Metal ions and beta amyloid: conformational modifications and biological aspects

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Abstract

Many molecular modifications such as senile plaques and neurofibrillary tangles are known to be associated with Alzheimer's disease and other neurodegenerative diseases. In this connection, metal dyshomeostasis has aroused great interest and considerable support in recent years as relevant pathological cofactors of neurodegeneration. It has been largely demonstrated both in vivo and in vitro that aberrant metal ion metabolism can lead to the development and/or worsening of several neurological disorders. In this chapter, we will focus recent biophysical findings on β-amyloid structural modifications triggered by metal ions and we will provide insights into the biological consequences of these phenomena.

Keywords

Alzheimer • Amyloid • Neurological disorders • Metals and brain • Aluminium

Abbreviations

AD	Alzheimer's disease
Aβ	β-amyloid
BBB	Blood–brain barrier
ESI-MS	Electrospray ionisation mass spectrometry
β-APP	β-amyloid precursor protein
τ	τ (tau) protein

Introduction

Biological systems rely on a huge number of protein interactions as they undergo a wide diversity of physiological functions. This is the case, for instance, for the ionotropic glutamatergic receptor, where its full function relies on the correct subunit arrangement for the formation of highly ion-specific tetrameric structures.

Although the cell quality-control systems provide for the correct folding of proteins during cell life, proteins miss-folded can still aggregate, which leads to a series of pathologies known as the "*conformational diseases*" including Parkinson's disease, Huntington's disease, prion disease, amyotrophic lateral sclerosis and Alzheimer's disease (AD) [1]. In particular AD is characterised by the miss-folding, aggregation and deposition of two proteins: tau (τ), a microtuble-associated protein, and β-amyloid (Aβ), a proteolytic cleavage by-product of the Aβ precursor protein (β-APP) [2].

Over the last two decades, a large amount of data has been reported in the literature relating to Aβ production and aggregation, and to its interactions with other sub-cellular elements. Despite this, the trigger(s) that sets off Aβ production and accumulation is not entirely understood, as well as its interactions with the τ protein.

In this review, we provide an insight into the roles of metal ions in Aβ aggregation and into some of the biological and pathological aspects of this phenomenon.

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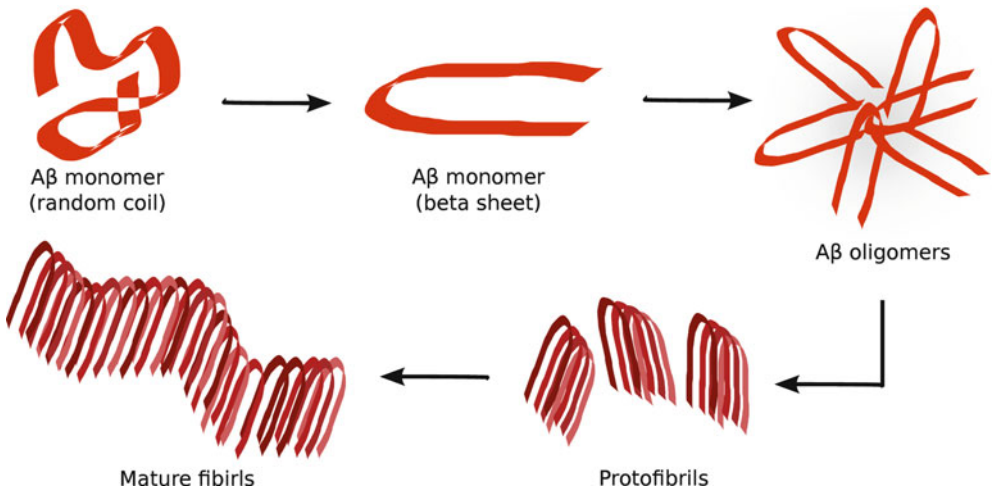

Fig. 1 The Aβ aggregation process follows a well-defined pathway. First, the Aβ monomers with a random-coil structure acquire a β-sheet conformation. Then, these monomers aggregate into oligomeric structures that contain a variable number of Aβ peptides (i.e. 2–50). These oligomers turn into higher ordered structures known as protofibrils, and then these protofibrils lead to the formation of mature fibrils that deposit as senile plaques

From β-amyloid to senile plaques

Aβ is a 39–43 amino-acid peptide and it is the main constituent of senile plaques. In patients with AD, the most common forms of Aβ have 40 or 42 amino acid residues, with the latter as the most amyloidogenic and prone to aggregation [3]. As mentioned earlier, Aβ derives from β-APP, which is itself a 695–770 amino-acid-residue transmembrane protein that has a physiological role that still remains largely unknown; the involvement of β-APP in metal homeostasis and cell trafficking and signalling has been proposed [4].

