Copper Binding Properties of Mets Motifs Found in Copper Transport Proteins

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Copper is required in virtually all cell types from bacteria to humans and is involved in such critical processes as electron transport, free radical detoxification, neurotransmitter production and others. Cells have elaborate systems for copper transport and distribution, starting with its acquisition from the extracellular environment to cellular uptake, delivery to end-point cuproenzymes, recycling and clearance. In order to elucidate the molecular mechanisms by which cells acquire copper, we are investigating the copper binding interactions of peptide sequences that are found on the extracellular region of high-affinity copper transport proteins in the Ctr family.

The amino-terminal region of Ctr1, which is the gate of entry for cellular copper, contains no cysteine or histidine residues. Instead, its unique feature is the presence of methionine-rich domains arranged as MXXM or MXM motifs containing 3–5 methionine residues per "Mets" motif. Yeast Ctr1 has 8 Mets motifs, with a total of 30 methionine residues in the extracellular domain. We have synthesized a series of MX_2MX_2M peptides and investigated their copper-binding properties by mass spectrometry, UV-vis spectroscopy and cyclic voltammetry. We have determined that Mets peptides bind selectively to Cu(I) with impressive affinity. Removing even one of the methionine residues abolishes this capability and establishes the MX_2MX_2M motif as a Cu(I) binding domain.