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Metal-associated amyloid-β species in Alzheimer's disease

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Highly concentrated metals such as Cu, Zn, and Fe are found in amyloid-β (Aβ) plaques within the brain of Alzheimer's disease (AD). *In vitro* and *in vivo* studies have suggested that metal binding to Aβ could facilitate Aβ aggregation and generate reactive oxygen species (ROS), which could contribute to the neuropathogenesis of AD. The connection between metal–Aβ interaction/reactivity and AD development, however, has not been clearly revealed owing to the complexity of the disease. In this review, metal–Aβ interaction/reactivity and its relation to neurotoxicity are briefly discussed. Additionally, our review illustrates the recent progress of small molecules, capable of targeting metal–Aβ species and modulating their interaction/reactivity, which could offer a promising approach to interrogate their role in AD.

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and affects approximately 5 million people in the United States [1]. Within the regions of the hippocampus and cortex, shrinkage can be observed along with an increase in ventricle pore size. Furthermore, diseased brains present the accumulation of amyloid-β (Aβ) peptide aggregates and neurofibrillary tangles, indicative of pathogenesis [2••,3••]. One well accepted hypothesis of AD is the 'amyloid cascade hypothesis,' which states that Aβ and its aggregated forms (*e.g.*, oligomers, protofibrils, fibrils) could cause toxicity leading to neurodegeneration [2••,3••,4]. Possible explanations for the accumulation of Aβ aggregated species may be excessive production of Aβ or the collapse of the Aβ clearance pathway [5,6]. In addition to deposition of Aβ aggregates, elevated levels of metals such as Cu, Zn, and Fe are localized with senile plaques, mainly composed of Aβ peptides [3••,7••,8,9••,10•]. These metals are suggested to have a relation to AD neuropathogenesis, namely, in the aggregation of Aβ peptides and the formation of reactive oxygen species (ROS), which could lead to oxidative stress and further neuronal death [3••,7••,8,9••,10•,11•,12,13,14•,15]. It, however, remains unclear whether and how metal-associated Aβ (metal–Aβ) species could be involved in the initiation and progression of AD. Herein, we present a concise discussion of the current understanding of Aβ generation/aggregation, metal–Aβ interaction/reactivity, metal–Aβ-involved neurotoxicity, and advances in small molecules for elucidating the contribution of metal–Aβ species to AD pathology.

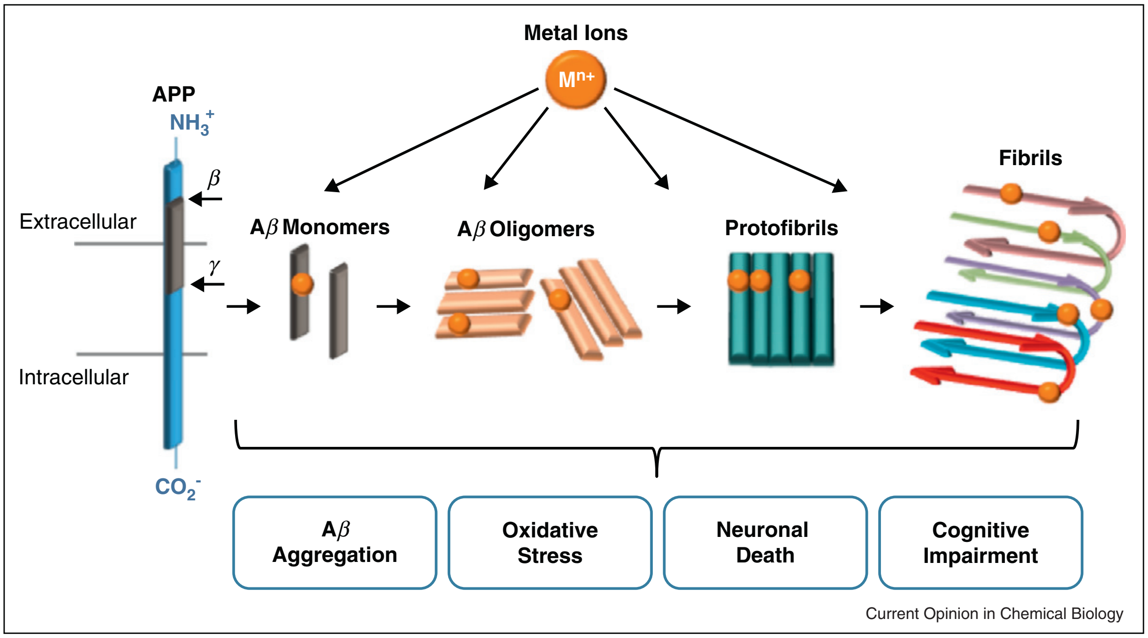
Amyloid-β (Aβ)

