincided with early-onset and sustained cognitive deficits offers the promise of a unique model for the future elucidation as to how CAA can promote vascular-mediated cognitive impairment and dementia (VCID)," commented Dr. Van Nostrand.

Structural changes were seen in cerebral capillaries as the amyloid accumulated, including vessel fragmentation and increased tortuosity (twisting). There was also evidence of neuroinflammation, such as an elevated number of activated microglia around the blood vessels compared to wild-type rats.

The rTg-DI transgenic rats also developed numerous microbleeds and occluded microvessels in areas of microbleeds. Microbleeds in the hippocampus and thalamus were detected at six months, and this increased as the rTg-rats aged to 12 months. "This was an especially important finding since we know that the presence of cerebral microbleeds is a prominent clinical feature of CAA in humans," noted Dr. Van Nostrand.

There were some differences noted between human and rat CAA. For instance, in humans, microbleeds are more common in cortical regions, not in deep brain regions like the thalamus. Despite these differences between rTg-DI rats and humans, Dr. Van Nostrand believes "this unique model provides new opportunities to investigate the pathogenic development of CAA and its relation to VCID. rTg-DI rats will provide an improved platform for the development of biomarkers and preclinical testing of therapeutic interventions for this common small vessel disease."

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