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Studies on Mechanisms of Copper Metabolism Using Comparative Models

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Organisms have evolved to use metal ions as cofactors for many proteins involved in critical biological processes. However, these metals are highly toxic when present in excess or if released in its free reactive form, and environmental contamination by non-physiological metals has been a concern for public health. Consequently, all living life must maintain delicate systems for the homeostasis in metal metabolism and the cellular defense against metal toxicity. My research projects have focused on the mammalian copper transporters. The trace metal copper is an essential micronutrient that is required for mitochondrial ATP generation, free radical detoxification, neurotransmitter synthesis and maturation, and iron metabolism. We have cloned human and mouse plasma membrane Ctr1 copper transporters, and characterized their biochemical properties and physiological roles using biochemistry, cell biology and genetic approaches in an eukaryotic model organism budding yeast, mammalian cell lines and mouse. These studies have demonstrated that Ctr1 is a major player in the acquisition of copper required for the activity of copper-containing enzymes and mouse embryonic development. In addition, Ctr1 copper transporter mediates the cellular uptake of the metal-based anticancer drug cisplatin. The long-term objectives of my current and future research are: 1) to elucidate the molecular mechanisms for metal ion metabolism and 2) to explore the underlying mechanisms of implication of metal ions in biological processes and disease states. The studies will provide insights into metal metabolism and will eventually aid in the development of novel strategies to prevent and treat metal and oxidative stress-related diseases.