

Ingenuity[®] Science Spotlight:

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High Copper Selectively Alters Lipid Metabolism and Cell Cycle Machinery in the Mouse Model of Wilson Disease.

Dominik Huster, Tina D. Purnat, Jason L. Burkhead, Martina Ralle, Oliver Fiehn, Franziska Stuckert, N. Erik Olson, Daniel Teupser and Svetlana Lutsenko. *J Biol Chem.* 2007 Jan 7; [Epub ahead of print].

<http://www.jbc.org/cgi/doi/10.1074/jbc.M607496200>

In a recent study published in the *Journal of Biological Chemistry*, researchers from Oregon Health & Science University used IPA to elucidate the molecular and metabolic changes that accompany the initial stages of the metabolic disorder Wilson Disease (WD). IPA analysis of copper-induced gene expression changes in a mouse model of WD enabled molecular characterization of the disease, and initial steps toward the identification of markers of disease progression.

To understand the molecular events associated with the early stages of copper overload in Wilson Disease, the research team measured changes in the hepatic mRNAs in 6-week-old *Atp7b*^{-/-} mice (a mouse model of WD). IPA analysis of copper-specific gene expression changes revealed selective perturbation of the cell-cycle machinery and lipid metabolism. Pathway analysis also revealed that oxidative stress is unlikely to be central to the early, pre-symptomatic stages of the disease. Network analysis further highlighted the impact of elevated copper on SREBP-2 activity, and the subsequent impact of SREBP-2 inhibition on its transcriptional targets.

These studies provide mechanistic insight into the initial stages of pathology induced by copper overload in WD, and may pave the way for detailed analysis of other copper-induced pathologies. The approach outlined by the OHSU team provides a viable strategy for identifying molecular changes and cellular responses specific to WD, which may eventually serve as useful diagnostic tools.