Metallochaperone control over metal ion delivery: The copper exchange mechanisms of yeast and human Atx1 with their physiological partner proteins

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Given the paradoxical role of metal ions such as copper – essential yet potentially toxic – it is not surprising that a variety of systems have been found to control the intracellular delivery of these cofactors. Disorders in these metal trafficking pathways can lead to fatal metabolic and neurodegenerative diseases in humans. An emerging picture of regulated intracellular metal ion trafficking has developed recently with the discovery and characterization of a new class of intracellular metal transport proteins, the metallochaperones.

Our goal in the current studies is to establish the energetics, chemical mechanism and physiological functions of the Atx1 family of metallochaperones. The well-characterized yeast copper chaperone Atx1 and its human homolog, Atox1 are known to interact with specific target proteins including Ccc2 in yeast or the Wilson and Menkes disease proteins in humans. Our studies of both the human and yeast partners reveal rapid metal exchange between the partner proteins with a shallow thermodynamic driving force ($K_{eq} < 20$). We have designed new spectroscopic probes to follow copper transfer as well as protein/protein interactions in these systems in order to evaluate kinetic and thermodynamic features of the metal transfer mechanism. Comparison of metal transfer reactions between partner proteins and non-partner proteins may elucidate control mechanisms of intracellular metal ion delivery.