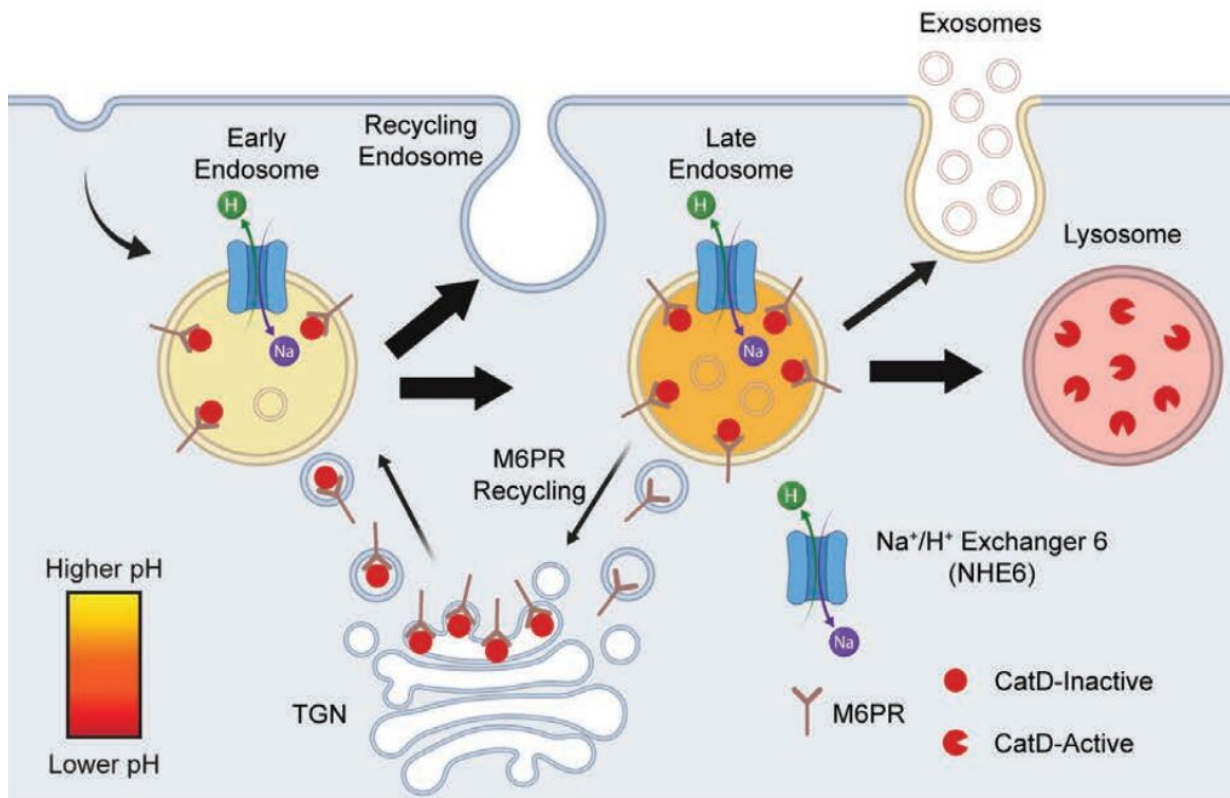


Novel cellular mechanism sheds light on causes of childhood developmental disorder

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Credit: Brown University

A new study provides insights into the cellular mechanisms involved in Christianson syndrome, an X-linked genetic disorder characterized by delayed development, cognitive disability and epileptic seizures as well as difficulties with speech, balance and mobility.

This research, published online in the *Journal of Neuroscience* on Wednesday, Sept. 15, demonstrates how a cellular process known as endosome trafficking, when defective, may lead to neurodegeneration, said study author Dr. Eric Morrow, a physician-scientist and director of Brown University's Center for Translational Neuroscience. There is evidence of defective endosomal trafficking in a number of neurodegenerative disorders, including Alzheimer's disease, he said.

The more scientists understand the biology of Christianson syndrome and other disorders, the more power they have to develop new treatments, Morrow said.

"The discovery of this novel cellular mechanism in Christianson syndrome is an important turn in the path towards progress," he said. "It shifts the focus to include what's happening with other disorders that we now know may be related, like the lysosomal disorders of childhood as well as Alzheimer's disease, and to consider what lessons from more common neurological disorders might be adapted to developing treatments for CS—and vice versa."

