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Structural and evolutionary insights into the vesicle fusion machinery. Dirk Fasshauer, Max-Planck Institut of Biophysical Chemistry, Göttingen.

Transport of cargo between organelles in eukaryotic cells is mediated by vesicles that bud from a donor compartment and specifically fuse with an acceptor membrane. Currently, it is becoming clear that the underlying molecular machineries involved in the principal aspects of vesicular trafficking are highly conserved, not only between different species but also between different vesicle trafficking steps. In all steps, the central machinery involved in the fusion process is composed of members of the SNARE protein family. Distinctive, heterologous sets of SNAREs proteins anchored in the vesicle and target membrane are thought to assemble in a zipper-like fashion into a four-helix bundle, providing the energy to mediate fusion of the two bilayers. Although SNAREs are highly conserved, not only between different species but also between different vesicle trafficking steps. In all steps, the central machinery involved in the fusion process is composed of members of the SNARE protein family. Distinctive, heterologous sets of SNAREs proteins anchored in the vesicle and target membrane are thought to assemble in a zipper-like fashion into a four-helix bundle, providing the energy to mediate fusion of the two bilayers. Although SNAREs are sufficient to drive membrane fusion when inserted into liposome membranes, this minimal machinery is organized and controlled by additional factors in vivo. Members of the cytosolic Sec1/Munc18 (SM) family of proteins have been established as essential factors in different intracellular transport steps, during which they functionally interact with the SNARE machinery. To come to a better understanding of the molecular events during vesicle fusion, we focus on a detailed structural, kinetic, thermodynamic, and phylogenetic characterization of the core vesicle fusion machinery.

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Self-Association of Quality Control Components in the ER. Jennifer Hanna, Anja Schütz, Franziska Zimmermann, Thomas Sommer, Udo Heinemann. Max Delbrück Center for Molecular Medicine, Berlin, Germany. Leibniz Graduate School of Molecular Biophysics. E-mail: j.hanna@mdc-berlin.de

To avoid accumulation of misfolded proteins in the endoplasmic reticulum, unfolded and misfolded proteins are disposed of by a pathway called ER-associated degradation. First, misfolding is recognized and distinguished from unfolded, but folding competent states. Misfolded proteins are then transported into the cytosol, where they are ubiquitinated and degraded by the proteasome. The Hrd complex is one of the protein complexes at the ER membrane which play a central role in this pathway. We have determined the structure of a protein-protein interaction domain of the quality control protein Yos9, a lectin which recognizes misfolded proteins by their sugar modifications. In this crystal structure, the domain adopts a dimeric arrangement. Here, we report that in vitro, the domain does not confer binding to the Hrd complex on its own, as was suggested by previous experiments. Instead, we propose that the domain is important for self-association of the protein, which is thought to promote binding to the Hrd complex.

Keywords: Quality control, glycoprotein, ER associated degradation

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The crystal structure of the ERGIC-53/MCFD2 transport receptor complex. Edvard Wigren, Jean-Marie Bourhis, Inari Kursula, Jodie E. Guy, Ylva Lindqvist. Dept. of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden. E-mail: Edvard.Wigren@ki.se

The membrane bound glycoprotein receptor ERGIC-53 in complex with the co-receptor MCFD2 (multiple coagulation factor deficiency 2) mediates export of the blood coagulation proteins, factor V (FV) and factor VIII (FVIII), from the Endoplasmic Reticulum (ER) to the Golgi complex. This calcium-dependent complex serves as a specific cargo receptor for the selective packaging of FV and FVIII into COPII-coated vesicles that bud from the ER for transport to the Golgi. Mutations in MCFD2 or ERGIC-53 cause a mild form of hemophilia known as combined deficiency of factors V and VIII (F5F8D). In order to facilitate understanding of the function of the ERGIC-53/MCFD2 transport complex and the mechanism by which mutations in the proteins cause F5F8D, we have determined the structure of the carbohydrate recognition domain (CRD) of ERGIC-53 in complex with MCFD2. Comparison of our structure with previous uncomplexed structures of the proteins shows that MCFD2 undergoes conformational changes upon complex formation, but no major structural changes can be detected in ERGIC-53. The interaction interface of MCFD2 involves most of the F5F8D-causing mutations known to date, clarifying the means by which several of these mutations result in inefficient secretion of FV and FVIII. The structure provides new information on