MS11-P02

The stucture of human ASCT2 neutral amino acid transporter

Albert Guskov[1], Alisa Garaeva[1], Gert Oostergetel [1], Cornelius Gati[2], Cristina Paulino[1], Dirk Slotboom[1]

1. Groningen Biomolecular Sciences and Biotechnology Institute / University of Groningen, Groningen, Netherlands (Holland, Europe)
2. Department of Structural Biology / Stanford University, Stanford, United States of America

email: a.guskov@rug.nl

Human ASCT2 belongs to the SLC1 family of secondary transporters and is specific for the transport of small neutral amino acids, including glutamine. ASCT2 is upregulated in cancer cells, and serves as the receptor for many retroviruses, thus it is a potential drug target. I will report a structure of human ASCT2 at 3.85 Å resolution obtained using single particle Cryo-EM. The structure of the functional and unmodified protein sheds light on the transport mechanism of SLC1 members in general, and reveals insight in specific functions of human ASCT2. ASCT2 forms a homotrimeric complex, in which each subunit contains a transport and a scaffold domain. Each of the scaffold domains contains a prominent extracellular extension, which is specific for human ASCT2 and forms the predicted docking site for retroviruses. The transporter adopts an inward-oriented state that resembles the unlocked state of a mutant of prokaryotic homologue GltPh, but in ASCT2 the transport domain is located farther towards the cytoplasmic side of the membrane where it is largely detached from the central scaffold domain. The domain detachment may be required for substrate binding and release on the intracellular side of the membrane. I will also provide a detailed comparison with the previously resolved structures of archaeal homologues of glutamate transporters Glttk and Gltph, as well as human EAAT1 transporter.

Keywords: glutamine transporter, ASCT2, membrane proteins

MS11-P03

Structure and function of proteins involved in targeting of tail-anchored membrane proteins to the membrane of ER or chloroplast

Chwan-Deng Hsiao[1], Tai-Wen Lin[1], Hsin-Yang Chang[2]

1. Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan
2. Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan

email: hsiao@gate.sinica.edu.tw

Nearly 5% of membrane proteins are guided to nuclear, endoplasmic reticulum, mitochondrial, Golgi, or peroxisome membranes by their C-terminal transmembrane domain and are classified as tail-anchored (TA) membrane proteins. During the biosynthesis of TA membrane proteins, their single C-terminal trans-membrane segment is inserted into the ER membrane for orientating the functional domain(s) towards the cytosolic side of the cell. The machinery responsible for this post-translational process has only recently come to light. In yeast, the proteins participating in TA protein insertion was previously identified to be conducted by the GET pathway (Guided *Entry of Tail-anchored proteins*) including Get1, Get2, Get3, Get4, Get5, Sgt2 and Ybr137wp. In my laboratory, we investigated the interactions between these components from Saccharomyces cerevisiae. Recently, we also determined the crystal structure of arsenite transporter 1 (ArsA1, the homologs of yeast ATPase Get3) from green alga. Our binding activity assay demonstrated that ArsA1 can specifically recognize the transmembrane region of chloroplast TA protein Toc34 but not ER TA protein Sec61β. Based on the ArsA1 structure, we uncover a distinct mechanism for specific filtering between ER and chloroplast TA proteins and successfully manipulate the specificity of mutant ArsA1 for a set of ER TA protein. Our biochemical and structural data provide new insight for the specific selection of ER and chloroplast TA proteins for membrane insertion.

Keywords: tail-anchored membrane protein, mitochondrial, chloroplast