The metabolism of β-APP involves three enzymes: the α-, β- and γ-secretases. Only when β-APP is cleaved by the last two of these Aβ is formed. This is the so-called *amyloidogenic pathway* [5]. On the contrary, during the physiological non-amyloidogenic pathway, β-APP is metabolised by α-secretase and γ-secretase, which releases neither toxic nor pro-aggregation by-products [6]. Once it has been released, Aβ follows a well-known and well-defined process of aggregation (Fig. 1).

The in vitro aggregation kinetics of the 42-residue Aβ peptide can be summarised as follows (see Fig. 1): (1) random coiled Aβ monomers turn quickly into (2) β-sheet Aβ monomers. This shift leads to the formation of (3) soluble, low-molecular-weight oligomers, which become (4) paranuclei (higher ordered structures), and then (5) protofibrils, and eventually (6) larger fibrils, which represent the main constituent of senile plaques [7]. Together with insoluble deposits of the τ protein, which are known as neurofibrillary tangles, senile plaques are the macroscopic event and hallmark of AD.

However, senile plaques are the downstream event of a more complex process. Over these last two decades, research interest has shifted "upstream", with the report that pre-fibrillar Aβ species, and especially Aβ oligomers, are significantly more toxic than mature Aβ fibrils [8]. These findings are in agreement with clinical observations, where it has been reported that patients lacking senile plaques can show AD-like cognitive impairment.

While in vitro Aβ aggregation is performed in a highly controlled environment, the behaviour of Aβ in vivo can be influenced by a large number of variables. Within these, metal ions have aroused great interest for three main reasons: (1) patients with AD show pronounced metal dyshomeostasis in the brain; (2) high metal concentrations have been found in senile plaques (Table 1) and (3) it is well established that metals can influence and/or alter the Aβ aggregation pathway [9].

In the following sections, the roles of some of the metal ions (Al, Fe, Cu and Zn) that can influence the folding behaviour of Aβ will be considered and critically discussed, along with the AD "metal hypothesis". Furthermore, a brief insight into the biological aspects of AD and Aβ will be provided.

Aluminium

Aluminium [Al(III)] is the most abundant element in the Earth crust, although it remains to be demonstrated that it is involved in any specific vital biological processes. For this reason, the discovery of relative high Al(III) concentrations in senile plaques of *post-mortem* brains from patients with

Table 1 Metal ion concentrations detected in the cores of senile plaques from patients with AD

Metal ion	Concentration (μg/g senile plaque)
Al(III)	40[a]
Cu(II)	30[b,c]
Fe(III)	53[b,c]
Zn(II)	87[b,c]

[a][10]
[b][50]
[c][51]

AD aroused great interest, with the consequent suggestion of a possible role for Al(III) in the pathology of AD ([10]; for a recent review see Ref. [11]).

Along with all of the other electrically charged elements and molecules, Al(III) cannot be passively transported through the blood–brain barrier (BBB). Once it has been absorbed through the digestive system, Al(III) enters the bloodstream; here, it appears to be linked mainly to citrate and transferrin. However, when it reaches the brain vessels, Al(III) can indeed pass across the BBB via a transferrin-receptor-mediated endocytosis mechanism [12]. Once in the cerebrospinal fluid, Al(III) can influence the Aβ folding process, although its role in the pathology of AD is still debated and controversial [13]. Furthermore, it has been demonstrated that Al(III) can pass through the BBB already complexed with Aβ. In this case, the Aβ–Al(III) complex has more ready access to brain cells than Aβ alone [14].

In contrast to Cu(II) and Zn(II) (see below), the Al(III) complexes that are formed with Aβ have been studied to a lesser extent. Nevertheless, data reported from our and other laboratories have indicated that Al(III) can maintain Aβ in its oligomeric or pre-fibrillar state and can promote Aβ exposure of hydrophobic clusters [15, 16]. On the contrary, other studies have supported a role for Al(III) in the coordination of higher Aβ structures, such as fibrils, and in the promotion of their deposition.

