Researchers uncover why a gene mutant causes young children to have strokes

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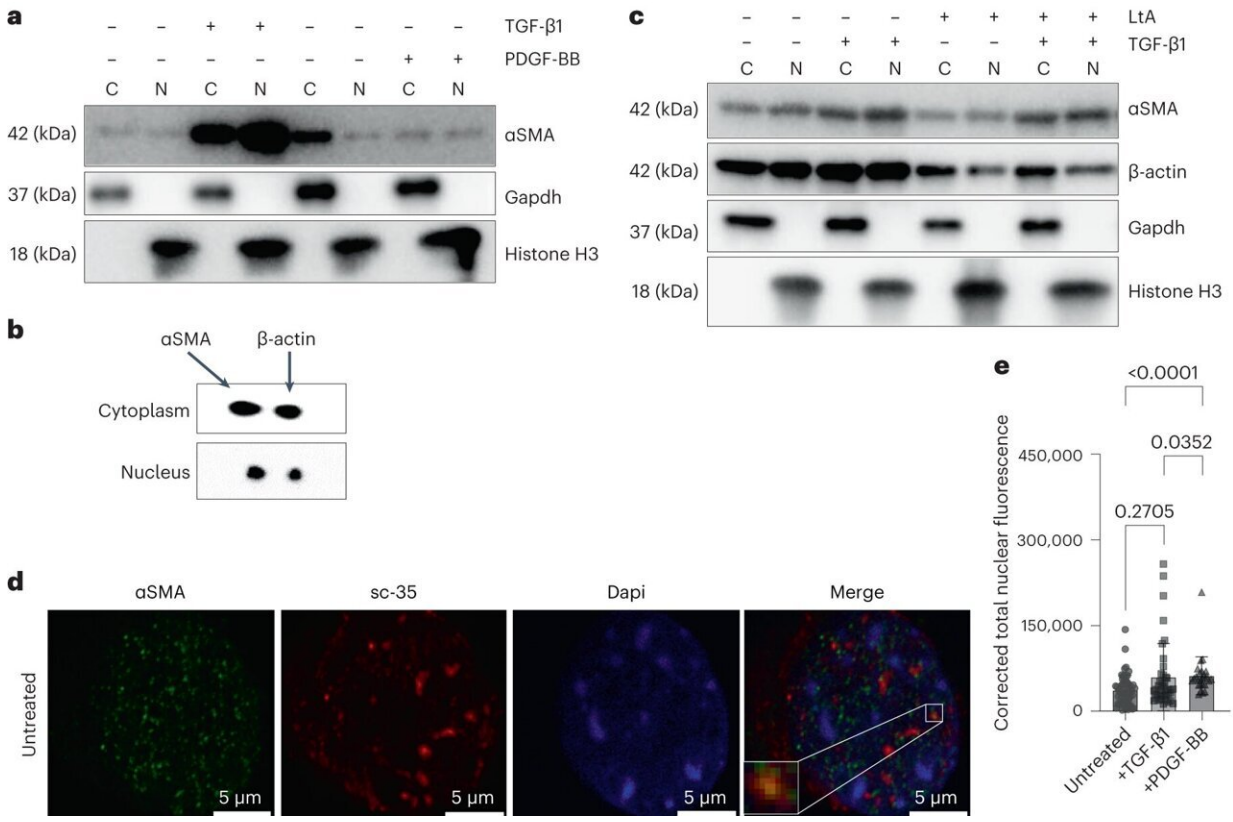

α-smooth muscle actin localizes to the nucleus concurrently with smooth muscle cell differentiation. a, Immunoblot of fractionated protein lysates from SMCs explanted from WT mice shows αSMA localizes to the nucleus in SMCs, and both cytosolic and nuclear αSMA levels increase with TGF-β1 stimulation, while PDGF-BB stimulation does not affect nuclear accumulation of αSMA. b, Two-dimensional gel electrophoresis shows both αSMA and β-actin in the nucleus of SMCs. c, LtA treatment does not alter the ratio of nuclear to cytosolic αSMA on immunoblot. d–f, Immunostaining of isolated nuclei (d) shows increased nuclear

