New lysosome atlas reveals cause of rare neurological disease

Together with colleagues from Stanford University, USA, researchers at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) have, for the first time, created a comprehensive cell type-specific atlas of lysosomes in the brain, the cell organelles which are responsible for degradation and recycling processes. The study shows that lysosomes in neurons differ significantly from those in other brain cells. Particularly striking is the previously little-noticed protein SLC45A1, which plays a central role in neuronal lysosomes. Mutations in this protein lead to a previously unclear neurological disease that can now be classified as a lysosomal storage disorder. The findings are not only important for understanding rare neurological diseases but also open up new perspectives for diagnosis and therapy.

Jena/Stanford. Lysosomes are membrane-bound cell components that play a central role in the degradation of macromolecules and the elimination of damaged cell structures. In this way, they contribute significantly to maintaining cellular homeostasis. This function is particularly important in the brain, as neurons must remain functional for decades and are hardly capable of renewal.

Although lysosomes are found in all tissues, their composition and function in different cell types of the brain are still poorly understood. In particular, it is unclear whether the amount and type of lysosomal proteins differ between different brain cells, and what relevance such differences have for disease processes. The cell type-specific functions of individual lysosomal proteins are also unclear.

Detailed lysosome atlas

An international research team led by Dr. Alessandro Ori from the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena, Germany, and researchers from Stanford University, USA, led by Prof. Monther Abu-Remaileh, have used mass spectrometry to systematically analyze the protein composition of lysosomes–isolated from different cell types of the brain–, including neurons, astrocytes, oligodendrocytes, and microglia, as part of a study now published in the journal *Cell*.

The resulting “atlas” clearly show that lysosomes vary in their composition depending on the cell type. “The diversity of lysosomes suggests that their recycling and signaling functions are highly specialized and have adapted to the specific requirements of each cell type of the brain” explains Dr. Julia Heiby from the FLI, first author of the study together with Dr. Ali Ghoochani.

SLC45A1 is a key factor in neuronal lysosomes

When analyzing these proteins, it was particularly striking that the protein SLC45A1 was exclusively found in the lysosomes of neurons. Further investigations revealed that this protein plays a central role in regulating the acidity of the lysosomes. Acidification is crucial for the

enzymes that reside inside the lysosome to optimally perform their degradative function. “If this process is disturbed, the lysosomal system loses its functionality,” adds Dr. Ori.

How can a molecular defect in SLC45A1 trigger a disease?

The researchers also found that mutations in the SLC45A1 gene, that have been previously associated to a rare neurological condition, prevents lysosomes from becoming sufficiently acidic. This results in disruptions in the cell's iron metabolism, which in turn impairs the function of mitochondria, the cell organelles responsible for the energy supply. This cascade of malfunctions explains the neurological symptoms of affected patients for the first time and allows the disease to be clearly classified as a lysosomal disease of the nervous system.

New insights into neurological diseases

Many rare neurological diseases are still poorly understood and difficult to diagnose. The newly developed lysosome atlas provides an important reference tool that can be used to assign disease-relevant changes to specific cell types in the brain. The study thus provides a basis for more precise diagnoses and opens up new perspectives for the development of future therapeutic approaches.

“Our results have shown that lysosomes in the brain are highly specialized and perform different tasks depending on the cell type,” Dr. Ori summarizes the study results. “With SLC45A1, we have also identified a protein that, when mutated, directly leads to a lysosomal disease of the brain.”

The cell-specific lysosomal signature could play a crucial role, particularly for medical applications. It is therefore to be hoped that the lysosome atlas will be widely used to further advance research in this field—both in understanding lysosomal storage disorders and other age-related neurological diseases such as Alzheimer's or Parkinson's.

Publication

Cell-type resolved protein atlas of brain lysosomes identifies SLC45A1-associated disease as a lysosomal disorder. Ali Ghoochani, Julia C. Heiby, Eshaan S. Rawat, Uche N. Medoh, Domenico Di Fraia, Wentao Dong, Marc Gastou, Mohit Rastogi, Vincent Hernandez, Kwamina Nyame, Nouf N. Laqtom, William Durso, Christina Valkova, Alina Isakova, Christoph Kaether, Marius Wernig, Natalia Gomez-Ospina, Christian Franke, Alessandro Ori, Monther Abu-Remaileh. Cell (2026) 189, 1-18; DOI: 10.1016/j.cell.2025.12.012