Focusing on the chemical level, the presence of binding sites for Al(III) on Aβ has not been well established yet. Two different binding mechanism for Al(III) with Aβ were proposed several years ago by Fasman [17]), and more recently by our group [18]. In the former study, it was suggested that Al(III) can coordinate with four Aβ amino acids: Asp, Ser, Tyr and Glu, probably because of their high –OH-group content. In our study, we broadened the possible interaction sites to the 1–16 and 20–35 amino-acid sequences [18].

As more recently reported by Kawahara and Kato-Negishi[19]), the ability of Al(III) to coordinate Aβ and to modify its folding properties is due to two properties of Al (III): (1) it has a strong positive charge that is coupled to (2) a small ionic radius (50 pm), as compared to the other metal ions discussed here. These features mean that Al(III) can be considered as an effective protein cross-linker. Consequently, a role for Al(III) in τ folding needs to be investigated, because of its great number of phosphorylated sites; indeed, these R-OPO_3^{2-} sites are the targets of choice for Al(III)-like metals.

ESI-MS (electrospray ionisation mass spectrometry) data, recently reported by Bolognin et al. [15], showed that a bare Al(III) ion can bind to a single Aβ peptide, although Chen et al. [16] have hypothesised that two Al(III) ions can coordinate each Aβ peptide. In the latter study, the authors correctly reported a lack of data concerning the Al(III) concentration in their stoichiometric experiments, which thus questioned the results they obtained. This arose because Al(III) can form hydroxide complexes at neural pH [20]; however, the use of aluminium lactate can help to avoid, or at least delay, Al(III) hydroxide precipitation [18].

Collectively, even though several biophysical and immunological techniques have been used to demonstrate that Al (III) can "freeze" Aβ in oligomeric and highly hydrophobic structures [15], two key data appear to be missing: (1) the structure of the exact Aβ–Al oligomeric complex; and (2) the association constant (K_a) of this complex. In this connection, Bolognin et al. [15] hypothesised that Al(III) can form Aβ oligomers *tout court*, while Chen et al. [16] proposed the formation of Aβ–Al annular protofibril structures.

The present lack of studies does not allow us to provide data concerning the issue of a K_a for this Aβ–Al interaction; however, at the same time, it is possible to state with confidence that K_a (Aβ–Al) is greater than the K_a for deferoxamine mesylate ($K_a = 10^{-22}$ M), indeed, this iron/aluminium chelating agent can reverse the Al(III) influence on the Aβ oligomerisation process [18, 21].

Copper

Copper (Cu(II)) is an essential metal ion involved in several biological processes and analytically found in senile plaques at lower levels (400 μM) together with other metal ions, such as Zn(II) (1 mM) and Fe(III) (1 mM). A potential role for Cu (II) in AD has aroused interest for two main reasons: the influence of Cu(II) on Aβ conformational changes, and the reduction of Cu(II) to Cu(I). This latter is particularly relevant for Aβ-derived reactive oxygen species (ROS) [22], in that the Aβ–Cu(II) complex exerts its toxicity via ROS production (see Ref. [23]). The electron that is necessary to reduce Cu(II) to Cu(I) can be donated by both internal amino acids of Aβ or its external reductant molecules [24, 25].

Focusing on the structural level, a role for Cu(II) in Aβ aggregation has been widely studied, and a large body of evidence supports the idea that Cu(II) might be involved in the acceleration of Aβ deposition into amorphous aggregates [15, 26]. State-of-the-art coordination chemistry of Aβ/Cu (II) has shown that there are four putative residues that have

been proposed as Cu(II) binding sites on Aβ: His6, His13, His14, Tyr10 [27–29]. Nevertheless, Cu(II) can bind other residues in the N-terminus of Aβ (e.g. Asp1, Glu11) [30, 31]. In agreement with Miller et al. [30, 31], this variability might be due to the different conditions under which the aggregation processes have been performed.

Conformational changes due to the Cu(II)/Aβ interaction appear to result in reduced exposure of the Aβ–Cu(II) hydrophobic clusters, as compared with Aβ alone or with its complexes with other metal ions, such as Zn(II) and Al(III) (see above) [32]. This event might lead to decreased interactions between the Aβ–Cu(II) complex and the hydrophobic cellular phospholipids [33], even though it has been proposed that in the presence of Cu(II), Aβ forms channel-like structures in cell membranes [34].

Recent findings supported by ESI-MS have reported that Aβ is metallated by a bare Cu(II) ion [15, 16]. This interaction appears to increase Aβ random coil content, which leads to the formation of non-fibrillar amorphous aggregates. Indeed, it has been shown that an elevated β-sheet content is required for fibril formation [35], while the random coil content leads to disordered aggregate deposition.

