Elusive protein acts as manager, addressing pH imbalance by transporting acid in and out of cells

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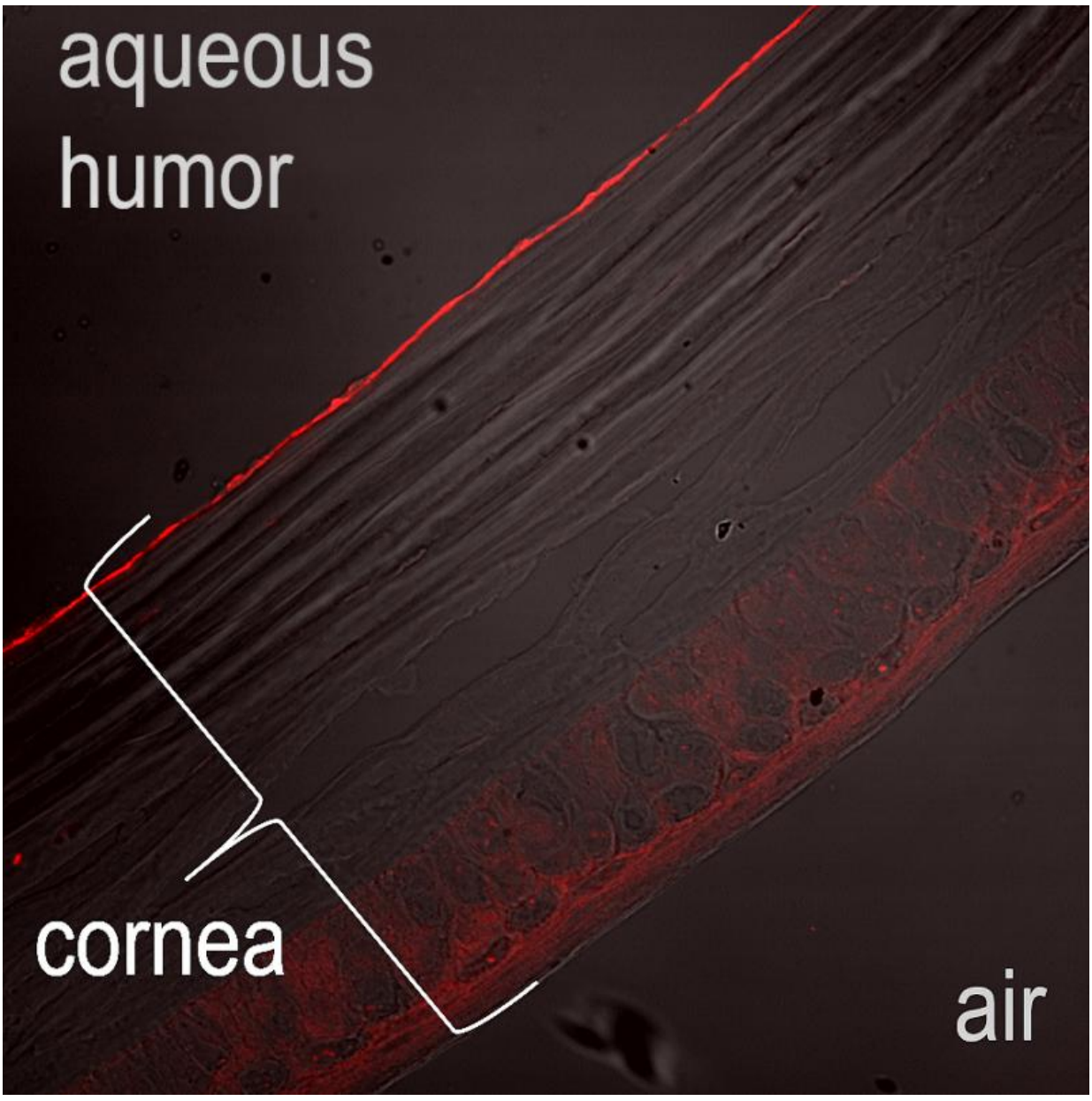

The membrane transport protein (red) is expressed at high density in the endothelial cells of the cornea. Credit: Mark Parker

For more than a decade, researchers have tried to figure out the role of a membrane transport protein involved with a rare, hereditary condition that results in vision loss. Numerous papers have been published, but no single strong hypothesis has emerged.

