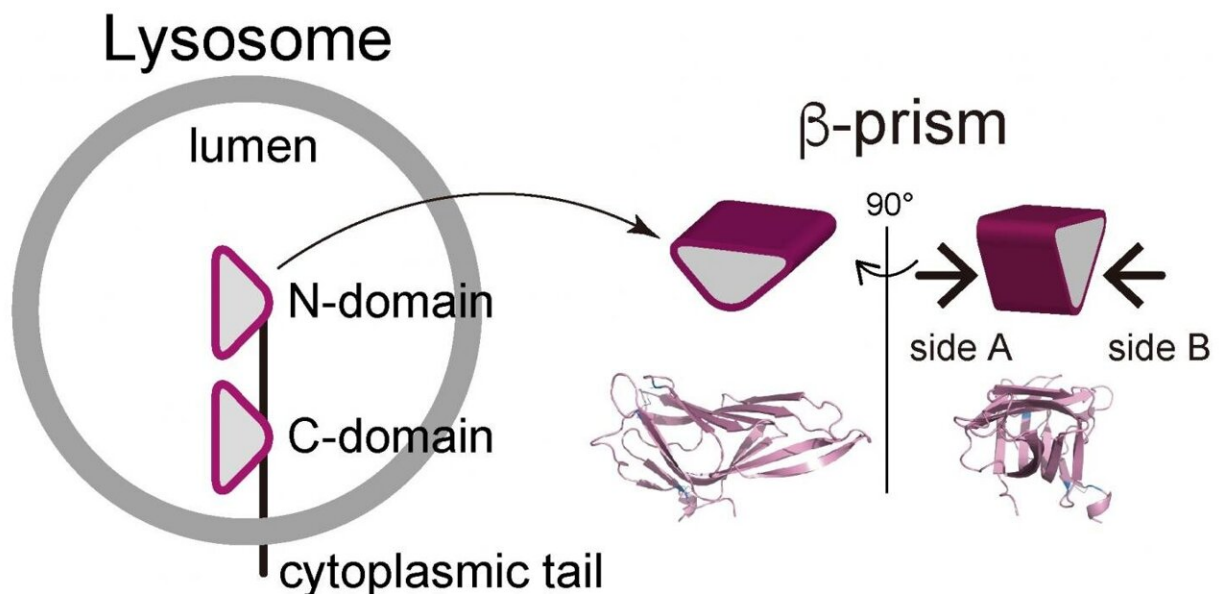


Using LAMP to reveal the mysteries of lysosomes

June 25 2021



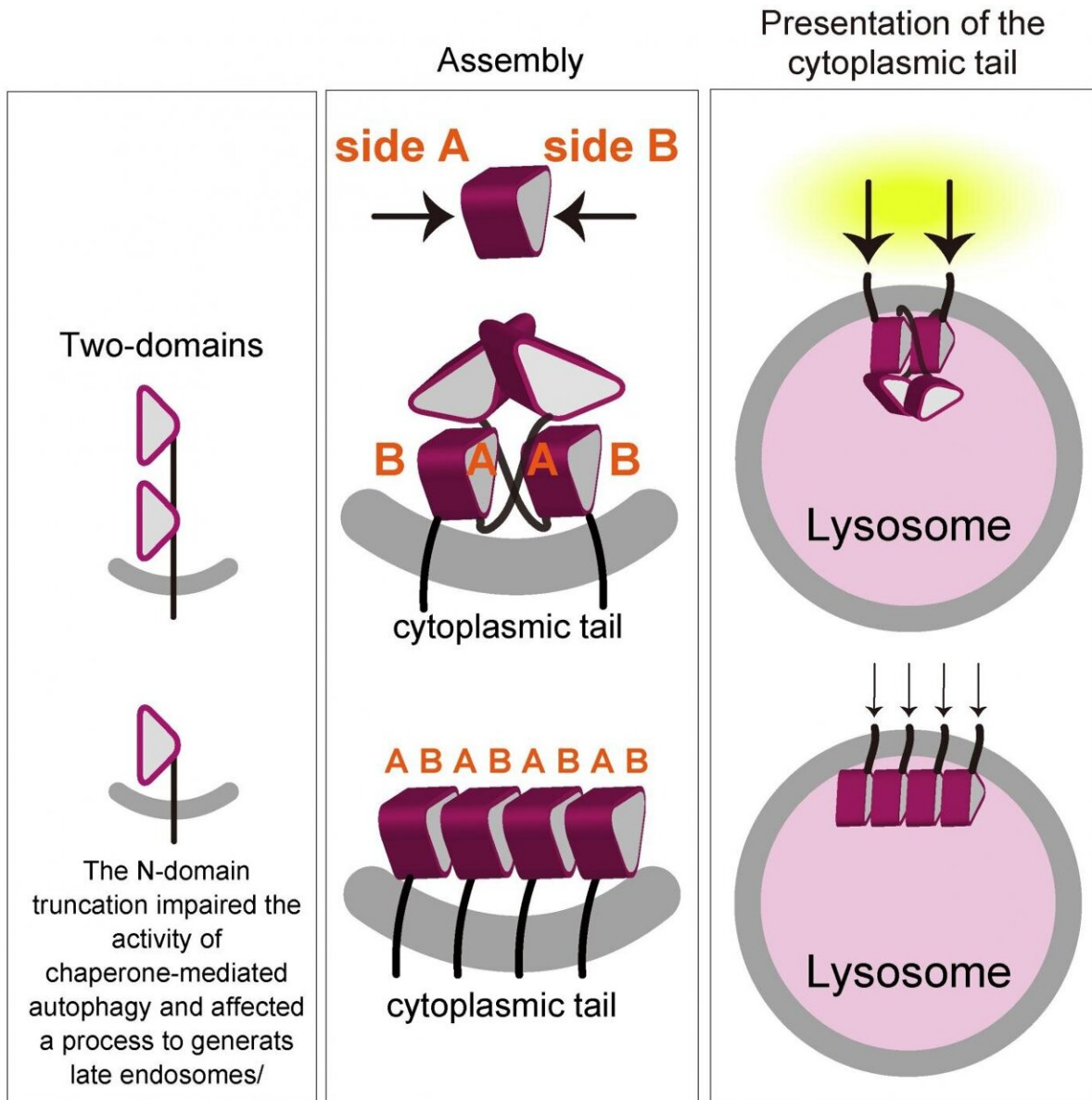
Domain architecture and orientation of LAMP1 and LAMP2 in the lysosome lumenal membrane(left). Schematic β -prism shapes and the structures of the C-domain of LAMP1(5GV0) are shown in two perpendicular views(right). We defined the surface of the N-terminal(N) side as Side A, and that on the C-terminal(C)side as Side B. Credit: Department of Biochemistry,TMDU

