Cryo-EM reveals the mechanisms of human membrane transporters

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Abstract

Membrane transporters are proteins that transport small molecules across the cell membranes and thereby play pivotal roles in human metabolism and physiology. At present, our understanding about the molecular structures and mechanisms of human membrane transporters relies on the studies into their prokaryotic homologues, because human transporters are notoriously difficult to isolate and crystallize. Recent breakthroughs in cryo-electron microscopy (cryo-EM) have enabled us to study the structures of human transporters without a need of crystallization [1]. Here, we present our progress in the structural studies into human L-type amino acid transporter 1 (LAT1), by using single-particle cryo-EM. We have visualized LAT1 in complex with its physiological partner, CD98 heavy chain (CD98hc). LAT1 and CD98hc form a tight heterodimeric complex, connected by a disulfide-bond and interacting with each other through the extracellular loops, transmembrane helices and lipid-mediated interactions. LAT1 shows a bacterial LeuT-like fold and harbors a central cavity that is open towards the cytoplasm. Numerous hydrophobic residues surround the cavity, which probably defines the substrate specificity of LAT1 for large hydrophobic amino acids and drugs. CD98hc stabilizes LAT1 by binding to its scaffold domain, supporting the movement of a flexible gating domain that is critical for the substrate transport. Taken together, these results show how LAT1 transports amino acids across the membrane in concert with CD98hc, and demonstrate the potential of cryo-EM in helping us understand transporter function and mechanism.

Keywords: *Cryo-EM, transporter, glycoprotein, complex*

References

[1] Werner Kühlbrandt. Resolution Revolution. Science 343, 1443 (2014).

Biography

Dr. Lee is a researcher at Max Planck Institute of Biophysics. In 2013, he joined Univ. of Tokyo's Prof. Nureki's lab to study structural mechanisms of membrane transporters with X-ray crystallography. During his PhD, he received Protein Science Society of Japan's Young Scientist Award. In 2018, he joined the current lab to learn single-particle cryo-electron microscopy to study human membrane protein complexes. He currently holds a Human Frontier Science Program Fellowship (HFSP LTF 2018).