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Proteostasis beyond chaperones – auxiliary systems in the management of damaged proteins

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Carl Kylberg, Medicinaregatan 7, fredagen den 17 december, klockan 09.00

av Rebecca Josefson

Fakultetsopponent:
Dr. Martin Graef
Max Planck Institute for Biology of Ageing, Tyskland

Avhandlingen baseras på följande delarbeten

I. Hill, S. M., Hao, X., Grönvall, J., Spikings-Nordby, S., Widlund, P. O., Amen, T., Jörhov, A., Josefson, R., Kaganovich, D., Liu, B., & Nyström, T. (2016). Asymmetric Inheritance of Aggregated Proteins and Age Reset in Yeast Are Regulated by Vac17-Dependent Vacuolar Functions. *Cell Rep, 16*, 1-13. doi:10.1016/j.celrep.2016.06.016

II. Josefson, R., Hao, X., Liu, B. & Nyström, T. (manuscript). The GET pathway is a major bottleneck for maintaining proteostasis in *Saccharomyces cerevisiae*.

III. Josefson, R., Hill, S. M., Hao, X. & Nyström, T. (manuscript). Vacuole inheritance-independent functions of Vac17 in spatial protein quality control and endocytosis.

SAHLGRENSKA AKADEMIN

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Proteostasis beyond chaperones – auxiliary systems in the management of damaged proteins

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Abstract

Aging entails loss of functionality and increased risk of death, even for unicellular organisms, such as the yeast *Saccharomyces cerevisiae*. On a cellular level, aging is accompanied by an accumulation of harmful aging factors, e.g. damaged and aggregated proteins. Environmental stress can also cause a protein to misfold, leading to loss of function and aggregation. Protein misfolding is counteracted by systems of protein quality control. The temporal protein quality control system acts to refold or degrade the misfolded protein, while the spatial protein quality control system sorts damaged proteins to specific inclusion sites to prevent toxicity.

The proteostasis network is defined as the cellular machineries involved in protein synthesis, folding and degradation. Other systems affecting proteins and protein folding status are considered auxiliary systems to proteostasis. This thesis is based on genome-wide studies of *S. cerevisiae* aimed at finding new components in asymmetric inheritance of damaged proteins and the overall capacity of the cell to prevent protein aggregates. Vac17 was identified as a limiting factor for asymmetric inheritance, inclusion formation, endocytosis and lifespan. The effect of Vac17 on these processes requires endosomal components and fusion to the vacuole. In addition, I found that the GET pathway is a limiting factor in protein folding, as disruption causes massive aggregation of several proteins, not only substrates of the GET pathway. Given the major impact of these auxiliary systems on proteostatic processes, they should be considered part of the proteostasis network.

Keywords: Aging, proteostasis, protein quality control, asymmetric inheritance, vesicle trafficking

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