Study finds astrocytic pH regulator can repair blood-brain barrier, reverse brain damage caused by ischemic stroke

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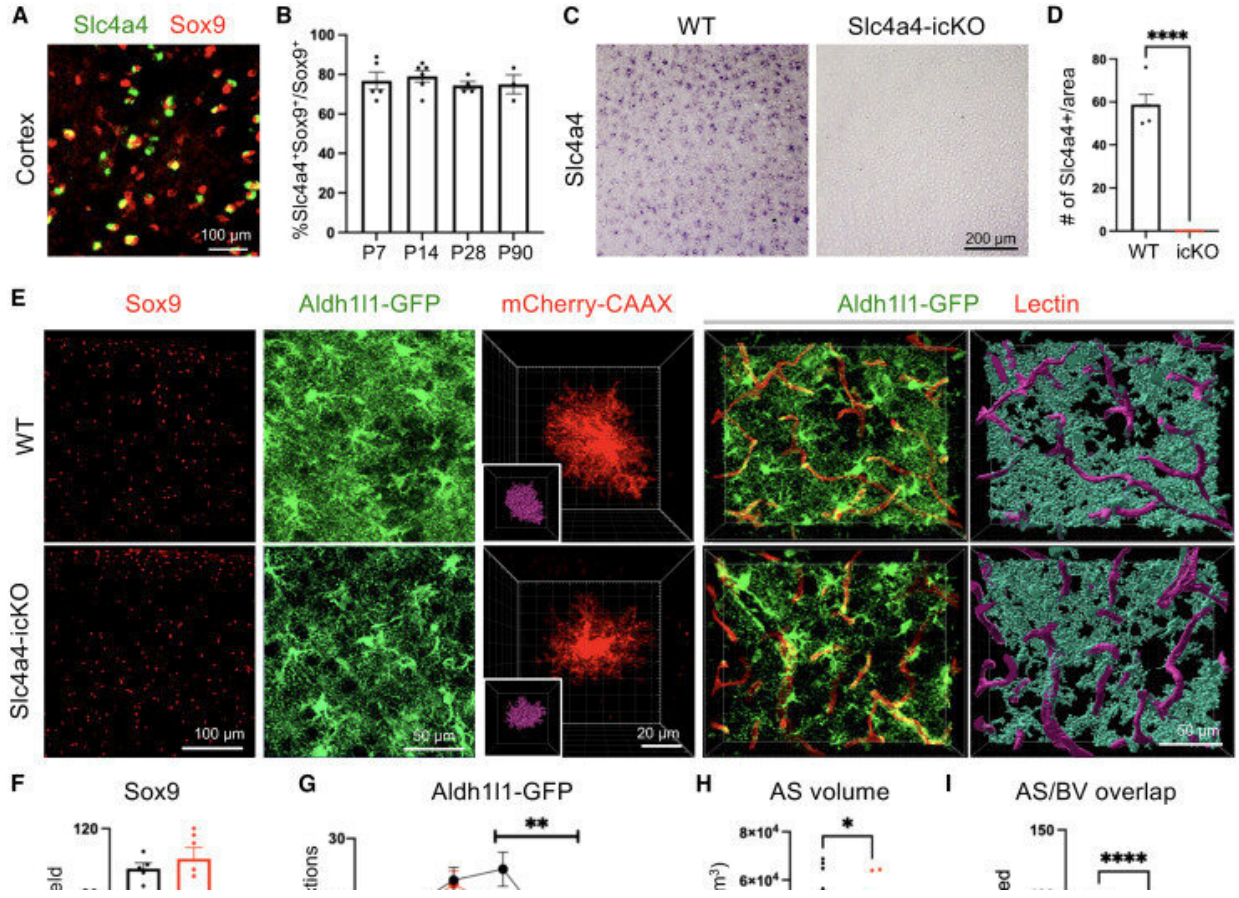

Slc4a4 is required for morphological complexity and proper Ca^{2+} propagation in the adult brain. Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114193

Ischemic stroke is a leading cause of death and disability, affecting about 15 million worldwide each year. Among the various factors contributing to the pathogenesis of this condition is the loss of the blood-brain barrier, a highly selective protective cellular barrier that prevents harmful chemicals from entering the brain through the blood.

Understanding the mechanisms that regulate the integrity of the blood-brain barrier, developing strategies to repair it, and reversing brain damage will have far-reaching benefits for patients suffering from stroke and related neurological conditions.

