FASSBERG SEMINAR SERIES

©photo: private

online

Melanie McDowell
Biochemistry Center
Heidelberg University

Structural characterisation of ER membrane targeting and insertion

After their synthesis by eukaryotic ribosomes, most integral membrane proteins (IMPs) are inserted into the endoplasmic reticulum (ER) membrane. This requires that the hydrophobic transmembrane domains (TMDs) of IMPs are faithfully chaperoned through the aqueous cytosol and polar membrane surface. The huge diversity in the topology and biochemical properties of IMPs necessitates several distinct pathways for their ER targeting and insertion. One such route, the guided entry of tail-anchored proteins (GET) pathway, mediates the post-translational insertion of tail-anchored (TA) proteins, which have a single transmembrane domain (TMD) at their extreme C-terminus. Within this pathway, the Get1/Get2 insertase in the ER membrane captures the TA protein from the Get3 cytosolic chaperone to mediate membrane insertion. To understand the molecular mechanisms associated with this process, we characterised human and yeast Get1/Get2/Get3 complexes using cryo-electron microscopy, native mass spectrometry and structure-guided mutagenesis (McDowell et al., 2020). Upon Get3 binding, Get1 and Get2 form a membrane heterotetramer that is further stabilised by phosphatidylinositol binding at the oligomeric interface, required for efficient TA insertion in vivo. A Get2 cytoplasmic helix forms an unanticipated 'gating' interaction with Get3 that is important for TA insertion. Structural homology with YidC and the ER membrane protein complex (EMC) reveals an evolutionary conserved mechanism for TA insertion utilising a hydrophilic groove. These approaches have provided a detailed structural and mechanistic framework for understanding TA protein insertion by the GET pathway.

Host: Marina Rodnina

Thursday / 14.01.2021 / 11:00

zoom access data will be mailed before the seminar!