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EDITORIAL

Wilson Disease: Epigenetic Factors Contribute to Genetic Mutations to Affect the Disease

Wilson disease is caused by autosomal-recessive mutations that affect the copper transporter *ATP7B*, resulting in accumulation of copper in liver, brain, and other organs. Accordingly, hepatic and neurologic manifestations are common presentations of this rare disease. Interestingly, these hepatic and neurologic presentations can vary widely between affected individuals: patients can present with mild hepatitis, cirrhosis, acute liver failure, profound depression, dysarthria, spasticity, involuntary movements, or combinations of signs and symptoms. Although ATP7B mutations define Wilson disease, they do not explain the phenotypic variations and diverse clinical presentations, and no firm correlations between genotype and phenotype exist. For this reason, environmental factors and epigenetic phenomena are thought to contribute to Wilson disease pathogenesis. Previous work from Valentina Medici's group determined that aberrant DNA methylation and abnormal 1-carbon metabolism are present in patients and animal models of Wilson disease.[1] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Sarode et al[2] advance the understanding of Wilson disease by examining the relationship between hepatic copper overload, histone acetylation, and gene expression in an animal model of Wilson disease (Jackson laboratory toxic milk mouse [tx-j]).

The researchers found that protein levels of histone deacetylase 4 and 5 (HDAC4/5) are 5- to 10-fold lower in 12- and 24-week-old tx-j mice compared with control animals. In vitro, copper overload in HepG2 cells reduced HDAC5 levels, and copper reduction by isoproterenol restored HDAC5 expression in a dose dependent manner. Further experiments provide evidence that AMPK increases HDAC phosphorylation, targeting it for cytosolic degradation. Consistent with reduced HDAC4/5 levels, the authors observed dysregulation of histone acetylation: H3ac, H3K9ac, and H3K27ac levels were increased in livers of tx-j mice. Furthermore, supplementing the tx-j mouse diet with methyl donors (via choline) or copper chelation restored levels of HDAC4/5. Integrated analysis of H3K9ac and H3K27ac by ChIP-seq and gene expression by RNA-seq demonstrated altered epigenetic regulation and transcripts of genes involved in energy metabolism and liver regeneration. Peroxisome proliferator-activated receptors (PPARs) are key regulators of energy metabolism and were selected for further analysis. PPAR α and γ were increased in tx-j mice and a high-fat diet further increased PPAR expression. Analysis of downstream targets (fibrosis, antioxidants, fatty acid oxidation) indicated that HDAC5 regulates PPAR α and γ and their associated pathways in Wilson disease.

Genome-wide analyses of patients with Wilson disease and in ATP7b$^{-/-}$ mice have revealed dysregulation of nuclear receptor signaling as an early and preferential consequence of copper toxicity. Pathway analysis and functional studies indicate that the PPAR, Liver X receptor (LXR),[3] and Farnesoid X receptor (FXR)[4] signaling pathways are abnormal in Wilson disease models, and activation of these pathways can correct hepatic disease. The findings in the paper presented by Sarode et al[2] nicely synergize with prior work in this field that seeks to explain the metabolic and lipid dysregulation found in Wilson disease and ultimately may explain its phenotypic diversity. Although alcoholic and nonalcoholic steatohepatitis represent 2 of the most common forms of liver disease in the world, single gene disorders are useful to gain a broader understanding of hepatic pathogenesis. One of the most common pathologic findings in Wilson disease is steatohepatitis. This paper presents crucial information that may help understand the metabolic underpinnings of common liver diseases with similar hepatic presentations.

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Conflicts of interest
The authors disclose no conflicts.


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