Structural Biology and Metallochemistry of Neurodegenerative diseases: The case of α-Synuclein

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Many proteins associated with neurodegenerative diseases (PrP, APP, Aβ peptide and SOD-1) have metal binding properties. In the documented examples metal binding relates to pathogenesis via an impact on aggregation or production of oxidative damage. Thus, defining binding sites and the molecular details of complex formation may provide important and practical insights into pathogenic processes and neuronal biology. The objective of our study was to elucidate the structural features of α-Synuclein[1,2] and establish the role of metal ions in synucleinopathies at the molecular resolution currently available for other amyloidoses[3,4]. The interaction of divalent metal ions with α-synuclein were studied under physiologically relevant conditions using a battery of low and high-resolution spectroscopic techniques (CD, EPR and NMR) and chemical modification.[3,4] Protein-metal interactions were characterized at single-residue resolution by NMR. The influence of metals on inducing α-synuclein fibrillation was strongly linked to their binding properties. A comparative analysis reveals a hierarchy in protein-metal interactions, dictated by structural factors involving different domains of the protein.[1-4] The new insights into the structural basis of copper interaction with α-synuclein support a tighter link with other amyloid-related disorders such as Alzheimer's disease and prion disease, indicating that perturbations in copper metabolism may constitute a more widespread element in neurodegenerative disorders than recognized previously.

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[2] Bertoncini *et al*, *Proc Natl Acad Sci USA* **2005**, 102, 1430-1435.
[3] Rasia *et al*, *Proc Natl Acad Sci USA* **2005,** 102, 4294-4299
[4] Binolfi *et al*, *J Am Chem Soc* **2006**, 128, 9893-901