Project Title: Mechanism and Function of the Rhomboid Pseudoprotease Dfm1 in Membrane Protein Degradation

Project Description:

Biogenesis of membrane proteins, representing about 30% of the human proteome, mainly occurs within the Endoplasmic reticulum (ER). Maintenance of protein homeostasis is fundamentally important to match the cellular needs and to counteract stress conditions. Misfolded or mistargeted proteins represent a high risk to cells, and deregulation of protein homeostasis mechanisms is linked to severe pathologies including diabetes and neurodegeneration. Therefore, the ER-associated degradation (ERAD) pathway performs an essential role to restore ER homeostasis under steady state and cellular stress conditions. ER resident, membrane-embedded E3 ubiquitin ligases serve as organizational centers for distinct protein complexes and collectively provide the essential substrate ubiquitination activity for degradation of ERAD substrates by the proteasome. Recent high-resolution structures revealed that the E3 ligase Hrd1 and the rhomboid pseudoprotease Der1 provide a sizable pore for the dislocation of luminal proteins into the cytoplasm. Despite years of genetic and biochemical work, still much less is known of how membrane proteins are extracted from the lipid bilayer in order to reach the cytoplasmic proteasome for degradation.

Previous work from our research groups, using budding yeast as a model system, showed that the rhomboid pseudoprotease Dfm1 is a crucial ERAD factor forming a putative extraction platform for membrane proteins. With this proposed project, we aim to define the precise physiological role of Dfm1 in *S. cerevisae*, identify endogenous substrates, and decipher the molecular mechanism of membrane protein degradation in the ER – potentially linking ERAD and ER-phagy.

References:

- Stolz A. and Grumati P. (2019) The Various Shades of ER-phagy. FEBS J. 286(23):4642-4649

- Avci D. and Lemberg M.K. (2018) Membrane Protein Dislocation by the Rhomboid Pseudoprotease Dfm1: No Pore Needed? Preview *Mol. Cell* 69, 161-162.

- Avci D. and Lemberg M.K. (2015) Clipping or Extracting: Two ways for membrane protein degradation. *Trends Cell Biol*. 25, 611-622.

- Avci D. et al. and Lemberg M.K. (2014) The yeast ER-intramembrane protease Ypf1 refines nutrient sensing by regulating transporter abundance. *Mol. Cell* 56, 630-640.

- Wolf DH, Stolz A. (2012) The Cdc48 machine in endoplasmic reticulum associated protein degradation. *Biochim Biophys Acta*. 1823(1):117-124.

- Stolz A, Schweizer RS, Schäfer A, Wolf DH. (2010) Dfm1 forms distinct complexes with Cdc48 and the ER ubiquitin ligases and is required for ERAD. *Traffic* 11(10):1363-1369

Profile of PhD Candidate:
We are looking for a highly motivated PhD student who holds a Master degree in biology, biochemistry or equivalent. Expertise in either yeast genetics, membrane protein biochemistry or proteomics are of advantage, but not essential.

The successful candidate will be part of a collaborative research team located both at the Institute of Biochemistry 2 in Frankfurt and the Center for Molecular Biology of Heidelberg University (ZMBH). The primary workplace will be Heidelberg. Weekly progress report meetings and journal clubs ensure a challenging, yet helpful environment, in which the candidate will broaden the theoretical and practical knowledge and independent investigative thinking skills. Our collaboration project offers an internationally competitive research environment with access to excellent core facilities. Our staff is international and the working language is English.

Responsible PIs
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Collaboration:
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