Novel model peptides for Atx1-like metallochaperones

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The CXXC binding motif is often encountered in metallo-proteins for the complexation of various ions (Fe$^{2+}$, Ni$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Pb$^{2+}$, Hg$^{2+}$) which can be either essential or toxic for living organisms. For instance, the metallochaperone Atx1 (73 amino acids) binds copper in the $+1$ oxidation state by means of a MXCXXC motif which is conserved in many soft-metal transporters. Proteins containing this motif seem highly selective in vivo, it is therefore important to investigate the factors that govern this selectivity.

We report here the design of a novel peptide that mimics the Atx1 binding loop. The 10-mer cyclodecapeptide c(GMTCSGCSRP) (1.H$_2$ Figure 1) provides the binding sequence MTCSGCS of the copper-chaperone, as well as a XPGX motif able to form a $\beta$-turn which rigidifies the peptide structure and act as an anchor for the metal binding site.

The solution structure of the apo form presents a MTCSGCS binding loop which is rather flexible, like its counter-part in apo-Atx1. The solution structure of the mercury (II) loaded form shows that the cyclodecapeptide reproduces the first and second coordination sphere interactions found in Atx1, demonstrating that it is a good structural model for the chaperone.

This peptide was also used to evaluate the selectivity of Atx1-like metallochaperones for several metal cations. Metal-binding titrations were performed to measure the affinity of 1 for Hg$^{2+}$, Cu$^+$, Pb$^{2+}$, Cd$^{2+}$ and Zn$^{2+}$.