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Commentary

Intricacies and Significance of Hepatic Copper Transporter CTR1

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DESCRIPTION

Hepatic copper transport is the process of moving copper from the blood into the liver and from the liver into the bile. Copper is an essential trace element that is involved in various biological functions, such as energy production, iron metabolism, antioxidant defense, and neurotransmission. However, excess copper can be toxic and cause oxidative stress, cellular damage, and inflammation. Therefore, hepatic copper transport is important for maintaining copper homeostasis and preventing copper overload. The first step of hepatic copper transport is the uptake of copper from the blood into the hepatocytes, the main functional cells of the liver. Copper in the blood is mostly bound to Ceruloplasmin (CP), a copper-containing enzyme that oxidizes ferrous iron to ferric iron for incorporation into transferrin. A small fraction of copper is bound to albumin or transcuprein, low-affinity copper-binding proteins that deliver copper to tissues that need it. The uptake of copper into hepatocytes is mediated by a membrane protein called CTR1 (copper transporter) which belongs to the solute carrier family. CTR1 is a high-affinity copper transporter that forms a homotrimeric channel on the plasma membrane and transports both cuprous and cupric ions into the cell. CTR1 expression is regulated by cellular copper levels, with higher expression under copper deficiency and lower expression under copper excess. After entering into hepatocytes, copper is not free in the cytosol but bound to specialized proteins called metallochaperones, which shuttle copper to its destination molecules. There are three main metallochaperones in hepatocytes:

- ATOX1 (antioxidant 1),
- CCS (copper chaperone for superoxide dismutase), and
- COX17 (copper chaperone for cytochrome c oxidase).

ATOX1 is responsible for delivering copper to the Trans-Golgi Network (TGN), where two copper-transporting ATPases reside: ATP7A and ATP7B. These ATPases are members of the P-type ATPase family that use ATP hydrolysis to transport metal ions across membranes. ATP7A and ATP7B have similar domain structures, consisting of six transmembrane segments, a large cytoplasmic loop with six Metal-Binding Domains (MBDs), andan ATP-Binding Domain (ATPase) at the C-terminus. ATP7Aand ATP7B have different functions and distributions in hepatocytes. ATP7A is mainly located in the TGN and mediates the incorporation of copper into CP and other secretory proteins, such as hephaestin and lysyl oxidase. ATP7A also transports excess copper out of the cell via transcytosis or exocytosis. ATP7B is normally located in the TGN as well, but it can relocate to vesicular compartments or the canalicular membrane (the apical membrane of hepatocytes that faces the bile duct) when cellular copper levels increase. ATP7B mediates the export of excess copper into the bile by loading it onto metallothioneins (MTs), low-molecular-weight cysteine-rich proteins that bind various metals with high affinity. CCS is responsible for delivering copper to SOD1 (superoxide dismutase, cytosolic enzyme that converts superoxide radicals to hydrogen peroxide and oxygen. SOD1 requires one atom of copper and one atom of zinc for its catalytic activity. CCS binds both metals and transfers them to SOD1 in a sequential manner. COX17 is responsible for delivering copper to COX (cytochrome c oxidase), a mitochondrial enzyme that transfers electrons from cytochrome c to oxygen as part of the respiratory chain. COX requires two atoms of copper for its catalytic activity: one in subunit I (COX1) and one in subunit II (COX2). COX17 binds one atom of copper and transfers it to SCO1 or SCO2, two proteins that facilitate the insertion of copper into COX subunits.

CONCLUSION

The final step of hepatic copper transport is the excretion of excess copper from hepatocytes into bile. This step is critical for maintaining whole-body copper balance, as biliary excretion accounts for about 98% of total copper elimination. The main protein involved in this step is ATP7B, which interacts with COMMD1 (copper metabolism MURR1 domain-containing, protein that regulates intracellular trafficking and stability of ATP7B. COMMD1 facilitates the translocation of ATP7B from the TGN to vesicular compartments or the canalicular membrane when cellular copper levels are high. In these locations, ATP7B loads excess copper onto MTs, which are thensecreted into bile. MTs can bind up to seven atoms of copper per molecule and protect the bile duct from copper-induced damage.

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