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Metal Ions and Intrinsically Disordered Proteins and Peptides: From Cu/Zn Amyloid-β to General Principles

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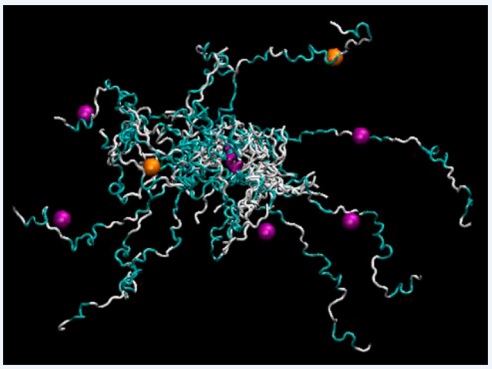
CONSPECTUS: The interaction of d-block metal ions (Cu, Zn, Fe, etc.) with intrinsically disordered proteins (IDPs) has gained interest, partly due to their proposed roles in several diseases, mainly neurodegenerative. A prominent member of IDPs is the peptide amyloid-β (Aβ) that aggregates into metal-enriched amyloid plaques, a hallmark of Alzheimer's disease, in which Cu and Zn are bound to Aβ.



IDPs are a class of proteins and peptides that lack a unique 3D structure when the protein is isolated. This disordered structure impacts their interaction with metal ions compared with structured metalloproteins. Metalloproteins either have a preorganized metal binding site or fold upon metal binding, resulting in defined 3D structure with a well-defined metal site. In contrast, for Aβ and likely most of the other IDPs, the affinity for Cu(I/II) and Zn(II) is weaker and the interaction is flexible with different coordination sites present. Coordination of Cu(I/II) with Aβ is very dynamic including fast Cu-exchange reactions (milliseconds or less) that are intrapeptidic between different sites as well as interpeptidic.

This highly dynamic metal−IDP interaction has a strong impact on reactivity and potential biological role: (i) Due to the low affinity compared with classical metalloproteins, IDPs likely bind metals only at special places or under special conditions. For Aβ, this is likely in the neurons that expel Zn or Cu into the synapse and upon metal dysregulation occurring in Alzheimer's disease. (ii) Amino acid substitutions (mutations) on noncoordinating residues can change drastically the coordination sphere. (iii) Considering the Cu/Zn−Aβ aberrant interaction, therapeutic strategies can be based on removal of Cu/Zn or precluding their binding to the peptide. The latter is very difficult due to the multitude of metal-binding sites, but the fast k_{off} facilitates removal. (iv) The high flexibility of the Cu−Aβ complex results in different conformations with different redox activity. Only some conformations are able to produce reactive oxygen species. (v) Other, more specific catalysis (like enzymes) is very unlikely for Cu/Zn−Aβ. (vi) The Cu/Zn exchange reactions with Aβ are faster than the aggregation process and can hence have a strong impact on this process.

In conclusion, the coordination chemistry is fundamentally different for most of IDPs compared with the classical, structured metalloproteins or with (bio)-inorganic complexes. The dynamics is a key parameter to understand this interaction and its potential biological impact.

1. INTRODUCTION

1.1. d-Block Metals and Amyloidogenic Proteins in Neurodegenerative Diseases

There is a large body of evidence in the literature that connects the binding of d-block metals (mainly Cu, Fe, and Zn) with amyloid diseases and in particular neurodegenerative diseases (NDs). Among the most prominent examples are Alzheimer (AD), Parkinson (PD), prion diseases, and amyotrophic lateral sclerosis (ALS), in which different peptides or proteins form deposits of amyloid fibrils. These amyloid fibrils are organized in β-strands that direct perpendicular to the fibril axis (cross-β-strands). The amyloidogenic proteins involved are normally disease specific, like amyloid-β and tau in AD, α-synuclein in PD, PrP in prion diseases, superoxide dismutase (SOD) in ALS, or amylin in diabetes. In several of the NDs, the amyloid deposits are rich in d-block metal ions. This stimulated interest in the interaction of amyloidogenic proteins with these metal ions.

