

The role of copper transport proteins in body copper homeostasis.

Francois Monty, Maree Bilandzic, Roxanna M. Llanos, Julian F. Mercer, and David Kramer.

Centre for Cellular and Molecular Biology, Deakin University Burwood 3125, Victoria, Australia

Copper ions are essential for maintaining cellular and physiological functions but excess levels are potentially toxic. Ctr1 (copper transporter-1) and ATP7A (Menkes protein) are copper transporters that are required for intestinal uptake and total body copper homeostasis. However, little is known about how intestinal copper absorption may be regulated. We produced a transgenic mouse expressing the human *ATP7A* cDNA to study the role of ATP7A in dietary copper uptake. We employed a perfusion technique to assess the affect of copper exposure on the cellular location of ATP7A and Ctr1 in the intestines of ATP7A transgenic and control mice. ATP7A exhibited a dose dependent response to copper involving a shift in its steady state location from a perinuclear arc to sub-basolateral vesicles. Ctr1 was found to be localized on the apical membrane of the small intestine in low copper exposures but was seen to shift to vesicular structures upon copper challenge. ATP7A and Ctr1 protein levels were unaffected after short-term copper-challenge. Our results indicate that the response of ATP7A to high copper exposure promotes the uptake of copper into the circulation. The alternative possibilities that the internalisation of Ctr1 upon copper exposure represents a functional mechanism to enable copper uptake or is a protective regulatory mechanism will be discussed.