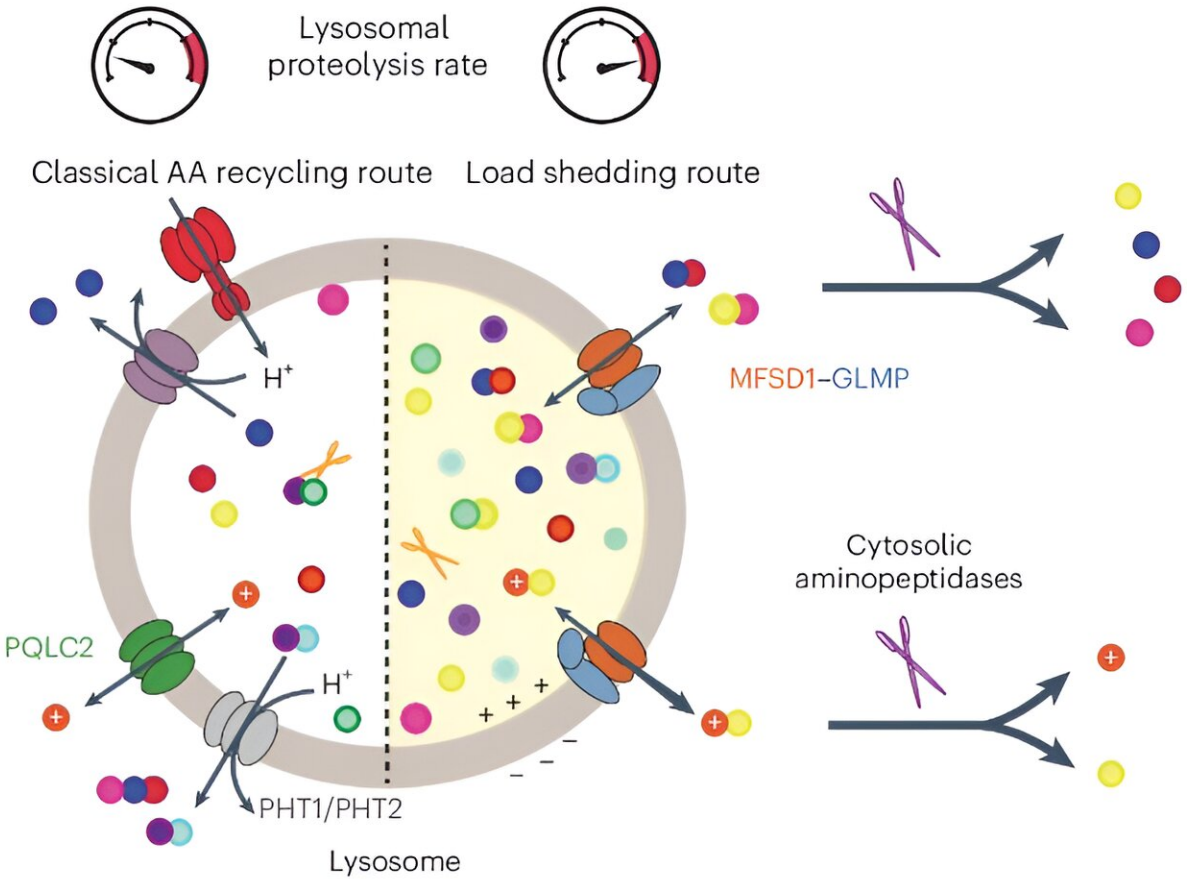
Structure and function of new lysosome transporter revealed

June 6 2024



Cellular model for the role of MFSD1 in the recycling of amino acids (AA) derived from lysosomal proteolysis. Credit: *Nature Cell Biology* (2024). DOI: 10.1038/s41556-024-01436-5

Researchers have revealed the structure and function of a previously unknown lysosome transporter. The groups of Christian Löw (CSSB, EMBL Hamburg), Markus Damme (Christian-Albrechts-University Kiel), and Bruno Gasnier (CNRS and Université Paris Cité) have published their findings in *Nature Cell Biology*.