The proteins or peptides involved can be divided into two classes: (i) the more classical proteins that have a defined 3D structure, like SOD in ALS, and (ii) the proteins with a nondefined 3D structure often called intrinsically disordered proteins (IDPs), like amyloid-β in AD. SOD is a metalloprotein in which the metal ions Cu and Zn are bound at a well structured site and are part of the catalytic center. Cu and Zn are inserted during the maturation and folding, and upon amyloid formation can stay bound. In contrast, for IDP like Aβ,

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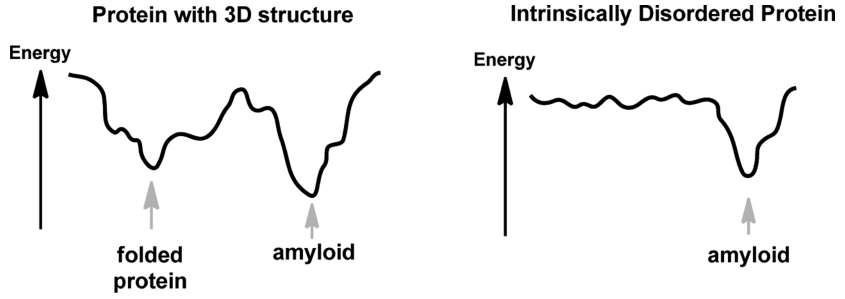

Figure 1. Energy landscape of well structured proteins (left) and intrinsically disordered proteins (IDP; right). Either type of protein can form amyloids that are often considered as the most stable structure (above a certain concentration).

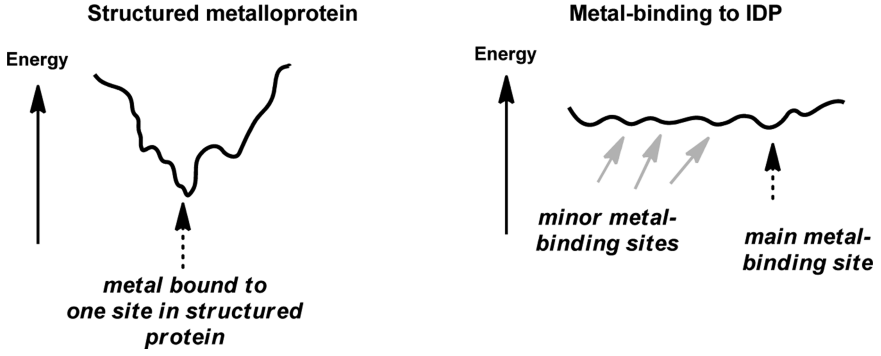

Figure 2. Energy landscape of well structured metalloproteins (left) and metal-binding intrinsically disordered proteins (right). The formation of amyloids is not depicted, but see Figure 1.

