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Golgi-Dependent Mechanisms of Cellular Copper Homeostasis

By

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Golgi-Dependent Mechanisms of Cellular Copper Homeostasis

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A.B., Princeton University, 2010

Advisor: Victor Faundez, MD PhD

An abstract of

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Abstract

Golgi-Dependent Mechanisms of Cellular Copper Homeostasis

By Heather Skye Comstra

Copper is required for diverse cellular processes including pigment production, neuropeptide synthesis and mitochondrial function, yet possesses the capacity to inflict oxidative damage to cells. Cells possess a network of chaperones and transporters that maintain appropriate copper levels both for its provision to cuproenzymes and to avoid oxidative damage. Mutations in copper-binding proteins strongly associate with neuropathologies, and neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease exhibit altered copper homeostasis. The cellular trafficking and regulation of copper has traditionally been described as occurring in a discrete, organelle-specific manner, yet emerging research supports a model of copper-sensing and communication taking place between organelles.

I hypothesize that genetic defects in molecules required for the subcellular localization of copper transporters will impair neuronal tissue viability. I define an interaction network for the copper transporter ATP7A and find it is enriched in genes associated with neuropathologies. Among these genes are those encoding subunits of the conserved oligomeric Golgi (COG) complex, a multimeric tethering complex required for retrograde intra-Golgi traffic. I present biochemical and genetic evidence of an interaction between ATP7A and COG, and establish a role for the COG complex in copper homeostasis at multiple cellular compartments. I find that COG null cells display decreased ATP7A levels and perturbed surface expression of both ATP7A and the copper importer CTR1. Further, both copper content and levels of copper-sensitive transcripts are altered in COG null cells. Reduced copper content, measured by inductively coupled plasma mass spectrometry, and impaired mitochondrial function, assayed by the activity of mitochondrial reductases, can be rescued by the addition of copper in conjunction with an ionophore. Finally, ATP7A and COG synthetically interact in *Drosophila melanogaster* to influence viability and the development of the neuromuscular junction.

These data support a model of global cellular copper homeostasis, and the altered copper homeostasis observed in COG null cells suggests a mechanism to account for neurodevelopmental phenotypes in patients bearing COG mutations. The ATP7A interactome offers avenues for future work to elucidate copper homeostasis mechanisms, and the observed interaction between copper homeostasis and mitochondrial function in this work illuminates a possible mechanism in the etiology of copper-related neuropathologies.

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