DEPARTAMENT
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Cicle de conferències de química

The function of metallothionein-3 in the brain is closely related to dynamics and reactivity of its metal-thiolate clusters

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Zinc and copper homeostasis plays a crucial role in brain physiology and in neurodegenerative diseases. Metallothionein-3 (Zn_7MT-3), a small cysteine- and metal-rich protein, is mainly expressed in the brain and is downregulated in Alzheimer's (AD) and prion diseases. This intra- and extracellularly occurring protein plays an important role in zinc and copper metabolism under physiological and pathological conditions. With the aim of gaining insights into the mode of action of Zn_7MT-3 at the molecular level, we have conducted structural and biochemical studies on recombinant M^{II}_7MT-3. By using EXAFS, CD, MCD and ^{113}Cd NMR of M^{II}_7MT-3 the existence of highly dynamic $M^{II}_4(CysS)_{11}$- and $M_3(CysS)_9$-clusters localized in two mutually interacting α- and β-domains, respectively, was demonstrated. Intracellular Zn_7MT-3 is present in high amounts in zinc-enriched neurons that release zinc from their synaptic terminals. A specific binding of Zn_7MT-3 to the small GTPase Rab3A indicates that Zn_7MT-3 actively participates in this process. In the brain, a major source of reactive oxygen species (ROS) derives from redox cycling of Cu(II). The involvement of copper catalyzed oxidative stress in neurodegenerative disorders such as Alzheimer, Parkinson and prion diseases is now well established. In AD brains, the ROS production is strictly linked to Cu(II) binding to Aβ peptides. This metal is also responsible for a copper-induced Aβ aggregation into amyloid senile plaques. The protective effect of extracellular Zn_7MT-3 from Aβ toxicity in neuronal cell cultures has been demonstrated, but its origin is not understood. We found that a metal swap between Zn_7MT-3 and soluble and aggregated Aβ-Cu(II) is the underlying mechanism by which the ROS production and the related cellular toxicity is abolished. In this process, Cu(II) is reduced by protein thiolates forming $Cu(I)_4Zn_4$MT-3, in which an air stable $Cu(I)_4$-thiolate cluster and two disulfide bonds are present. In a similar process Zn_7MT-3 removes Cu(II) from prion peptides. The studies provide insights into the protective role of Zn_7MT-3 from Cu(II) toxicity in the brain.

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