INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Cellular Responses to Arsenite and Cadmium - Mechanisms of Toxicity and Defense in *Saccharomyces cerevisiae*

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Abstract

All biological systems have to cope with a wide range of metals that are present in the environment. Metals can be essential or beneficial for life, inert or non-essential and toxic, often depending on their chemical form and concentration. Most organisms have evolved defense mechanisms in order to deal with toxic metals. The toxic effect of a certain metal depends on cellular uptake, the mode of action inside the cell, on the efficacy of cellular defense systems, and on the intracellular localization of the compound. In this thesis, the main focus has been to investigate toxicity mechanisms and cellular responses to arsenite and cadmium. Arsenite is a trivalent, abundant and highly toxic form of arsenic found in nature and used in medical therapy. Cadmium is a heavy metal that has been used e.g. in paint, batteries and electronic industry with an increasing use during the industrialization. As a biological model system the budding yeast *Saccharomyces cerevisiae* has been used in this study, since it is a powerful and versatile tool to uncover fundamental traits in eukaryote cells.

First we identified a novel extracellular defense mechanism to arsenite; yeast cells export glutathione that chelates arsenite in the extracellular environment and prevents arsenite from entering the cell. We next measured intracellular arsenic content in a variety of mutants and used the data to create a mathematical model. This model predicted the role and contribution of different proteins in the cellular response to arsenite, and predicted that intracellular arsenite is mainly protein-bound upon acute exposure, while the main intracellular pool of arsenite after chronic exposure is bound to glutathione. Finally, we found a novel mode of action of arsenite and cadmium, namely the induction of widespread protein aggregation. We show that both arsenite and cadmium target newly synthesized proteins for aggregation. Arsenite also affected chaperone activity *in vivo*. Cadmium does not seem to inhibit chaperone activity *in vivo*. Instead, displacement of zinc in proteins seems to play an important role in the induction of protein aggregation upon cadmium exposure. Proteasomal degradation is involved in the clearance of protein aggregates induced upon arsenite and cadmium exposure.
Thus, we have provided new insights regarding both mechanisms of toxicity and defense.

Keywords: arsenic, arsenite, cadmium, glutathione, extracellular defense, protein aggregation, chaperones, proteasome, *Saccharomyces cerevisiae*.