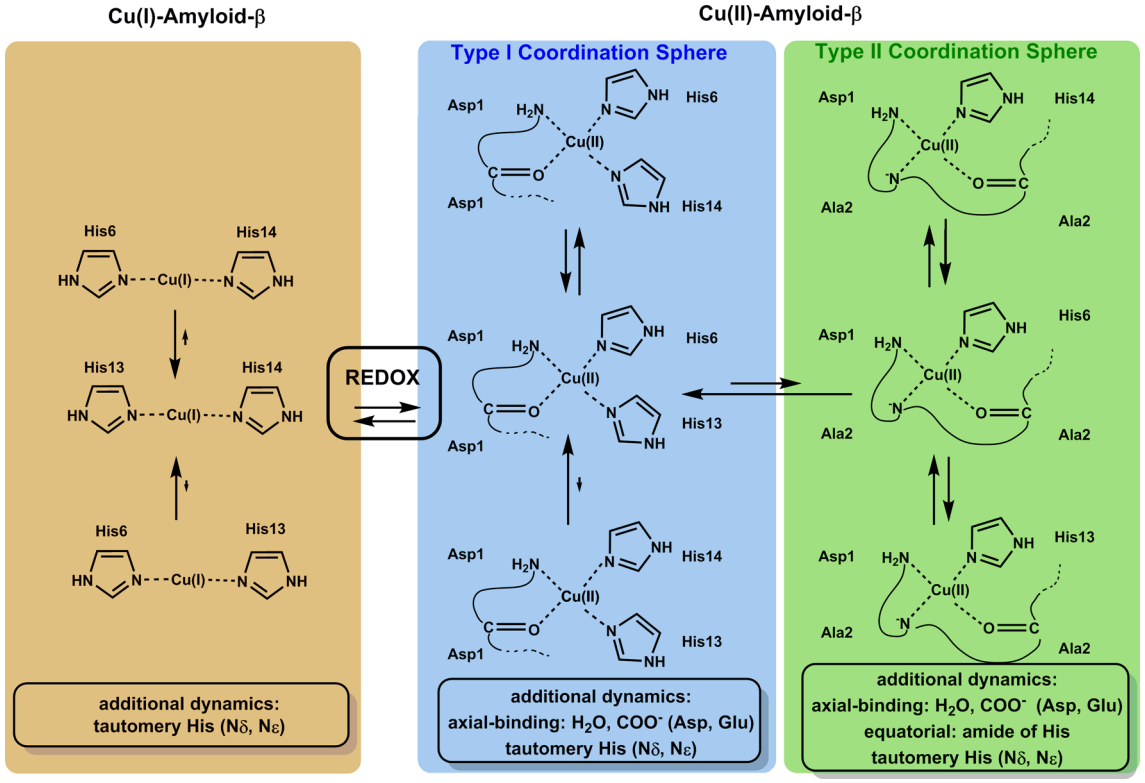

Figure 3. Coordination spheres of Cu(I)− and Cu(II)−Aβ.

it is not clear whether there is a physiological role for metal-binding or whether metal-binding occurs only during amyloid formation.

1.1.1. Scope of this Account. During the research on metal ions and Aβ in the last years, we realized that there are fundamental differences in its interaction of metal ions compared with structured metalloproteins like SOD, and a main parameter is the dynamics. This parameter explains many of the observed features and has an impact on the biological properties. In this Account, we will work out the difference on

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Table 1. Conditional Dissociation Constants (cond. K_d, in M)[a] of Some Metalloproteins

			Aβ	
metal	SOD	metallothionein	monomer	aggregate
Cu(II)	6×10^{-18} (ref 8)		$\sim 1 \times 10^{-10}$ (ref 9)	$\sim 1 \times 10^{-11}$ (ref 10)
Cu(I)	2.3×10^{-16}, (ref 11) 6×10^{-15}, (ref 12)	$\sim 10^{-19}$,[b,c] 0.4×10^{-15} (ref 11)	$\sim 5 \times 10^{-8}$ (ref 13)	
Zn(II)	4.2×10^{-14} (ref 8)	$\sim 10^{-12}$[c] (ref 14)	$(1-10) \times 10^{-6}$ (ref 15)	$(1-10) \times 10^{-6}$ (ref 15)

[a]Cond. K_d is defined as K_d at pH 7.4 in the absence of buffer. [b]Estimated value. [c]Overall binding affinity.

the example of Cu (and Zn) interaction with Aβ and related peptides and then discuss the impact on reactivity and the biological role. We think that most of the principles could also apply for other kinetically labile metal ions (Mn^{2+}, Co^{2+} etc.) with other IDPs, such as α-synuclein and amylin.

1.2. Intrinsically Disordered Proteins (IDPs) and Their Relation to d-Block Metal Ions

Intrinsically disordered proteins (IDPs) are a class of proteins or peptides that lack a unique 3D structure when the protein is isolated.[1] They are highly dynamic and flexible but can adopt a 3D structure if they interact with their physiological binding partner, like another protein or lipids (Figure 1). IDPs are also called naturally unfolded proteins, unstructured proteins, etc.

Amyloid-β is an IDP. The most abundant forms of amyloid-β are 40 and 42 amino acids long. In their monomeric state in aqueous solution around pH 7, the two peptides are intrinsically disordered. Monomeric Aβ shows NMR shifts typical for random coil structures, and often only short-range NOEs are observed. In line with this, CD and FTIR show the little ordered α-helical or β-sheet structure. Thus, in general Aβ is flexible with little 3D structure. However, this does not mean that there is no structural element at all. Aβ fluctuates among different structures and hence can acquire transitory elements of secondary structure and possess secondary structure propensities.[2] The degree of defined structure is condition dependent and can go up to a partially folded structure.[3]

2. METAL BINDING TO AMYLOID-β, AN IDP

Here we will restrict the discussion mostly to the interaction of amyloid-β with Cu(II) and Cu(I), since they are the best known and they serve as examples also for other metal ions.