Recently, different Aβ–Cu(II) affinities have been proposed for the $A\beta_{1-40}$ peptide, which depend on the Aβ secondary structure: 0.14 μM^{-1} for $A\beta_{1-40}$ in a random-coil structure and 0.05 μM^{-1} for $A\beta_{1-40}$ in the beta-sheet stimulated conformation [36]. This scenario is further complicated by the variable molar ratios of Aβ and Cu(II) in the extracellular space. It has been reported that a sub-equimolar Aβ/Cu(II) ratio leads to amorphous and stable aggregates; vice versa, supra-equimolar ratios can lead to the formation of more toxic oligomeric structures [24, 25]. This hypothesis was recently confirmed by Pedersen et al. [37], where the discovery of distinct Cu(II)-concentration-dependent Aβ-aggregation pathways supports a key role for metal homeostasis in the folding of Aβ and, consequently, for its toxicity.

Together with our recent findings [15, 32], these data support the idea that Aβ–Cu(II) complex exerts its toxicity via ROS production.

Iron

As for Al(III), iron (Fe(III)) has also been studied to a lesser extent than some other metals, despite its key role in several biological functions (e.g. as a cofactor or an O_2 carrier, among other functions) and its redox properties. Here, we focus our attention on Fe(III) instead of the reduced Fe(II) form.

Data in the literature support the idea that Fe(III) can lead to the formation of a heterogeneous population of amorphous aggregates, thus shifting from oligomers to larger, high-molecular-weight structures. ESI-MS analyses has shown that Aβ can bind two Fe(III) ions [15, 16]. These Fe(III) ions appear to be coordinated via His13, His14 and Tyr10, as suggested by Alì-Torres et al. [38]. The same study also supported the idea that Aβ forms more stable complexes when it binds to Fe(III) rather than to Fe(II). It has been reported recently that Fe(III) increases the Aβ random coil content [39], which promotes the deposition of amorphous aggregates, as described for Cu(II). This conformational change is associated with decreased exposure of hydrophobic clusters [15, 16], which reduces the possible interactions between the Aβ–Fe(III) complexes and the lipid bilayers of the cell [33]. Again, as with Cu(II), Fe(III) interactions with Aβ can catalyse the generation of hydrogen peroxide (H_2O_2); consequently, a lack of detoxifying enzymes or an accumulation of Aβ–Fe species (both Fe(II) or Fe(III)) can trigger ROS formation via the Fenton reaction [9].

Very little is known about the Aβ affinity for Fe(III), as the lack of studies does not provide much data relating to this complex. Despite this, as for Aβ–Al(III), it is possible to assume that the Aβ affinity for Fe(III) is lower than that of the Fe(III)-chelating agents (e.g. deferoxamine mesylate); indeed, these compounds can revert the Aβ–Fe(III) aggregation process [21].

Collectively, the data reported here support the concept that Aβ–Fe(III) exerts its toxicity through two independent mechanisms. One mechanism involves ROS production, and the other involves the changes in Aβ conformation. This latter appears to be less convincing for two reasons: (1) Fe(III) only delays Aβ deposition in large amorphous aggregates, as the Aβ–Fe(III) oligomers are limited in time and tend to deposit into senile plaques; (2) data that support this hypothesis appear poor [39], because they do not discriminate between toxicity due to ROS production or to conformational changes in Aβ; moreover, the Aβ concentration used was largely higher than that of other studies reported in the literature (10 μM vs. 0.5 μM).

Zinc

The role of zinc (Zn(II)) in the pathophysiology of the central nervous system has been widely debated, and its involvement in neurodegenerative disorders appears to be well established. Its deregulation also appears to have an important role in AD [40]. At the same time, Zn(II) has key roles in synaptic functions, neurotransmission and cell signalling. Zn(II) in cells is usually maintained at low basal concentrations through three mechanisms: (1) Zn(II) transporters; (2) Zn importing proteins and (3) the buffering action of the metallothioneins. In addition to the metallothioneins, Zn(II) is stored at high concentrations (~1 mM) in presynaptic vesicles and co-released with glutamate during neurotransmission [41]. Once in the synaptic cleft, Zn(II) can bind to Aβ, promoting its conformational modifications.

