The Role of Trafficking of Cu-ATPases in mammalian copper homeostasis

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Copper homeostasis is tightly regulated to provide copper-dependent enzymes with copper without concomitant generation of free radicals. Cells maintain safe levels of copper by regulating both uptake and efflux of copper. The efflux mechanism involves the Cu-ATPases, ATP7A and ATP7B, proteins that are affected in the genetic copper disorders Menkes and Wilson diseases respectively. These Cu-ATPases have several roles in copper homeostasis: they provide copper to secreted cuproenzymes by pumping the ion into the lumen of the transGolgi network vesicles; they efflux copper from cells; and ATP7A has a role in transporting copper across epithelial barriers such as the intestinal epithelium and the blood brain barrier. The particular role played by these enzymes is determined in part by their intracellular location, which in turn is regulated by the copper status of the cell. In low copper environments, the Cu-ATPases are located on the transGolgi network, but when cytoplasmic copper rises, the ATPases traffic to the plasma membrane (ATP7A) or vesicles (ATP7B), and from this location copper is effluxed from the cell.

We have been studying the molecular basis of the trafficking of the Cu-ATPases and the importance of this process in maintaining physiological copper balance. By expressing normal and mutant forms of the Cu-ATPases in cultured cells the effect of mutations on the intracellular location and trafficking of these proteins is being assessed. This talk will focus on recent work with ATP7B that indicates that it traffics to a subapical vesicle compartment, and this trafficking may depend on copper binding to an unidentified copper binding site on the molecule. In addition, analysis of mice with mutations in Atp7a or Atp7b, and transgenic mice that express human ATP7A, is providing evidence for the physiological role of the copper ATPases and the importance of copper-induced trafficking for maintaining physiological copper balance.