Protein quality control:
From mechanisms to disease

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Organizer: Bernd Bukau
Co-organizer: Eilika Weber-Ban

ABSTRACT BOOK

Aggregate formation by the transcriptional regulator Sfp1 causes toxicity in yeast cells by more than one mechanism

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Andrew G. Matveenko [1], Varvara E. Ryzhkova [1], Polina B. Drozdova [1, 2], Galina A. Zhouravleva [1, 3]

[1] *Department of Genetics and Biotechnology, Saint Petersburg State University, St. Petersburg, Russia*

[2] *Present address: Institute of Biology, Irkutsk State University, Irkutsk, Russia*

[3] *Laboratory of amyloid biology, Saint Petersburg State University, St. Petersburg, Russia*

Yeast is a convenient model organism for studying protein misfolding and quality control systems, specifically, mechanisms of conversion of a protein to amyloid or prion form. The most studied yeast prion, [PSI+], is a heritable amyloid of the eRF3 (Sup35) protein. The [PSI+] prion is known to exhibit toxicity to the host strain. One of the factors affecting [PSI+] toxicity is Sfp1, a global transcriptional regulator, known to affect the Isp+/Isp- phenotype, previously thought to be caused by a prion-like determinant.

Our studies of toxicity caused by Sfp1 revealed that it is able to form detergent-resistant aggregates in vivo and aggregation of Sfp1 is responsible for the prion-dependent lethality in the [PSI+] strains. Similarly to the bona fide [PSI+]-dependent lethality, Sfp1-dependent lethality was alleviated by additional production of Hsp40-Sis1 chaperone. Additionally, Sfp1 aggregates partially colocalized with Sup35 and Sis1 in [PSI+] cells. We carried out a deletion analysis of the SFP1 gene which revealed that the regions critical for the Sfp1 aggregation differ from those necessary for the toxicity of SFP1 overexpression. Moreover, Sfp1 formed aggregates only when the respective gene was regulated by copper-inducible CUP1 promoter. Overexpression with galactose-inducible GAL1 promoter did not result in any aggregate formation while strong constitutive overexpression under control of GPD (TDH3) promoter led to detection of fluorescent foci in the minority of the cells; the amyloid nature of these foci remains questionable as the Sfp1 protein could not be detected in these cells by the western blot. However, the toxicity in this case was also slightly alleviated by additional Sis1. It is thus evident that Sfp1 misfolding and partitioning interfere with various processes, and the toxicity of excess Sfp1 may be caused by at least two distinct mechanisms.

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