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The effect of zinc and D-penicillamine in a stable human hepatoma ATP7B knockout cell line.

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Author information

Abstract

Mutations in the copper (Cu) transporter gene ATP7B, the primary cause of Wilson disease (WD), result in high liver Cu and death of hepatocytes. Cu chelators and zinc salts are the two most important drugs used in the treatment of WD patients; however, the molecular mechanisms of the drugs with regard to ATP7B expression have not been determined. A targeted knockout of ATP7B (KO) was established in the most widely used human hepatoma cell line, HepG2 for molecular studies of the pathogenesis and treatment of the disease. KO cells showed similar growth, Cu uptake, release, and gene expression as compared to parental cells. However, in the presence of Cu, morphological changes, oxidative stress, apoptosis, and loss of viability were observed. Induction of metallothionein (MT1X) after Cu exposure was significantly reduced in KO cells. Following zinc treatment, MT1X expression was strongly induced and a high percentage of KO cells could be rescued from Cu induced toxicity. D-penicillamine treatment had a minor effect on the viability of KO cells whereas the parental cell line showed a pronounced improvement. Combined treatment displayed a highly synergistic effect in KO cells. The data suggest that zinc has a previously unrecognized effect on the viability of hepatocytes that lack ATP7B due to a high induction of MT1X expression that compensates low gene expression after Cu exposure. A combination therapy that simultaneously targets at MT1X induction and Cu chelation improves the overall survival of hepatocytes for most efficient therapy of patients having WD.

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