Surprising discovery links Piezo1 and cholesterol during brain development

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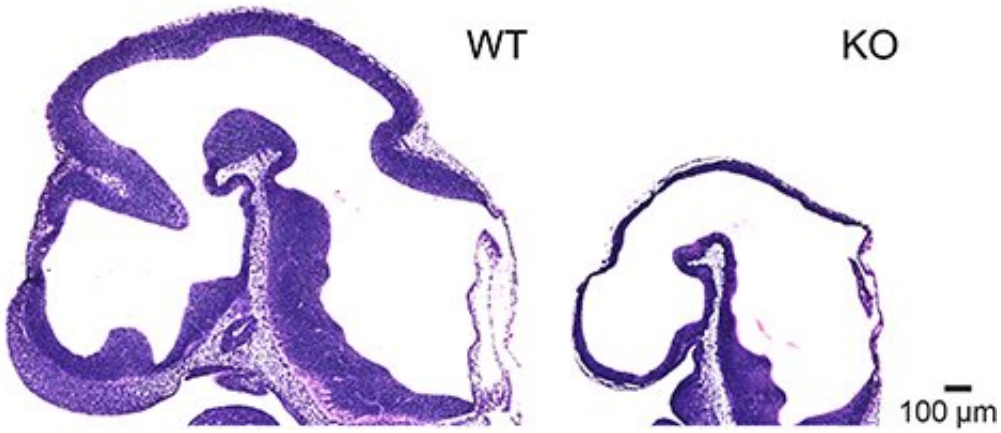

Histological analysis reveals abnormalities in the brains of mice lacking Piezo1 (Piezo1 KO, right) compared to wildtype (WT, left) mice. Credit: UCI School of Medicine

A new University of California, Irvine-led study reveals how mechanical forces and tissue mechanics influence the morphology of the developing brain, and establishes a direct link in neural stem cells between Piezo1, a mechanically-activated ion channel, and intracellular cholesterol levels during neural development.

The study, titled "Piezo1 regulates cholesterol biosynthesis to influence neural stem cell fate during brain development," was published today in the *Journal of General Physiology* . Study findings demonstrate a role for Piezo1 in the neurodevelopmental process that modulates the quantity,

quality, and organization of cells by influencing cellular cholesterol metabolism.

"Our surprising discovery linking Piezo1 and cholesterol also motivates investigations for Piezo1 in neurodegenerative diseases linked to cholesterol homeostasis, such as Alzheimer's Disease," said Medha Pathak, Ph.D., an assistant professor in the Department of Physiology & Biophysics at UCI School of Medicine. "By controlling Piezo1 activity through therapeutics we may be able to develop novel treatments for some of these diseases."

Neural development is a multi-step process that involves the orchestration of many complex events to generate the brain and spinal cord. As the brain develops, cells multiply and organize into structures and connect with other cells. These processes produce mechanical forces that further shape brain patterning, but how cells detect these mechanical signals is not fully understood.

"We previously found that Piezo1 channels are activated in response to both externally applied and cell-generated mechanical forces in human fetal brain-derived neural stem/progenitor cells, and we now show in our current study that Piezo1 is important for proper brain development," said Jamison Nourse, Ph.D., assistant project scientist in the Department of Physiology & Biophysics and first author on the study. "Through our research, we discovered a novel link between Piezo1 and cholesterol biosynthesis, which opens up new lines of investigation into how mechanical forces influence lipid metabolism in the brain."

Prior research has established the role the Piezo family of mechanically-activated ion channels plays in mechanotransduction in many physiological systems, including vascular development, cardiovascular homeostasis, lymphatic development, red blood cell volume regulation, the baroreceptor response in neurons, cartilage mechanics, bone

formation, macrophage polarization responses, keratinocyte migration in wound healing, and neural stem cell fate. In 2021, Dr. Ardem Patapoutian of The Scripps Research Institute, San Diego, was awarded a Nobel Prize in Physiology or Medicine for the groundbreaking discovery of the Piezo channels.

"Improper brain development can cause life-long malformations and functional defects," said Pathak. "And, while we still do not understand the reason behind many brain developmental defects, our work provides new approaches for understanding how brain defects may arise."

Pathak and her research team are continuing to explore Piezo1 and its effect on cholesterol metabolism in early human brain development and in adult-onset neurodegenerative diseases.

More information: Jamison L. Nourse et al, Piezo1 regulates cholesterol biosynthesis to influence neural stem cell fate during brain development, *Journal of General Physiology* (2022). DOI: 10.1085/jgp.202213084

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