Monomeric Aβ peptides (39–43 amino acids in length) are generated *via* the cleavage of amyloid precursor protein (APP) by β-secretases and γ-secretases (Figure 1) [2••,3••,4,7••,14•]. These peptides are composed of a hydrophilic *N*-terminal region (1–28) and a hydrophobic *C*-terminal region (29–39/43). Two common forms of amyloidogenic Aβ peptides found in the AD brain are Aβ_{1-40} and Aβ_{1-42}, with present indication being that Aβ_{1-42} is the predominant component in senile plaques; it is also considered to be more toxic than Aβ_{1-40} [2••,3••,4,7••]. The generated monomeric Aβ species have the capability to aggregate, mainly through hydrophobic interactions [3••]. Residues Leu17–Ala21 and Gly29–Met35 have been suggested to form an internal β-sheet structure, which is stabilized by a salt bridge (residues Glu22/Asp23 and Lys28). Leu17–Ala21 have been proposed to be a self-recognition site for other Aβ species, which can be important in forming Aβ aggregates *via* hydrophobic interactions. The continued interaction of Aβ monomers and oligomers with these aggregated species could lead to higher order structures such as fibrils through hydrophobic and hydrogen bonding interactions (Figure 1) [3••]. Recent reports indicate that low molecular weight oligomeric Aβ species may be the most relevant to AD pathogenesis [3••,14•,16]. It is, however, still not completely understood which conformation of Aβ species is responsible for the pathology of AD.

Metal ions and Aβ

Metal ions play essential roles throughout the body, especially in the brain [7••,17–20]. Maintaining the homeostasis and compartmentalization of metal ions in the brain is necessary for proper neurological functions. Evidence has demonstrated that transition metals such as Cu, Zn, and Fe are found in high micromolar to low millimolar concentrations in amyloid plaques (*ca.* 0.4 mM for Cu, 1 mM for Zn, and 0.9 mM for Fe)

Figure 1



Scheme of the generation of amyloid-β species (Aβ) and the potential involvement of metal ions associated with Aβ species in Alzheimer's disease (AD). Amyloid precursor protein (APP) undergoes cleavage *via* β-secretases and γ-secretases to produce monomeric Aβ species. Aβ monomers tend to aggregate (*e.g.*, oligomers, protofibrils, fibrils). Metal ions are shown to interact with Aβ species, facilitating Aβ aggregation and enhancing reactive oxygen species (ROS) generation, which can lead to oxidative stress, neuronal death, and cognitive impairment.

[3••,7••,14•,20,21•,22]. This observation may serve as a link to explain metal ion dyshomeostasis in the AD brain.

Copper (Cu) exists under physiological conditions in both reduced (Cu(I)) and oxidized (Cu(II)) forms and is controlled tightly by biological ligands (*e.g.*, proteins) [17–19]. Zinc, on the contrary, is not redox active and exists as Zn(II) in biological systems. Both Cu and Zn ions have been found to serve a role in neurotransmission activity and are present in micromolar concentrations in the synaptic cleft [7••,9••,19,20,21•]. Also, Cu and Zn have been shown to co-purify with Aβ plaques in *post mortem* brains. Different from Cu and Zn, Fe has not been determined to co-purify with Aβ, but is still present in high amounts in Aβ plaques [7••,22]. Taken together, the findings of the abundant levels of Cu, Zn, and Fe in Aβ plaques have triggered extensive investigations of metal–Aβ interaction/reactivity and its implications in AD pathology.

Through a variety of techniques, Cu(II) and Zn(II) have been shown to interact with Aβ in a 1:1 metal to Aβ binding stoichiometry; however, binding modes and coordination environments of metal ions in Aβ are variable and highly dependent on experimental conditions [14•,23••,24••,25–27]. Although pH-dependent coordination of Cu(II) to Aβ can be observed, two forms exist primarily in the physiological pH range: component I (between pH 6.0 and 8.0) and component II (slightly above pH 8.0). At pH 7.4 (physiological pH), it has been observed that Cu(II) binding to Aβ involves three nitrogen donor atoms and one oxygen donor atom (3N1O, component I). In this binding mode, the nitrogen donor atoms are possibly from three histidine (His) residues (His6, His13, and His14) or two His ligands and the amine of the *N*-terminal region. Based on EPR and isotopic labeling studies the source of the oxygen donor atom has been proposed to be most probably from Asp1 in both nitrogen binding modes [28]. Ligands in component I have been suggested to be interchangeable leading to a dynamic coordination environment [26]. At pH *ca.* 8.0, metal binding (component II) could occur *via* three His residues (nitrogen donor atoms) and the carbonyl group of Ala2 (oxygen donor atom) or a combination of the *N*-terminal amine, a His residue, and amide (deprotonated, nitrogen donor atom) and carbonyl groups from Ala2 [14•,23••,24••,25–28]. It has also been proposed that the four coordinating ligands in component II are the *N*-terminal amine or a deprotonated backbone amide with three His residues. In the case of Zn(II), the metal ion has shown to bind to Aβ *via* three His residues, but a total of four to six coordinating ligands on the metal center has been suggested [7••,14•,23••,24••]. Other ligands proposed to be involved in Zn(II) binding are Asp1, Glu11, and possibly, Arg5. Unlike Cu(II) and Zn(II), relatively less has been known about the coordination