

Identification of Differentially Expressed Proteins in Livers of the Wilson Disease Gene Knock-out Mice using Quantitative Mass Spectrometry

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Wilson disease (WD) is a genetic disorder in which copper accumulates in tissues due to inactivation of the copper-transporting P-type ATPase ATP7B, Wilson Disease Protein. To better understand the mechanism of copper-induced pathologies, we are using the *Atp7b*^{-/-} mice, a genetically engineered animal model for WD. These animals display marked copper accumulation in the liver, which is associated with a series of morphological and biochemical changes culminating in development of cholangiocarcinoma. In the 6 weeks old *Atp7b*^{-/-} livers, copper reaches its highest level, however the pathological changes are still minimal, providing the opportunity to identify the initial molecular targets of copper toxicity. Consequently, we have utilized the liver tissue from the control and *Atp7b*^{-/-} 6 weeks-old mice to perform a quantitative proteomic analysis of differentially expressed proteins. Two major fractions (soluble and membrane proteins) were prepared and each was analyzed using Isotope Coded Affinity Tagging (ICAT) and multidimensional chromatography coupled to tandem mass spectrometry. The differentially expressed proteins were detected and identified. [The work is supported by NIH grant PO1 GM067166]