Adaptation and Protein Quality Control Under Metalloid Stress

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Abstract

Toxic metals and metalloids are emerging as major environmental pollutants, having ecological consequences as well as being linked to a broad range of degenerative conditions in animals, plants and humans. While the toxicity of several metalloids is well established, the underlying molecular mechanisms are often not clear.

Several human degenerative diseases are linked to misfolding and aggregation of specific proteins. I have shown that many of these proteins have yeast homologs that are particularly prone to misfolding and aggregation during *arsenite* exposure. The yeast proteins are highly dependent on chaperones for proper folding, whereas arsenite is capable of inhibiting chaperone function as well as causing additional aggregation through a propagating effect. Computational analyses further revealed that aggregation-prone proteins are abundant and have a high translation rate, but are down-regulated when the cell encounters arsenite.

The mechanisms behind *tellurite* toxicity have eluded scientists for over a century. By using a genome-wide phenotypic screen, it was found that tellurite toxicity is linked to accumulation of elemental tellurium. Sulfate metabolism and mitochondrial respiration were found to mediate toxicity.

An understanding of cellular function requires knowledge of the evolutionary processes that have formed it. However, distinguishing between adaptive and non-adaptive differentiation remains an extraordinary challenge within evolutionary biology. The last part of this thesis tests a method for exposing the role of natural selection in evolution of stress tolerance. Analysis of concerted optimization of performance in distinct fitness components followed by mapping of the genetic basis for the optimizations, compellingly suggests that the method is able to detect natural selection.

The results presented here are likely to be relevant in gaining a better understanding of the mechanisms behind arsenite and tellurite poisoning and cellular defense, and may form a basis for elucidating evolutionary adaptations in other environments and organisms.