Novel model peptides for Atx1-like metallochaperones

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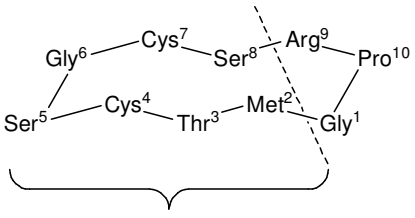
The CXXC binding motif is often encountered in metallo-proteins for the complexation of various ions (Fe^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}) which can be either essential or toxic for living organisms. For instance, the metallochaperone Atx1 (73 amino acids) binds copper in the +I oxidation state by means of a MXCXXC motif which is conserved in many soft-metal transporters.[1] 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 β-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.[2]

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+}.

1. Pufhal, R. A.; Singer, C. P.; Peariso, K. L.; Lin, S.-J.; Schmidt, P. J.; Fahrni, C. J.; Culotta, V. C.; Penner-Hahn, J. E.; O'Halloran, T. V. *Science* **1997**, 278, 853-856.

2. Sénèque, O.; Crouzy, S.; Boturyn, D.; Dumy, P.; Ferrand, M.; Delangle, P. *Chem. Commun.* **2004**, 769-770.