Molybdenum Cofactor Biosynthesis: The Mechanism of Metal Transfer to Molybdopterin Involves Copper

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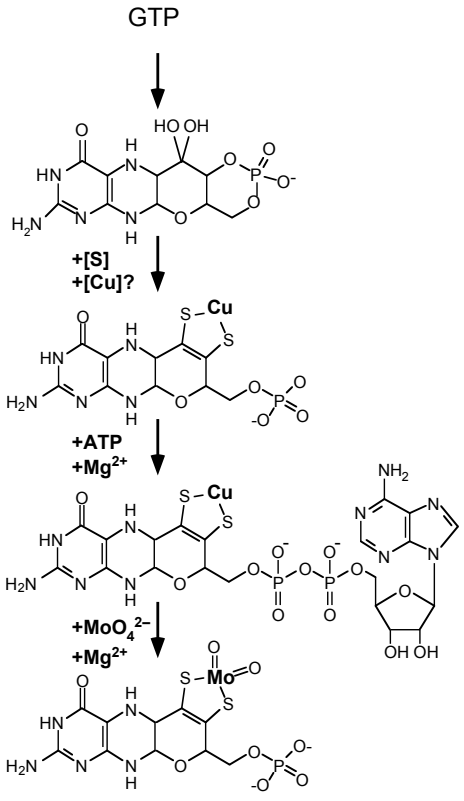
The molybdenum cofactor (Moco) is part of the active site of all molybdenum (Mo)-dependent enzymes, except nitrogenase. As catalytic center Moco plays important roles in the global carbon, sulfur and nitrogen cycles. Mo enzymes are important for diverse metabolic processes, like sulfur detoxification and purine catabolism in mammals or nitrogen assimilation and phytohormone synthesis in plants. Human Moco deficiency results in the pleiotropic loss of all Mo enzyme activities with neurological abnormalities and early childhood death. Moco is synthesized by a highly conserved multi-step biosynthetic pathway. In plants, the multi-domain protein Cnx1 catalyzes the insertion of Mo into molybdopterin (MPT), the metal-free precursor of Moco. The Cnx1 G domain (Cnx1G) binds MPT with high affinity. Two high-resolution crystal structures of Cnx1G in complex with MPT and with adenylated MPT (MPT-AMP), a novel mechanistically important intermediate, will be presented. MPT-AMP is the reaction product of Cnx1G, which adenlytes MPT in a Mg-ATP-dependent manner. MPT-AMP is subsequently processed in an Mg- and molybdate-dependent reaction by the C-terminal E domain of Cnx1 thus yielding active Moco. Furthermore, in both complex structures of Cnx1G copper has been identified as novel MPT ligand occupying the position of Mo. The unexpected identification of copper and the observed copper inhibition of Moco synthesis provide a molecular link between molybdenum and copper metabolism.



Moco biosynthetic pathway