Now, a team of University at Buffalo researchers led by Mark Parker, PhD, assistant professor in the Department of Physiology and Biophysics in the Jacobs School of Medicine and Biomedical Sciences, has proposed a single, unifying model for the SLC4A11 protein. The research is relevant to the rare disorder Congenital Hereditary Endothelial Dystrophy (CHED), in which SLC4A11 mutation results in vision loss by affecting cells in the cornea as well as hearing loss.

The UB researchers describe SLC4A11 as a highly-selective acid-conducting protein that regulates the pH level of cells.

The research was published online Sept. 28 in the *American Journal of Physiology—Cell Physiology*. Evan J. Myers, a doctoral candidate in the UB Department of Physiology and Biophysics, is first author.

The paper is accompanied by an editorial by Keith Nehrke of the University of Rochester School of Medicine and Dentistry, who cited the UB researchers' "robust data and detailed analysis," noting that the work on the protein "suggests that it utilizes a novel conductance pathway to support corneal physiology and health."

SLC4A11 is a clinically important protein found in endothelial cells in the cornea, the inner ear and the kidneys. The protein is in the SLC4 family of transport proteins that are of interest in part because they're linked to disorders ranging from blindness and epilepsy to hypertension and cancer; they also are implicated in a rare disease in which an individual's blood becomes acidified.

Varying hypotheses

Parker began working on SLC4A11 in 2001 when he was involved in the original cloning of the gene as a postdoctoral scholar at the University of Bristol in England.

"The function of the protein eluded us at the time so I moved onto working with other related proteins," he said.

In the intervening decade numerous papers were published hypothesizing that SLC4A11's function was to transport various molecules, including boron, sodium, ammonium and water.

But few of those data have been repeated, and much of the data was controversial, Parker said. So having established a new laboratory at UB, Parker and Myers began to look at the protein again in 2014.

"In order to develop a therapy to restore vision and hearing in individuals with SLC4A11 mutations, we need to understand how SLC4A11 normally promotes eye and ear health," said Parker. "Perhaps the most crucial question is, 'what does this protein transport?' "

"Our research found that the Slc4A11 protein transports the equivalent of pure acid, only the second such protein identified in mammals," said Parker.

His focus on the SLC4 family of membrane proteins has been concerned with how cells attempt to maintain the proper pH level, essential for healthy functioning.

"Blood plasma needs to stay at a pH of 7.4, and most cells maintain an internal pH close to 7.2," said Parker "Those are the magic numbers." Even slight deviations can result in devastating physiological effects, he added.

Healthy corneal cells

"Corneal cells are no exception. It's very important to maintain that pH balance in the cornea," Parker explained. "That means the tissues stay properly hydrated and transparent, which allows light to pass to the lens without distortion."

The role of SLC4A11 had always been a mystery, he explained, because there seemed to be other acid- and alkali-transporter proteins in corneal cells that also are capable of balancing pH.

"We find SLC4A11 to be a very flexible protein that can either move acid into or out of a cell depending on prevailing conditions," he said.

If the actions of the acid- and alkali-transporting proteins in the cornea are not perfectly balanced, he continued, then the pH will be disturbed and these cells will not function effectively.

"We propose that SLC4A11 acts as sort of an overseeing manager, able to rapidly redress any pH imbalance, ensuring that the cells function properly," said Parker.

The research was supported by startup funds from UB, by a Carl W. Gottschalk Research Scholar Grant from the American Society of

Nephrology, and by the National Institutes of Health.

In addition to Parker and Myers, co-authors are Aniko Marshall, a research technician with the UB Department of Physiology and Biophysics and Michael L. Jennings with the University of Arkansas for Medical Sciences. Parker also has appointments with the UB Department of Ophthalmology and the State University of New York Eye Institutes.

Earlier this year, Parker and his colleagues at UB and other institutions published a paper in the *Journal of Physiology* on another protein in the same family. That study, performed in collaboration with a team of physicians in Beijing, described a novel case of a rare disease called proximal renal tubular acidosis (pRTA). This disease is caused by mutations in SLC4A4 (a close relative of SLC4A11), a membrane transport protein that neutralizes blood acid by supplying the plasma with sodium bicarbonate (baking soda). Individuals with pRTA have acidic blood and numerous eye defects such as cataracts and glaucoma.

Parker's lab showed that the SLC4A4 protein in that case was not able to do its job due to being misfolded, which in turn, causes it to be withheld from the cell membrane. An image of a kidney cell expressing the displaced mutant protein was shown on the journal cover.

Provided by University at Buffalo