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# Arsenic-induced protein aggregation and toxicity in *Saccharomyces cerevisiae*

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# ABSTRACT

Arsenic is prevalent in the environment and this toxic metalloid poses a substantial threat to human health with 100-200 million people worldwide estimated to be at risk. Chronic exposure to arsenic is associated with neurodegenerative and age-related disorders that are characterized by the accumulation of protein aggregates, including Parkinson's and Alzheimer's disease. Despite of the undisputed toxicity of arsenic, our understanding of the underlying mechanisms and cellular responses is limited. This thesis has focused on arsenic-induced protein aggregation and toxicity in yeast, with the aim of elucidating how these aggregates are formed *in vivo*, the mechanisms by which they affect cells, how cells prevent their accumulation as well as how cells regulate the protein quality-control system to protect against toxic aggregates. The impact arsenic has on protein homeostasis may contribute to its toxicity and suspected role in protein misfolding diseases. Main findings of this thesis include the identification of novel genes whose overexpression conferred arsenic resistance. We also demonstrated the importance of accurate transcriptional and translational control for mitigating protein aggregation and toxicity during arsenite stress. In addition, we showed that the ubiquitin-proteasome system (UPS) is the main pathway that clears arsenite-induced aggregates, whilst the autophagy-vacuole pathway and the chaperone-mediated disaggregation both contribute to clearance but their roles appear less prominent than the UPS. Our findings provide novel insights into the biology of arsenic and a valuable resource for further studies on the mechanistic details of arsenic toxicity and pathogenesis.

**Keywords**: arsenic, protein aggregation, protein quality control, yeast.