2.1. The Binding Sites of Cu(II) and Cu(I) in Monomeric Amyloid-β

Metalloenzymes with a defined 3D structure have normally a well-defined and unique binding site for each metal in their folded state (Figure 2, left). In contrast, monomeric Aβ is flexible and has several binding sites for Cu and Zn (Figure 2, right). The main coordination sphere of Cu(I)−Aβ is a digonal coordination by two histidines (Figure 3). His13 and His14 are the predominant ligands, but minor species include His6−Cu(I)−His13 and His6−Cu(I)−His14. Other sparsely populated states are likely present but were not identified so far. For Cu(II), the situation is even more complex (Figure 3). At pH 7.4, two different types of coordination spheres are present. The major one includes NH_2 and C═O of Asp1 and two histidines, and the minor one includes NH_2 of Asp1, NH (amide) and C═O (amide) of Ala2, and one histidine. In each sphere, additional dynamics are present because different histidines can be exchanged. Moreover, different ligands (carboxylate or water) can bind apically to Cu(II). Thus, for monomeric soluble Cu(I)− and Cu(II)−Aβ, several coordination environments exist, with different populations in a relatively flat energy landscape (Figure 2, right).[4,5]

2.2. Binding Affinities of Cu(I/II)− and Zn(II)−Amyloid-β Are Lower than Those in Structured Metalloproteins

The binding affinities of Cu(I/II) and Zn(II) to proteins are often described as dissociation constants. In general, the reported K_d are apparent, that is, at a given pH value and in the presence of buffer and salt. Apparent K_d's that are corrected for the affinity of the buffer are often called conditional. This is in contrast to the thermodynamic affinity constant in inorganic chemistry that can be directly evaluated by potentiometric measurements applicable to shorter peptides but not to proteins.

Although the K_d is difficult to measure, the values obtained recently do converge. More generally, it seems clear from the literature that Cu(I/II) and Zn(II) binding to Aβ is weaker than that for the classical structured proteins, which have K_d's in the nanomolar to picomolar range for Zn and femtomolar to attomolar for Cu. As an example, SOD and metallothionein (both can bind bind Zn and Cu)[6,7] are compared with Aβ in Table 1.

2.3. Kinetics of Cu(II) and Cu(I) in Monomeric Amyloid-β

Different types of reactions concerning the interaction of Cu ions with Aβ can be considered (Figure 4): (1) association (k_{on}) and dissociation (k_{off}) reactions, (2) intrapeptidic metal transfer, and (3) interpeptidic metal transfer (Figure 4).

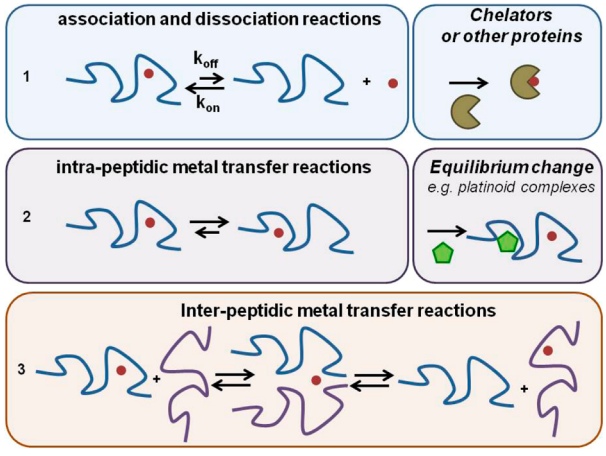

Figure 4. Three different types of reaction (1−3) are considered here (left part). They are fast (milliseconds or less) and contribute to the dynamic binding. Some of their biological relevance is shown on the right (see also section 3). (1) Association and dissociation reactions. They are important for the metal transfer from or to chelators and proteins. (2) Intrapeptidic metal transfer between different binding sites on the same molecule. The equilibrium can be influenced by second sphere changes, pH, or reaction with other compounds like platinoid complexes. (3) Interpeptidic metal transfer reaction between two peptides. In the case of Cu(II)−Aβ, this is shown to occur via a ternary complex. This reaction might be important for the metal-induced aggregation.