αSMA after treatment with TGF-β1 or PDGF-BB, quantified in e, and confirms colocalization of αSMA (green) with the nuclear speckle marker sc-35 (red), quantified in f. For e, n = 59 untreated nuclei, 40 + TGF-β1 nuclei and 26 + PDGF-BB nuclei across four independent experiments. For f, n = 28 untreated nuclei, 19 + TGF-β1 nuclei, and 20 + PDGF-BB nuclei across three independent experiments. For e and f, significance was assessed by the Kruskal–Wallis test followed by Dunn's multiple-comparisons test. g, Quantitative RT–PCR shows exponential increases of SMC contractile gene expression during the time course of NEPC-to-SMC differentiation. h, Immunoblot of fractionated protein lysates taken at time points during the differentiation of NEPCs (day 0) to SMCs (day 12) shows early and dramatic accumulation of nuclear αSMA. β-actin is decreased in the nucleus of NEPCs. Time points match between g and h. Data shown are representative of at least three independent experiments. Quantifications of immunoblots can be found in Extended Data Fig. 1. Negative controls for immunostaining can be found in Supplementary Fig. 1. All data are presented as the mean ± s.d. Credit: *Nature Cardiovascular Research* (2023). DOI: 10.1038/s44161-023-00337-4

A discovery of a mutation in the gene ACTA2 has given researchers, led by Dianna Milewicz, MD, Ph.D., with UTHealth Houston, insight into understanding the cause of a rare and progressive problem with arteries in the brain and a cause of strokes in young children, called moyamoya disease.

The findings were published today in *Nature Cardiovascular Research.*

Moyamoya disease is a condition where the arteries going through the neck and into the brain become blocked right when the arteries enter the brain. Moyamoya disease can lead to strokes and seizures. Children only a few months old can suffer a stroke due to the disease. Current treatments are limited to medications to reduce the risk of stroke and surgery to open or bypass blocked arteries.

"This disease is one of the major causes of stroke in children and nobody knows why this happens or why these arteries get clogged," said Milewicz, senior author of the study and professor and director of the Division of Medical Genetics at McGovern Medical School at UTHealth Houston. "These children don't smoke; they don't have hypertension and they don't have any of the other usual risk factors that cause strokes in adults."

Researchers identified that a change in the gene called ACTA2 caused children to have moyamoya disease and strokes starting shortly after birth, a condition called Smooth Muscle Dysfunction Syndrome, and have been working to figure out how and why this ACTA2 change causes moyamoya disease and strokes. Previous research led by Milewicz identified that ACTA2 mutations are the cause of Smooth Muscle Dysfunction Syndrome. In addition to moyamoya disease, this condition causes dysfunction of smooth muscle cells throughout the body.

ACTA2 is found in the smooth muscle cells, which line the arteries and allow them to contract to control blood pressure and flow. Using model systems, including cells from patients with the ACTA2 variant that causes moyamoya disease, Milewicz and her team found that a mutation in ACTA2 causes the cells in the walls of the arteries in the brain to not differentiate properly, an essential component of vascular development.

"We found a new job that the ACTA2 protein is supposed to do that the mutant version cannot: to help make differentiated smooth muscle cells that stay in the blood vessel and contract to regulate blood pressure," said Callie Kwartler, Ph.D., first author of the study and assistant professor in the Division of Medical Genetics at McGovern Medical School.

The result is that the cells with the ACTA2 variant continue to grow out of control and move into the inside of the artery, which may be the cause

of blockages in the arteries.

"This is the first step into really understanding the cause of moyamoya disease," said Milewicz, the President George Bush Chair in Cardiovascular Medicine with McGovern Medical School. "This is a disorder that starts out in childhood, and children with Smooth Muscle Dysfunction Syndrome die from strokes. We are working to use the information to prevent strokes in these children."

Researchers will continue to focus on exploiting the mechanism of disease that they identified to find new treatment options for children with moyamoya disease.

More information: Callie S. Kwartler et al, Nuclear smooth muscle α-actin participates in vascular smooth muscle cell differentiation, *Nature Cardiovascular Research* (2023). DOI: 10.1038/s44161-023-00337-4

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