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Proteostasis under arsenite stress in *Saccharomyces cerevisiae*

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ABSTRACT

Around 200 million people are exposed to high levels of arsenic through contaminated soil and, consequently, contaminated food and drinking water. Arsenic exposure is associated with several malignancies, from different types of cancer to neurodegenerative disorders. At a cellular level, arsenic exerts its toxicity by affecting a variety of protein functions. Arsenic increases production of reactive oxygen species, interferes with protein function and cellular pathways, and induces aggregation of newly synthesized polypeptides. This thesis focusses on arsenite-induced protein aggregation and aims to provide new insights on how cells regulate the formation and degradation of protein aggregates and the role of protein quality control systems in this process, using *Saccharomyces cerevisiae* as a model organism. A genome-wide study revealed that protein aggregation induced by arsenite can be influenced by a series of different cellular processes. Particularly, strict transcriptional and translational control is essential to alleviate protein aggregation and sensitivity during arsenite stress. A systematic evaluation of protein quality control and protein degradation systems revealed that co-translational folding aids in mitigating protein aggregation. Furthermore, the protein aggregates formed in the presence of arsenite are polyubiquitinated and mainly degraded by the ubiquitin-proteasome system, while disaggregation by Hsp104 and the autophagy pathway play minor roles. Our data also suggest that arsenite influences aggregate structure making it less accessible for chaperone-mediated disaggregation. In summary, our findings reveal that an interplay between different quality control systems is crucial to maintain proteostasis during arsenic stress.

Keywords: proteostasis, protein aggregation, toxicity, arsenite, *S. cerevisiae*