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2.3.1. Metal-Binding Kinetics (Association (k_{on}) and Dissociation (k_{off}) Reaction). The association of Cu and Zn is very fast and likely close to diffusion controlled.[16,17] As a consequence, the k_{off} is also elevated, since the K_d is relatively high ($K_d = k_{off}/k_{on}$). The k_{on} and k_{off} are in line with the dynamic nature and the absence of a preorganized site of Cu/Zn−Aβ binding. For comparison, in SOD half-lifetimes for the release of Cu and Zn were reported to be about 11 and 46 h, respectively.[8] This means that Cu and Zn ion can rapidly exchange, and this has to be taken into consideration for the possible functions of the metal ion.

2.3.2. Intramolecular Dynamics, Different Metal-Binding Sites in Fast Exchange (Intrapeptidic Metal Transfer). A consequence of the flat energy landscape for Cu−Aβ is that for Aβ the stability (or binding affinity) of the different sites are relatively similar and that the exchange between the different states is relatively fast. The movement of the metal ion from one site to the other is faster than the time resolution of NMR, that is, time scales of milliseconds or lower.[18]

2.3.3. Intermolecular Dynamics, Fast Exchange between the Peptides (Interpeptidic Metal Transfer). In the case of Cu(II) and Cu(I), NMR shows that the interpeptide exchange of the metal ion is also faster than the NMR time scale (millisecond). Addition of substoichiometric amounts of Cu(II) or Cu(I) lead to the broadening of the entire Aβ population and in the case of Cu(II) suggested a ternary Aβ−Cu(II)−Aβ complex as transient.[19] Further analysis by Pedersen et al. proposed an association constant of Aβ to Cu−Aβ of ∼1 μM^{-1} s^{-1} and a dissociation constant of $\sim 3 \times 10^2$ s^{-1}.[20,21]

2.4. Metal Binding in Aggregated Amyloid-β

Little is known about the metal-binding sites in the aggregated state (oligomers or fibrils), but in general, it seems that the binding sites are similar to those in the monomeric peptide.[5] The metal mobility in aggregated Aβ is not known, but several experiments point to a fast metal exchange at least for fibrils. First, the N-terminal part of Aβ, that is, the metal-binding domain, is quite flexible even in the amyloid fibrils.[21] Further EPR did not show significant differences between monomeric and fibrillar Cu−Aβ.[22] Moreover, ssNMR showed that interpeptidic Cu-exchange is still present and fast on the NMR time scale.[23] In addition, Zn-chelators were able to retrieve Zn from Zn−Aβ aggregates within seconds.[15] All this indicates that the situation resembles the case in solution, that is, fast intra- and intermolecular metal exchange (time scale of milliseconds or lower). However, caution has to prevail due to the polymorphism of the aggregated states of Aβ, and there are recent indications that metal-binding can be different in oligomeric forms compared with larger aggregates like fibrils.[5,24,25]

3. IMPACT OF DYNAMICS OF METAL−IDP ON BIOLOGY AND REACTIVITY

We discuss first briefly the potential biological roles of Cu- and Zn-binding to Aβ in order to evaluate later the impact of the dynamics.

The physiological role of Aβ is ill defined. It seems that metal ion binding to Aβ occurs only under AD conditions. It is clear from in vitro and in vivo experiments that the metabolism of Aβ and metal ions are connected in AD. However, it is not clear whether metal deregulation is a cause or a consequence of Aβ aggregation or of other events connected to the etiology of AD. It has been shown that metal ion binding to Aβ modulates the aggregation behavior and cell toxicity. In the latter, oxidative stress might be involved. Indeed, there are also indications that Cu−Aβ might contribute to the oxidative stress in AD, including the possibility to be a catalytic center for ROS production. Thus, some central questions about the role of metal ions in AD are as follows:

- What is the effect of metal ion binding on aggregation in terms of kinetics and structures formed? For example, do metal ions induce or prevent more or less toxic aggregates?
- Do metal−Aβ complexes have a catalytic activity? If so, what activity and is it physiologically or pathophysiologically relevant?
- What is the connection between the metabolism of metals and Aβ and their dishomeostasis? Where do the metals bound to Aβ come from?
- What about metal ions as therapeutic targets in AD?