A recent study from the laboratory of Dr. Hyun Kyoung Lee, associate professor at Baylor College of Medicine and an investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital, has found that an ion transporter protein that regulates the pH of specific brain cells can repair the blood-brain barrier and restore normal brain function after ischemic stroke.

The study, published in Cell Reports, is the first to reveal novel and specific therapeutic targets for ischemic stroke and related brain conditions for which no targeted treatments exist currently.

The blood-brain barrier and pH regulation are disrupted in stroke and other neurological conditions

"Disruption of blood-brain barrier integrity is a pathophysiological hallmark of stroke and several devastating neurological disorders," Dr. Lee, a Cynthia and Anthony G. Petrello Endowed Scholar in Neurological Research, said.

"A damaged blood-brain barrier often leads to severe consequences such as brain edema, neuronal damage, and eventually, motor and cognitive

deficits. Very little was known about how stroke damages the blood-brain barrier prior to this study."

While endothelial cells form the core of the blood-brain barrier, emerging evidence suggests astrocytes, which are the most abundant and diverse type of support cells in the central nervous system, play a critical role in maintaining the integrity of this structure.

In addition to this barrier, a strict balance of pH (a measure of acidity or alkalinity of a solution) within the brain cells and their surrounding environment is crucial for optimal brain function. Dysregulation of pH homeostasis in the brain is often implicated in a range of neurological conditions.

Ischemic stroke injury is associated with a drastic reduction in pH. However, until this study, the precise reason for this alteration and the role of astrocytes in this process was not known.

Astrocytic Slc4a4 plays a critical role in the maintenance of the blood-brain barrier

Previous studies have demonstrated that a sodium-carbonate cotransporter 1 (Slc4a4), which is enriched in the astrocytes, is responsible for shuttling acid-base ions across the cell membrane in a bidirectional manner to regulate both intra- and extracellular pH in response to internal and external stimuli. Moreover, patients with Slc4a4 variants have been associated with many brain disorders, including ischemic stroke.

This is the first study to investigate whether and how Slc4a4 governs astrocyte-endothelial cell interaction in blood-brain barrier maintenance and repair after stroke.

To test the biological role of Slc4a4, the Duncan NRI team generated a conditional mouse model of Slc4a4 using which they could specifically delete the expression of this gene in the brain astrocytes during development and in adult mice.

Using this mouse model, they found that deleting Slc4a4 from astrocytes altered their structure and function.

"We found that the brain vasculature was altered in the absence of astrocytic Slc4a4—there was >40% increase in the diameter of the blood vessels in the brain, a three-fold increase in the number of small molecules that were able to infiltrate the brain along with the loss of junctional markers—which together provided compelling evidence that the blood-brain barrier was disrupted in the absence of astrocytic Slc4a4 in these mice," Dr. Qi Ye, lead author and postdoctoral fellow in the Lee lab said.

Slc4a4 is critical for remodeling the blood-brain barrier after ischemic stroke

To test if astrocytic Slc4a4 was important for remodeling the blood-brain barrier after ischemic stroke, they used a cortical photothrombotic stroke model in Slc4a4 animal models. This stroke injury model in animals closely mimics the size, location, as well as reactive gliosis, a scar-like inflammatory response to ischemic stroke injury in human brains.

In this model using multi-omics analyses, they found that loss of astrocytic Slc4a4 increased the secretion of a CCL2, a pro-inflammatory molecule, which activated the CCR2 receptor present on the nearby endothelial cells to increase permeability, damaging the blood-brain barrier and increasing leakage between the two cell types. Finally, they

found this breakdown of the blood-brain barrier was mediated by increased levels of specific metabolites (arginine and nitrous oxide) caused by changes in astrocytic pH levels.

"By revealing the precise mechanism and key players involved in the breakdown of the blood-brain barrier after stroke, this study has opened potential new avenues to treat ischemic stroke and several associated brain pathologies," Dr. Lee said.

"It is promising that key players identified in this pathway—the Slc4a4 transporter protein, the CCL2-CCR2 axis as well the metabolites—are 'druggable' and can be developed into potential therapeutic targets."

More information: Qi Ye et al, Astrocytic Slc4a4 regulates blood-brain barrier integrity in healthy and stroke brains via a CCL2-CCR2 pathway and NO dysregulation, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114193

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