UKE Paper of the Month Oktober 2022

The human disease gene LYSET is essential for lysosomal enzyme transport and viral infection

Christopher M. Richards, Sabrina Jabs, Wenjie Qiao, Lauren D. Varanese, Michaela Schweizer, Peter R. Mosen, Nicholas M. Riley, Malte Klüssendorf, James R. Zengel, Ryan A. Flynn, Arjun Rustagi, John C. Widen, Christine E. Peters, Yaw Shin Ooi, Xuping Xie, Pei-Yong Shi, Ralf Bartenschlager, Andreas S. Puschnik, Matthew Bogyo, Carolyn R. Bertozzi, Catherine A. Blish, Dominic Winter, Claude M. Nagamine, Thomas Braulke*****, Jan E. Carette***** (***** corresponding authors)

Science, 2022, 378 (6615): eabn5648

ABSTRACT:

Lysosomes are key degradative compartments of the cell. Transport to lysosomes relies on GlcNAc-1-phosphotransferase-mediated tagging of soluble enzymes with mannose 6-phosphate (M6P). GlcNAc-1-phosphotransferase deficiency leads to the severe lysosomal storage disorder mucolipidosis II (MLII). Several viruses require lysosomal cathepsins to cleave structural proteins and thus depend on functional GlcNAc-1-phosphotransferase. We used genome-scale CRISPR screens to identify lysosomal enzyme trafficking factor (LYSET, also named TMEM251) as essential for infection by cathepsin-dependent viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). LYSET deficiency resulted in global loss of M6P tagging and mislocalization of GlcNAc-1-phosphotransferase from the Golgi complex to lysosomes. Lyset knockout mice exhibited MLII-like phenotypes, and human pathogenic LYSET alleles failed to restore lysosomal sorting defects. Thus, LYSET is required for correct functioning of the M6P trafficking machinery and mutations in LYSET can explain the phenotype of the associated disorder.

STATEMENT:

Our findings not only provide insights into molecular mechanisms to regulate lysosomal functions with relevance for a fatal hereditary disorder but also plays a crucial role in infections by diverse highly pathogenic viruses.

BACKGROUND:

This work was performed in the IOBM group Cell Biology of Rare Diseases of the corresponding author Thomas Braulke holding a UKE professorship since 1999, and the Department of Electron Microscopy, headed by Michaela Schweizer at the ZMNH. Both authors have strong research interests in biogenesis of lysosomes, autophagy and lysosomal diseases. Together with the Stanford University, including Nobel Prize winner 2022 Carolyn Bertozzi, the significance of lysosomal regulation and pathogenic virus infections was demonstrated. This work was funded by the DFG: CRC (SFB877) “Proteolysis as a Regulatory Event in Pathophysiology“ and the research group “Mechanisms of lysosomal homeostasis” (FOR2625).