Due to the importance of Zn(II) in cell physiology, its ability to modify the Aβ structure and the Aβ aggregation pathway has been largely characterised. As for the other metal ions, to assess Aβ–Zn(II) stoichiometry, ESI-MS has been carried out. The data reported in the literature support the idea that a single Zn(II) ion binds to Aβ [15, 16]. According to many nuclear magnetic resonance studies ([42, 43]; reviewed in Ref. [44]), the bare Zn(II) ion binds the N-terminal region of Aβ, which probably involves the same Cu(II)-binding residues, His6, His13 and His14, even though four other potential binding sites have been proposed: Asp1, Glu3, Asp7 and Glu11 [30, 31].

The morphology of Aβ–Zn(II) aggregates has been investigated by different groups, with the use of several biophysical and immunological techniques. The results reported appear comparable and have become largely accepted. Atomic force microscopy and transmission electron microscopy, together with dot-blotting, have shown that Zn(II) promotes Aβ deposition into amorphous aggregates that can coexist with heterogeneous oligomers [15, 16, 30, 31].

Despite the similarities between Aβ–Cu(II) and Aβ–Zn(II) (which can be attributed to their comparable ionic radii: 74 pm for Zn(II), and 73 pm for Cu(II)), Zn(II) is more effective in the promotion of Aβ exposure of the hydrophobic clusters [15, 16, 32]. This supports the idea that the Zn(II) binding sites are different from the Cu(II) ones (see above).

The apparent dissociation constants of Zn(II) from Aβ were reviewed by Faller and Hureau [44], where they hypothesised that the Aβ–Zn(II) K_d lies in the range of 1 μM–20 μM. This variability is mainly due to the different conditions that are used to assess K_d values (e.g. buffer, metal-ion concentration, protein concentration, metal/protein stoichiometry).

Brief insights into the biological aspects

A plethora of Aβ mechanisms of toxicity have been reported over the last decade, although only a fraction of these have addressed AD metal dyshomeostasis or the roles of these metal ions in Aβ miss-folding. The most studied mechanism through which Aβ-metal complexes exert their toxicity is the production of ROS. Aβ produces H_2O_2 in the presence of biological reducing agents [45]. Aβ ROS generation is promoted by the presence of the transition metals, such as Cu(II) and Fe(III), which can lead to the formation of free radical species through the Fenton reaction (for a detailed review, see Ref. [22]). The metal ions that are not involved in redox reactions (i.e. the aforementioned Al and Zn) appear to be involved indirectly in ROS production. As recently demonstrated by Duce et al. [46], Aβ–Zn can inhibit iron-export ferroxidase activity; this results in Fe(II) accumulation, which then leads to oxidative stress in cortical neurons. Also, Al(III) has a pro-oxidative role, as it promotes Fe(II)-induced lipid peroxidation [47]. Unfortunately, data concerning the role of Aβ–Al(III) in lipid peroxidation is missing; the shedding of light on this issue would be of great interest.

As well as ROS production, we have recently demonstrated a second way through which Aβ-metal complexes exert their toxic effects. In comparing Aβ-metal aggregation data with the effects of Aβ-metal complexes on membrane models and in toxicity essays, we found a strict correlation between Aβ-metal exposure of hydrophobic clusters and membrane damage. This effect, together with other data in the literature that we have reported here, might explain why our Aβ–Al(III) complex was the most effective in the reduction of cell viability in our cellular model. Indeed, Aβ–Al(III) has three characteristics that justify its toxicity under our experimental conditions: (1) it is the most effective Aβ-metal complex for the retaining of its oligomeric structure; (2) it is the most effective Aβ-metal complex for the exposure of hydrophobic clusters and (3) it can induce lipid peroxidation, as mentioned earlier. The other Aβ-metal complexes express no more than two of these features.

In addition to these two main mechanisms, others have been reported in the literature, and in particular, Aβ interactions with synaptic receptors, such as the metabotropic glutamate receptors and NMDA receptors. In these cases, direct binding of Aβ to the receptor might not occur. It appears more likely that Aβ can indirectly modulate synaptic receptors through its membrane association [48]; this hypothesis confirms the need for highly hydrophobic Aβ oligomers that can penetrate into lipid bilayers.

This scenario is further complicated by the difficulty of isolating well characterised and homogeneous Aβ or Aβ-metal aggregates. Furthermore, data reported in literature show large differences in data obtained with synthetic or with naturally occurring Aβ oligomers. Indeed, the latter require much lower concentrations to exert comparable toxic effects on cellular models [49], highlighting possible structural, as well as biochemical (e.g. glycosylation), differences between these in vitro and in vivo Aβ aggregates.

