# Diverse roles of the metal binding domains and transport mechanism of copper transporting P-type ATPases

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Copper transporting P-type ($_{P1B-1}$-) ATPases are essential for cellular homeostasis. Nonetheless, the E1-E1P-E2P-E2 states mechanism of $P_{1B-1}$-ATPases remains poorly understood. In particular, the role of the intrinsic metal binding domains (MBDs) is enigmatic. Here, four cryo-EM structures and molecular dynamics simulations of a $P_{1B-1}$-ATPase are combined to reveal that in many eukaryotes the MBD immediately prior to the ATPase core, $MBD^{-1}$, serves a structural role, remodeling the ion-uptake region. In contrast, the MBD prior to $MBD^{-1}$, $MBD^{-2}$, likely assists in copper delivery to the ATPase core. Invariant Tyr, Asn and Ser residues in the transmembrane domain assist in positioning sulfur-providing copper-binding amino acids, allowing for copper uptake, binding and release. As such, our findings unify previously conflicting data on the transport and regulation of $P_{1B-1}$-ATPases. The results are critical for a fundamental understanding of cellular copper homeostasis and for comprehension of the molecular bases of $P_{1B-1}$-disorders and ongoing clinical trials.