Summary

Metal swap between Zn_7-metallothionein-3 and amyloid-β-Cu protects against amyloid-β toxicity *

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Alzheimer disease (AD) is the most diffuse age-dependent neurodegenerative disorder and the most common cause of dementia, affecting nearly 2% of the population in industrialized countries and up to 40% of individuals over the age of 85. Clinical pathological hallmark of AD is the progressive loss of memory and other high cognitive functions. The microscopic main hallmarks of AD brains are the presence of extracellular amyloid senile plaques and intracellular neurofibrillary tangles of aberrantly phosphorylated Tau, a microtubule-associated protein. Amyloid senile plaques are extracellular depositions of 39-43 amino acid β-amyloid peptides (Aβ) generated by a proteolytic cleavage of the membrane amyloid precursor protein (APP). Essential transition metals are involved in AD progression by modulating the formation and toxicity of soluble and insoluble oligomers and aggregates of Aβ peptide. Whereas the copper-induced Aβ aggregation potentiates the reactive oxygen species (ROS) production, oxidative stress and neurotoxicity, the zinc-induced Aβ aggregation is neuroprotective. A small intra- and extracellularly occurring metalloprotein, metallothionein-3 (Zn_7MT-3), is highly expressed in the brain where it plays an elusive role in regulation of zinc and copper homeostasis. MT-3 is downregulated in AD and, by an unknown mechanism, protects neurons from aberrant neuritic sprouting and from the toxicity of Aβ. By using complementary spectroscopic, biochemical, and cell biological techniques we discovered that Zn_7MT-3 not only scavenges free Cu(II) ions, but is capable to remove Cu(II) abnormally bound to Aβ. A metal swap between Zn_7MT-3 and soluble and aggregated Aβ-Cu(II) is the underlying mechanism by which the ROS production and related cellular toxicity is abolished. In this process, copper is reduced by the protein thiolates forming $Cu(I)_4Zn_4$MT-3, in which an unusual redox silent $Cu(I)_4$-thiolate cluster and two disulfide bonds are generated. The peculiar reactivity and structural properties of metal-thiolate clusters in MT-3 afford the bases for the metal swap reaction thus conferring to the protein its neuroprotective function. In light of this finding, therapeutic strategies pointing towards induction of MT-3 expression or drug design mimicking the metal coordination properties of MT-3 represent new venues to be explored for the treatment of AD.

* G. Meloni, V. Sonois, T. Delaine, L. Guilloreau, A. Gillet, J. Teissié, P. Faller, M. Vašák (2008), *Nat. Chem. Biol.*, 4, 366-372