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# Defining the pathways involved in spatial protein quality control in Saccharomyces cerevisiae

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, torsdagen den 15 december, klockan 9.00

av Kara L. Schneider

Fakultetsopponent:

Prof. Elçin Ünal

University of California, Berkeley, CA, United States

**Avhandlingen baseras på följande delarbeten**

I. Schneider KL, Wollman AJM, Nyström T, Shashkova S. Comparison of endogenously expressed fluorescent protein fusions behaviour for protein quality control and cellular ageing research. Sci Rep. 2021 Jun 17;11(1):12819.

II. Schneider KL, Ahmadpour D, Keuenhof KS, Eisele-Bürger AM, Berglund LL, Eisele F, Babazadeh R, Höög JL, Nyström T, Widlund PO. Using reporters of different misfolded proteins reveals differential strategies in processing protein aggregates. J Biol Chem. 2022 Sep 9:102476.

III. Babazadeh R*, Ahmadpour D*, Jia S, Hao X, Widlund P, Schneider K, Eisele F, Edo LD, Smits GJ, Liu B, Nystrom T. Syntaxin 5 Is Required for the Formation and Clearance of Protein Inclusions during Proteostatic Stress. Cell Rep. 2019 Aug 20;28(8):2096-2110.e8.

IV. Babazadeh R*, Schneider KL*, Fischbach A, Hao X, Liu B, Nystrom T. The yeast guanine nucleotide exchange factor Sec7 is a bottleneck in spatial protein quality control and detoxifies neurological disease proteins. Manuscript.

V. Schneider KL, Hao X, Keuenhof KS, Berglund LL, Goméz P, Ahmadpour D, Höög JL, Nyström T, Widlund PO. Heat-induced protein aggregates co-localize with mitochondria and virus-like particles. Manuscript.

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR BIOMEDICIN**

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# Defining the pathways involved in spatial protein quality control in Saccharomyces cerevisiae

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**Abstract**

Proteins need to be folded into specific three-dimensional conformations to be functional. An extensive network of factors, the protein quality control (PQC) machinery, ensures that the cell maintains a healthy proteome by coordinating their synthesis, folding, transport and degradation. A disruption in this machinery can lead to accumulation of protein aggregates, which is a hallmark of aging and many human pathologies. A key question in research on PQC is why and how certain aberrant proteins cause proteotoxicity, while others can be efficiently handled by the PQC. Sequestration of aggregates into larger inclusions and their deposition at distinct cellular sites have been suggested to be cytoprotective functions of spatial PQC.

The articles included in this thesis use budding yeast to study spatial PQC in heat-stressed cells. Expanding the toolbox by a set of misfolding reporters and comparing their behavior revealed that diverse protein species are cleared at differential rates, even when residing in shared, intermixed protein inclusions. Using genome-wide screens, we pinpointed Sed5 and Sec7, major regulators of vesicle trafficking, as key factors controlling spatial PQC and disease protein detoxification. Electron microscopy of heat-stressed cells showed that aggregates localize predominantly in proximity to both mitochondria and virus-like particles. Our findings contribute to an increased understanding of three major features of spatial PQC: aggregate clearance, sequestration and intracellular location.

**Keywords:** proteostasis, chaperones, aggregation, yeast, heat shock, stress, aging, mitochondria, virus-like particles

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