Elucidating the mechanisms of protein aggregation and clearance in heavy metal/metalloid toxicity and tolerance.

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Research Abstract

Despite increasing concerns about arsenic and cadmium as environmental toxins, surprisingly little is known about the mechanisms by which they affect living organisms. We recently demonstrated that arsenic disrupts protein homeostasis and affects cell viability by interfering with protein folding processes in living cells. We also showed that both arsenic and cadmium cause widespread protein aggregation in vivo. This proposal aims at elucidating the mechanistic

details of this novel mode of toxic heavy metal/metalloid action. Specifically, we will uncover: (1) the molecular mechanisms by which arsenic and cadmium interfere with protein folding and promote protein aggregation in vivo, (2) how aggregates impair cellular functions, and (3) how cells regulate the protein quality-control systems to protect against aggregate toxicity. For this, we will use high-content screening technology, bioinformatics, and classical molecular and biochemical approaches with yeast as model system. The potential of arsenic and cadmium for human exposure and the extensive links between metals/metalloids, protein aggregation and human disorders underscore the importance of elucidating heavy metal/metalloid-induced protein aggregation and clearance mechanisms. The knowledge gained in yeast will be of value for a greater scientific community and provide novel insights into mechanisms relevant for human disease processes.

Further information available at:

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