CS is caused by mutations in the gene SLC9A6, which provides instructions for making a protein called sodium/hydrogen exchanger 6 (NHE6). The NHE6 protein is found in the membrane of compartments within cells known as endosomes, which shuttle proteins and other cellular materials around cells, helping them decide whether to recycle these materials or dispose of them in another cell compartment called the lysosome.

"Endosomes are like little transit vehicles, trafficking proteins and other cargo around the cell," Morrow said.

Endosomes may fuse with a cell's plasma membrane and expel their contents, a process known as exocytosis, or they may degrade and

dispose of cargo. When preparing to dispose of their contents, the endosome matures and ultimately fuses with the lysosome, a membrane-bound organelle with an acidic internal compartment that's involved in cellular waste management.

People with CS don't have the NHE6 protein, Morrow said. Previous research published by his team showed that this lack of NHE6 protein means that the endosome compartment can become more acidic. A major scientific question, in Morrow's laboratory and others, has been what happens to the cell when the cargo is over-acidified.

For the new study, the researchers used a microscopic marker to highlight and monitor the activity in and around the brain cells of laboratory mice with a genetic mutation mimicking CS.

"We were able to visualize the fusion of lysosomes and endosomes as well as the release of the endosome's cargo outside of the neuron," said Matthew Pescosolido, a first author on the paper who earned his neuroscience Ph.D. from Brown working in Morrow's lab and is now a post-doctoral fellow in biology at Brandeis University. "This expulsion of endosomes was notably increased in the CS cells."

There are three main components to the team's discovery.

The first is that lysosomes in people with Christianson syndrome are functionally impaired and don't work as well as lysosomes in normal neurons. This is important, Morrow said, because it makes it likely that CS is related to other lysosomal disorders, a group of other childhood neurologic diseases with defective lysosome function that include conditions such as Tay Sachs disease, Batten disease and Nieman-Pick disease, among others. One promising area of research for these disorders is the use of gene therapy, Morrow said, and that could extend to CS as well.

"Knowing what's happening in the cell in people with CS gives us an idea of what gene replacement therapy would need to counteract in order to be beneficial," Morrow said, adding that lysosome dysfunction may also be factor in neurodegenerative diseases like Alzheimer's.

The second key observation described in the paper is that the maturation of the endosome, which is carrying a cargo of waste, is also impaired—the endosome has trouble fusing to the lysosome.

Thirdly, the researchers discovered that these malfunctioning, late-stage endosomes were fusing with the cell's plasma membrane and dumping their contents there. Using advanced imaging tools such as time-lapse microscopy and total internal reflection fluorescence microscopy, they could see the cellular activity of endosomes being ejected from the neurons.

"This discovery gave us a more complete picture of how the endocytic pathway was responding to the loss of NHE6," Pescosolido said. "This likely reflects, in part, a compensatory mechanism to get rid of waste outside the cell rather than trafficking it to an impaired lysosome, which wouldn't be able to degrade this waste. In the future, it will be interesting to see how these endosomal contents influence other nearby cells."

These findings significantly expand the focus of CS research, Morrow said: "It's not that over-acidification isn't an important part of the story. But this paper shows it isn't the whole story."

When Pescosolido was working under Morrow's mentorship at Brown, he had the opportunity to meet families affected by CS, which he said was a great privilege.

"Our goal has always been to provide these families, as well as clinicians and researchers, with high-quality information about the causes and

course of CS," Pescosolido said. "It has been so rewarding to collect the stories of these families and to be able to provide them with a more comprehensive understanding of the causes of CS."

Morrow's research team is currently expanding its studies with families affected by CS, with the goal of integrating this basic knowledge into information about the natural history of the disease as well as into an initiative for developing new treatments.

More information: Matthew F. Pescosolido et al, Loss of Christianson Syndrome Na⁺/H⁺ Exchanger 6 (NHE6) Causes Abnormal Endosome Maturation and Trafficking Underlying Lysosome Dysfunction in Neurons, *The Journal of Neuroscience* (2021). DOI: [10.1523/JNEUROSCI.1244-20.2021](https://doi.org/10.1523/JNEUROSCI.1244-20.2021)

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