A cell is composed of numerous organelles, each with a unique role that helps contribute to its overall functionality. The lysosome is an organelle that contains digestive enzymes and functions as a molecular garbage

disposal and recycling center. Since the role of lysosome is crucial to maintaining the cellular homeostasis, the lysosomal dysfunction causes neurodegenerative and metabolic diseases, cancer, and lysosomal storage disorders.

In a new article published in *Autophagy*, researchers at Tokyo Medical and Dental University (TMDU) performed a novel type of structural analysis to demonstrate how a certain molecular interaction is crucial for one lysosomal membrane protein to perform effectively.

LAMP1 (lysosomal-associated membrane protein 1) and LAMP2 are the most abundant protein components of lysosome membranes. Both LAMP1 and LAMP2 are composed of a large luminal domain, a [transmembrane domain](#), and a short C-terminal cytoplasmic tail. The luminal domains of LAMPs are composed of two domains (N-domain and C-domain, which are membrane-distal and -proximal, respectively). Each domain has the unique β -prism fold structure (a triangular prism). On the other hand, [genetic experiments](#) have shown that mice embryos without both LAMP-1 and 2 die a little more than two weeks after fertilization. Mice without LAMP-1 are born and can thrive, while those without LAMP-2 often die a few weeks after birth, suggesting that LAMP-2 is more important for lysosome activity. The research of the TMDU group further investigates this protein's biological role.



Schematic representation of the interaction of the full-length LAMP2A molecules and the N-domain truncated LAMP2A molecules on the luminal membrane. Credit: Department of Biochemistry, TMDU

"Mice lacking LAMP-2 also display issues with autophagy progression," says one of the lead authors of the study Kazuo Terasawa. "Expanding our knowledge of how LAMP-2 interacts and operates at the [molecular](#)

[level](#) will ultimately help us understand autophagy better."

The researchers demonstrated LAMP2 molecules assemble by facing each other with one side the β -prism (defined as side A) of the C-domain. The N-domain truncation permitted the nonspecific involvement of both sides of the β -prisms (side A and side B). In combination with some biochemical studies, "we believe that the homophilic interaction we demonstrated is crucial for function of LAMP-2, via ensuring a proper arrangement of the cytoplasmic tails, which is crucial for the function of LAMP2, on the [lysosome](#) membrane," says Miki Hara-Yokoyama, senior author.

More information: Kazue Terasawa et al, Direct homophilic interaction of LAMP2A with the two-domain architecture revealed by site-directed photo-crosslinks and steric hindrances in mammalian cells, *Autophagy* (2021). [DOI: 10.1080/15548627.2021.1911017](https://doi.org/10.1080/15548627.2021.1911017)

Provided by Tokyo Medical and Dental University

Citation: Using LAMP to reveal the mysteries of lysosomes (2021, June 25) retrieved 23 June 2024 from <https://phys.org/news/2021-06-lamp-reveal-mysteries-lysosomes.html>

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