Conclusions

As generally reported in the literature and briefly summarised here, it is clear that metal ions have heterogeneous influences on Aβ miss-folding and deposition (Fig. 2). This variability modifies the pathways through which Aβ and its metal complexes exert their toxicity: from ROS production, to cell membrane damage [52].

The ability to change the impact of metal ions in Aβ aggregation pathway appears a possible and promising

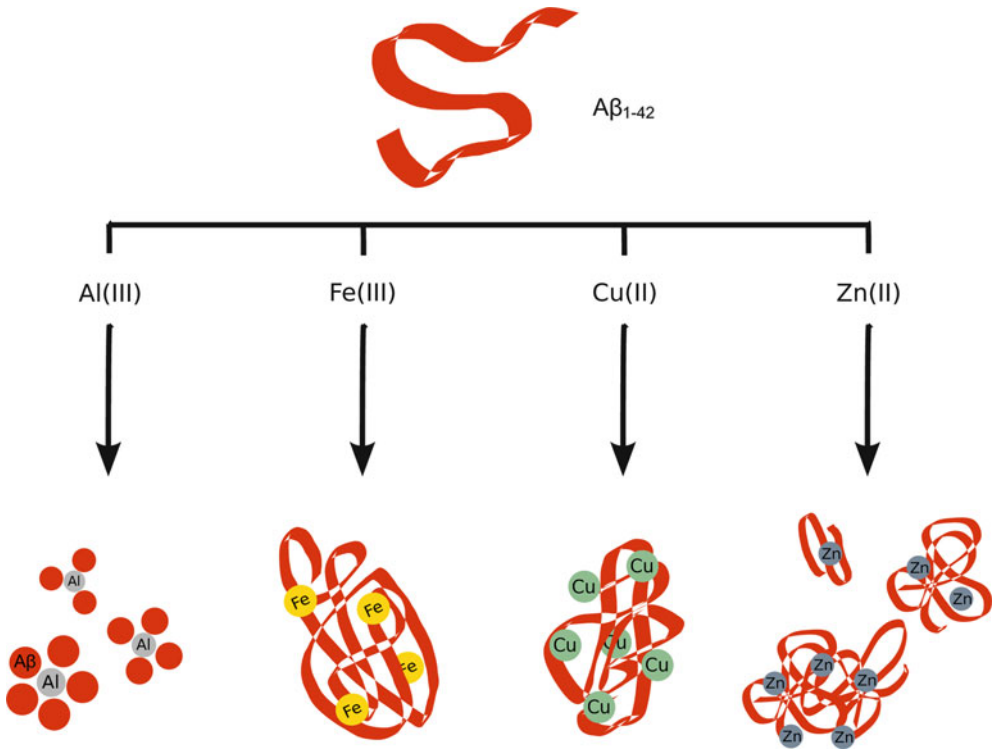

Fig. 2 Aluminium, iron, copper and zinc differentially alter Aβ aggregation. Al(III) promotes the formation of highly hydrophobic Aβ oligomers (i.e. from trimers to hexa-heptamers); Fe(III) promotes Aβ deposition into amorphous structures; Cu(II) leads to the formation of disordered/amorphous structures and Zn(II) triggers the formation of amorphous aggregates

therapeutic challenge. However, metal ions that are involved in therapeutic strategies (e.g. chelation therapy) should be approached with caution. First of all, focusing on a single metal ion can lead to generation of a cascade of events that will involve the homeostasis of other life-essential metal ions, as seen by the so-called *domino effect* [9]. Accordingly, a new therapeutic approach has focused on molecules that can compensate for cellular metal-ion dysregulation, potentially by sequestering essential ions from senile plaques and "ferrying" these into the cell without compromising the homeostasis of other metal ions.

Moreover, a process to revert this Aβ-metal aggregation might cause more harm than good. This has been reported for toxic species of Aβ in solution that can be deposited in stable high-molecular-weight metal aggregates.

Despite these promising therapeutic strategies, multifactorial pathologies like AD should not be addressed by focusing on a single feature (e.g. Aβ accumulation, metal dyshomeostasis) without further considerations of others (e.g. τ-hyperphosphorylation, APOE4, synaptic failure, ROS production). Thus, approaching the treatment of patients with AD in this way might be reductionist and could ultimately be ineffective.

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