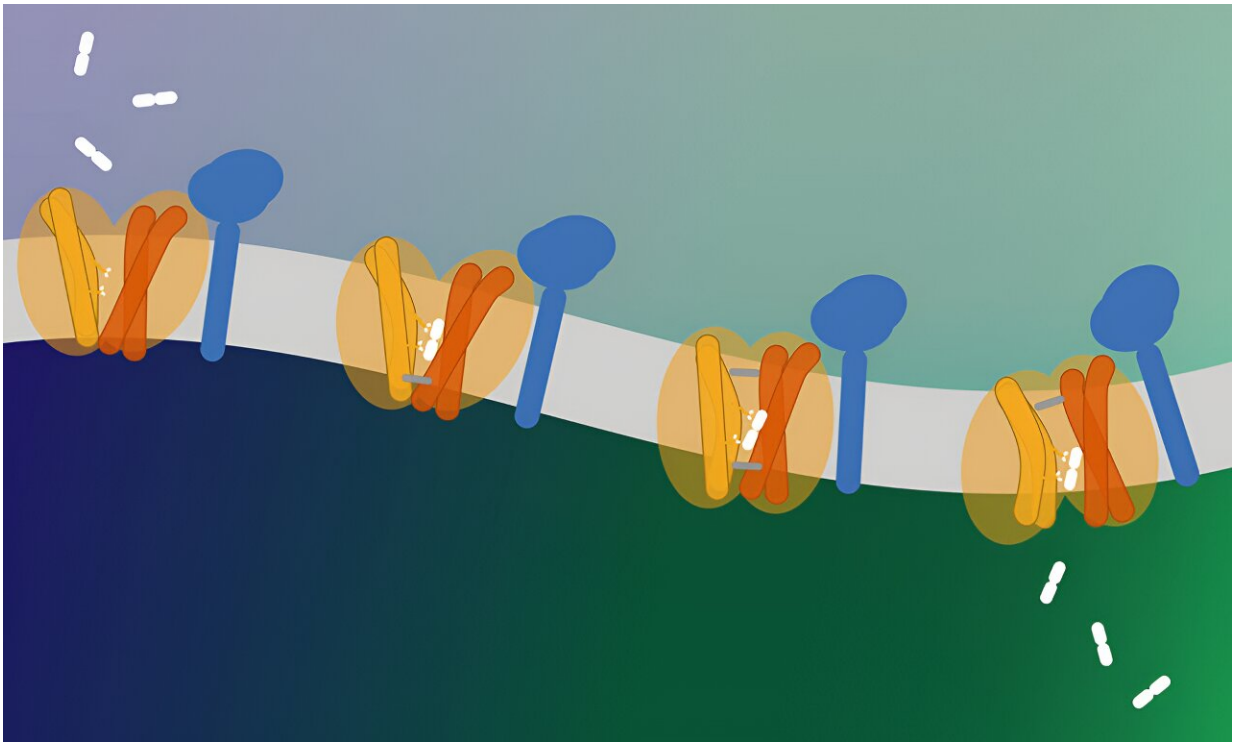
Lysosomes are organelles that function as a waste disposal and recycling system within the cell. They break down larger macromolecules such as proteins and lipids into smaller, lighter compounds like amino acids, monosaccharides, or fatty acids. These smaller compounds, known as metabolites, are then transported into the cell's cytoplasm.

The Damme group at Christian-Albrechts-University Kiel seeks to elucidate the function of specific proteins on the lysosome's membrane.

"Several years ago, we noticed that the Glycosylated Lysosomal Membrane Protein (GLMP) binds tightly with an orphan transporter named Major Facilitator Superfamily Domain Containing 1 (MFSD1)," noted Markus Damme, one of the study's three corresponding authors. As the term "orphan transporter" indicates, MSFD1's function and substrate were unknown.

To help reveal MFSD1's function, Damme reached out to the Löw group at the Center for Structural Systems Biology (CSSB) and EMBL Hamburg. The Löw Group's research focuses on understanding peptide transporters known as POTs (proton-coupled oligopeptide transporters).

"I was intrigued by MFSD1 and wanted to help figure out its role in the lysosome," explained Löw, currently a visiting group leader at EMBL Hamburg and another of the study's corresponding authors. "I was also confident that the different technologies and methodologies available to us at CSSB would be essential in helping us unravel this mystery."



A schematic of transport of dipeptides (white sticks) by the GLMP–MFSD1 complex. The transporter undergoes the common alternating access mechanism transitioning from outward-open conformation after dipeptide binding in the lysosomal lumen, to the occluded state where both sides of the binding site are closed, to the inward-open conformation enabling dipeptide release to the cytoplasm. Credit: Katharina Jungnickel/EMBL and CSSB, Isabel Romero Calvo/EMBL

Using a combination of techniques, including fluorescence spectroscopy and differential scanning fluorimetry (nanoDSF), the researchers discovered that MFSD1 not only binds but also transports dipeptides, peptides comprised of just two amino acids. The researchers were then able to show how the MFSD1/GLMP complex binds to dipeptides.

"We were able to determine the complex's structure in an outward-open

conformation," explained Katharina Jungnickel, an EMBL EIPOD Fellow and one of the first authors of the paper. "We additionally saw density of the dipeptide at the binding site. Together with molecular dynamics simulations (by Reza Mehdipour, Ghent University), we verified that dipeptide binding is mainly facilitated by the coordination of its N- and C-termini."

The Gasnier group at the Université Paris Cité performed some clever experiments which enabled the researchers to discover the mechanism used by MFSD1 to transport the dipeptides.

"We discovered that MFSD1 is a passive uniporter that only transports dipeptides along its own gradient," stated Bruno Gasnier, the paper's third corresponding author. "This led us to develop a new assay which revealed that MFSD1 transports a much wider spectrum of dipeptides than initially thought."

The insights gained by the researchers indicate that MFSD1 provides an alternative route to supply amino acids for biosynthetic pathways when other lysosomal amino acid exporters are overloaded.

"This was an amazing collaborative effort which combined labs with different expertise that were driven by the need to answer biological questions," noted Löw. "I am looking forward to finding out more about MFSD1 and its overall role in nutrition sensing."

More information: Katharina Esther Julia Jungnickel et al, MFSD1 with its accessory subunit GLMP functions as a general dipeptide uniporter in lysosomes, *Nature Cell Biology* (2024). DOI: 10.1038/s41556-024-01436-5

Provided by European Molecular Biology Laboratory