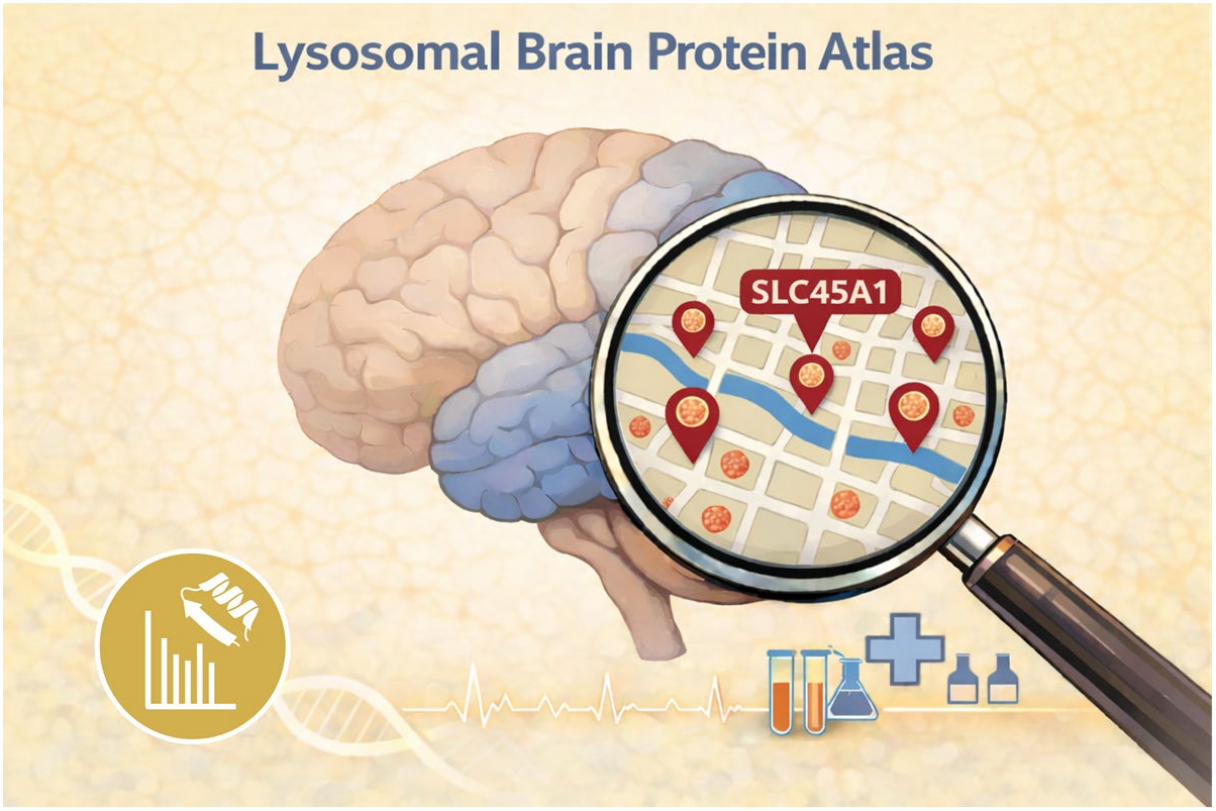
https://www.cell.com/cell/fulltext/S0092-8674(25)01425-4

Additional material

Browser-based web application of the **Lysosomal Brain Protein Atlas**

(Knight Initiative for Brain Resilience / Stanford University)
https://brainresilience.stanford.edu/lysosomal-brain-protein-atlas

Picture



Lysosomal Brain Protein Atlas: For the first time, a comprehensive cell type-specific atlas of lysosomes in the brain has been created – the cell organelles responsible for degradation and recycling processes. (Image: FLI / Julia Heiby; generated with ChatGPT)

Contact

Dr. Kerstin Wagner
Press & Public Relations
Phone: 03641-656378, Email: presse@leibniz-fli.de

Background

The Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena is a federal and state government-funded research institute and member of the Leibniz Association (Leibniz-Gemeinschaft). FLI conducts internationally recognized, high-impact research on the biology of aging at the molecular, cellular, and systems levels. Scientists from around 40 countries investigate the mechanisms of aging to uncover its root causes and pave the way for strategies that promote healthy aging. Further information: www.leibniz-fli.de.

The **Leibniz Association** connects 96 independent research institutions that range in focus from natural, engineering, and environmental sciences to economics, spatial, and social sciences and the humanities. Leibniz Institutes address issues of social, economic, and ecological relevance.

They conduct basic and applied research, including in the interdisciplinary Leibniz Research Alliances, maintain scientific infrastructure, and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer, particularly with the Leibniz research museums. It advises and informs policymakers, science, industry, and the general public.

Leibniz institutions collaborate intensively with universities – including in the form of Leibniz ScienceCampi – as well as with industry and other partners at home and abroad. They are subject to a transparent, independent evaluation procedure. Because of their importance for the country as a whole, the Leibniz Association Institutes are funded jointly by Germany's central and regional governments. The Leibniz Institutes employ around 21,400 people, including 12,170 researchers. The financial volume amounts to 2 billion euros. For more information: www.leibniz-gemeinschaft.de/en/.