Contribution ID: **27** Type: **Submitted**

Metal ion interaction of peptides imitating the metal binding domain of CueR metalloregulatory proteins

Wednesday 27 November 2013 11:50 (20 minutes)

Metalloregulatory proteins are key elements of bacterial metal homeostasis and resistance regulating the metal ion transport/storage/detoxification systems at a transcriptional level. The copper-efflux regulator CueR belongs to the MerR protein family the members of which are dimers and all possess a characteristic short metal binding domain close to the C-terminus of each monomer. The sequential/structural diversity found in this Cys-Xn-Cys (n = 6-10) loop is a key factor in allowing the sensing of a variety of metal ions [1] and in many cases, the selection of the cognate ones. CueR exhibits an outstanding selectivity for monovalent group 11 metal ions but no transcriptional regulation activity for Hg(II) or Zn(II).[2] It was shown that the thiolate donor groups of the metal binding loop restricts the metal ions into a linear coordination geometry, but besides this, other factors were also suggested to play a role in distinguishing between divalent and monovalent ions. To have a better understanding of this metal ion selectivity we have synthesized oligopeptides comprising fully or with slight modifications the metal binding loop of various CueR proteins and investigated their interaction with the group 12 metal ions Zn(II), Cd(II) and Hg(II). pH-potentiometry, UV-titrations, SRCD, NMR and 199mHg PAC spectroscopy (performed in the ISOLDE Facility at the CERN) have all been applied to monitor whether Asp or His residues, besides the Cys units of the ligands, or the flexibility of the sequences may significantly influence the metal binding features. We have found that while Hg(II)-binding takes place via the sulfur donors of the Cys-thiolates only, side chains of His and/or Asp also play a role in coordinating Cd(II) and Zn(II).[3] Preliminary results on the Ag(I)-binding of one of the peptides suggests surprising differences in the binding modes of Ag(I) and Hg(II). While further experiments with the peptides and monovalent metal ions (studies with Cu(I) are also planned) are in progress, we are also working on the synthesis of the native CueR of E. coli. Comparison of the metal binding features of the macromolecule and the related peptides is likely to provide answers for the question: on what level the metal ion recognition really occurs.

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Acknowledgements: HURO/1001/232/2.2.2-METCAP, TÁMOP-4.2.2/B-10/1-2010-0012, János Bolyai Research Grant (Hungarian Academy of Sciences).

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Session Classification: Applications II