Göteborg, 2021

On chaperone co-operation in temporal and spatial protein quality control

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i 2119, Arvid Wallgrens Backe 1, fredagen den 23 april, klockan 13:00, via länk: https://gu-se.zoom.us/j/68507701063?pwd=cXZFTlJrYldHRVZ0a2FNVkV1NmtzQT09

av Rebecca Andersson

Fakultetsopponent:
Dr. Mark S. Hipp
University of Groningen, Nederländerna

Avhandlingen baseras på följande delarbeten

I. Hanzén S., Vielfort K., Yang J., Roger F., Andersson V., Zamarbide-Forés S., Andersson R., Malm L., Palais G., Biteau B., Liu, B., Toledano M. B., Molin M. and Nyström T. *Lifespan Control by Redox-Dependent Recruitment of Chaperones to Misfolded Proteins*. Cell. 2016 Jun 30;166(1):140–51.

II. Andersson R., Eisele-Bürger AM., Hanzén S., Vielfort K., Öling D., Eisele F., Johansson G., Gustafsson T., Kvint K. and Nyström T. *Differential role of cytosolic Hsp70s in longevity assurance and protein quality control.* PLoS Genet. 2021 Jan 11;17(1)

III. Andersson R., Syga L. and Nyström T. *Image-based analysis of the nucleolus associated protein deposit in yeast*. Manuscript

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On chaperone co-operation in temporal and spatial protein quality control

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Abstract

In order for a protein to be able to function correctly it needs to adopt its proper fold. Because of this, protein quality control (PQC) is vital at every level of cellular function. The central protein in PQC networks across all kingdoms of life are the Hsp70 molecular chaperones. In my thesis I present work into the adaptability of the chaperone network during different types of stress, and the functional variability between highly homologous yeast Hsp70 chaperones.

During heat stress, Hsp70s collaborate with other chaperones to sequester misfolded proteins into inclusion bodies and later resolve them. Hydrogen peroxide stress however requires additional activity from the peroxiredoxin Tsa1. Tsa1 is needed to recruit chaperones to misfolded proteins during oxidative stress. Interestingly, this is also true for stress caused by ageing, and increasing the level of Tsa1 can prolong the lifespan of yeast.

The Stress Seventy subfamily A (Ssa1-4) is an important Hsp70 family in yeast. Loss of Ssa1 and Ssa2 decreases cellular viability and lifespan even though Ssa3 and Ssa4 remain. Overproduction of Ssa4 can restore many but not all of the functions usually carried out by Ssa1/2, and restore a full lifespan. We show that preventing proteins from misfolding or sequestering them into inclusion bodies is enough to ensure a full lifespan, while disaggregation of inclusion bodies is not required for longevity assurance. We also describe a novel, Hsp70-dependent site for sequestration of misfolded proteins around the yeast nucleolus that forms after heat shock. The site is also the basis for the asymmetric segregation of damaged proteins in the nucleus during cell division, in a manner that is distinct from previously described asymmetry pathways in yeast.

Keywords: Molecular chaperones, Heat shock proteins, Hsp70 chaperones, Proteostasis, Ageing, Asymmetric damage segregation, Peroxiredoxins, Spatial protein quality control

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