Wilson Disease: New Insights into Pathogenesis, Diagnosis, and Future Therapy

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Introduction

Our understanding of Wilson disease, an autosomal recessive disorder of copper metabolism, has changed dramatically over the past century when this disorder was first described. We have learned how to diagnose Wilson disease using clinical and biochemical studies and how to treat afflicted individuals effectively with medicines or liver transplantation. The discovery of the responsible gene, the copper transporting ATPase ATP7B, helped elucidate the molecular basis for the disruption in copper metabolism responsible for this disorder. Our focus has turned toward molecular diagnosis for identification of affected individuals and to the understanding of disease modifiers. Future efforts for treating this disorder will likely include genetic therapy and other novel interventions that may effect a cure for Wilson disease. This review focuses on our evolving understanding of the function of ATP7B in copper metabolism, molecular diagnosis of this disorder, and discussions of the initial studies of gene therapy and hepatocyte transplant trials using an animal model of Wilson disease.

The Wilson Disease Gene Encodes a Copper Transporting ATPase

The recognition that Wilson disease is a genetic disorder inherited in an autosomal recessive fashion predated the discovery of the gene for Wilson disease by over half a century. The carrier frequency for this disorder is about one in 150 to 180 individuals, with a disease prevalence of approximately one in 30,000 in all populations. The gene for Wilson disease, ATP7B, is localized specifically to the long arm of chromosome 13 (13q14.3) [1••,2–4]. The gene product is a copper transporting P-type ATPase, ATP7B, mainly but not exclusively expressed in hepatocytes. ATP7B is thought to be critical for the process of biliary copper excretion and for copper incorporation into ceruloplasmin. Copper is an essential element, and its ingestion, absorption, and excretion involve transport from the intestine, uptake by liver cells, and excretion of excess into bile. Studies in animal models of Wilson disease and in liver cells in vitro have yielded information as to how the ATP7B protein may function in normal individuals and how its malfunction results in hepatic copper accumulation in Wilson disease (Fig. 1A) [5•,6•]. Copper that is transported by hepatocytes derives mainly from the portal circulation and is used for metabolic processes, including incorporation into proteins, such as the cytochrome oxidases and ceruloplasmin, among others. The processes involved in hepatocellular copper trafficking are summarized in Figure 1B. The metal chaperone ATOX1 helps direct the copper to the ATP7B protein in the cytosol, though copper can be bound to glutathione and metallothionein and other peptides. Excess copper is taken up by hepatocytes and excreted from these cells via the apical bile canaliculus. At a steady state of copper balance, the copper transporting ATPase predominantly resides in the trans-Golgi membrane, where it serves to transport copper into this site for incorporation into ceruloplasmin that is bound for export. When intracellular copper concentrations rise, there appears to be a redistribution of some of the ATP7B protein to endosomal or...
prelysosomal vesicles destined for delivery into bile, favoring increased copper excretion [7]. This process of protein redistribution in response to copper was first described by Australian investigators for the Menkes disease gene product [8], another copper transporting ATPase, ATP7A, expressed mainly in extrahepatic cells. The change in the functional subcellular site for the protein accounts for its predominant function—to distribute copper to synthetic sites in the Golgi—or to serve as a portal into pathways for biliary copper excretion. Absence or malfunction of ATP7B results in reduced biliary copper excretion and toxic accumulation of copper in the liver and brain that leads to clinical disease. A failure of the normal rate of copper incorporation into ceruloplasmin leads to the secretion of the peptide without copper that has a shorter half-life, leading to the reduced steady-state concentration of ceruloplasmin in the circulation of most patients with Wilson disease.

The ATP7B protein has several features that are common to many other ATPases, but unique to the class of metal binding ATPases are the presence of cysteine-rich metal binding sites on the amino terminus of the protein and another region that contains the sequence cysteine, praline, and cysteine in a membrane spanning region that may serve as the site for metal transfer across membranes.