3.1. IDPs Have Lower Metal-Binding Affinity: What about the Biological Relevance?

Cu and Zn affinity for Aβ is much lower than most known metalloproteins (Table 1). This poses immediately the question about the biological relevance of metal-binding, because "free" Cu(I) and Zn(II) concentrations in a cell are estimated to be in the femtomolar to attomolar range and nanomolar to picomolar range, respectively,[12,26] in line with the affinity of the Cu/Zn proteins. Thus, it is very unlikely that Aβ can bind Cu and Zn intracellularly in the cytosol under classical conditions. Aβ, mainly found in cellular compartments and extracellularly, likely needs special conditions and special places to be able to bind Cu/Zn. Certain synapses are enriched in moderately bound Zn, Cu, or both under physiological conditions. It is well established that a subclass of glutamatergic neurons release a high amount of Zn (∼100 μM) into the synaptic cleft upon excitation. There is also increasing evidence reported that Cu is released as well yielding micromolar concentrations in certain synaptic clefts.[27] The reported Zn and Cu concentrations are clearly above the dissociation constants of Aβ, and hence occupation of the metal-binding site in Aβ seems possible. Moreover, the loosely bound pool of metal ions has been reported to be increased in AD.[28] Interestingly, amyloid plaques form preferentially in these Zn-releasing regions.[29] Another example is the amyloidogenic IDP amylin (or iAPP) that occurs in the Zn-rich β-cells in the pancreas.[30] However, to what extent the metals bind to Aβ and other IDP compared with all the other biomolecules with moderate affinity remains to be determined.

3.2. Impact on Metal-Based Therapy for AD: 1. Removing Metals by Chelators

Based on the idea that the Cu−Aβ interaction is detrimental, the first approach was to use a chelator to remove Cu (or Zn) from Aβ. The lower affinity of Aβ for Cu and Zn compared with most other proteins allows their specific removal by using a chelator with an affinity stronger than Aβ and weaker than the essential metalloproteins. The dynamics of the Cu−Aβ interaction above suggests that Cu is quite accessible to chelators even for smaller aggregates, and hence design to access the Cu-site in Aβ is less important. Nevertheless access to metal ions buried in larger plaques might be a problem, but these ions are not supposed to contribute much to toxicity.

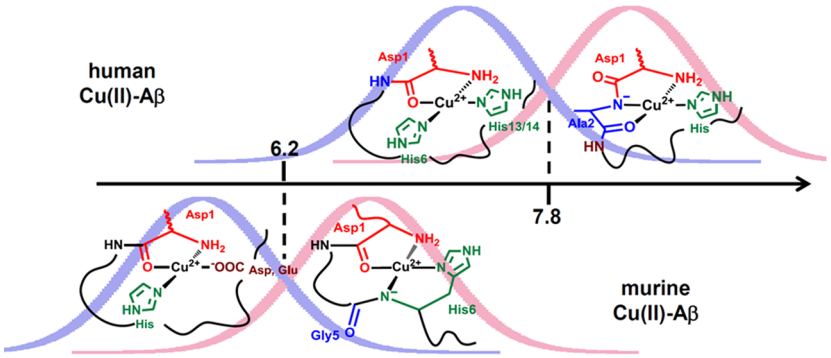

Figure 5. pH dependence of the Cu(II)-coordination of human and mouse Aβ around neutral pH. The change from arginine (in human) to glycine at position 5 is responsible for this different coordination chemistry. Arg5 and Gly5 do not directly bind Cu(II) (second sphere) but change dramatically the predominant form at neutral pH (e.g., murine, but not human, has amidyl ligand at pH 7).

3.3. Mutation and Cu-Binding: Second Sphere Interaction Can Have Strong Influence on Coordination

There are several mutations in the sequence of Aβ linked to familial AD, that is, genetic forms of AD in which mutations are responsible for early onset of the disease. Thus, the question can be asked whether there is a link with the metal-binding properties. Most of these mutations do not concern the main metal-binding sites, although there are exceptions (like His6Arg or Asp7Asn). Nevertheless, mutations in the second sphere of the metal-binding sites can have a large impact on the metal-binding properties due to the high flexibility of the metal–peptide complex. As can be seen from Figure 2, the flat landscape allows a shift in the population by only subtle changes in the Aβ sequence. For instance, we could show that the key "mutation" between human and murine Aβ is the Arg5Gly. Neither arginine nor glycine side chains are Cu ligands. However, this subtle change had a large impact on the Cu-binding, and the most populated state at pH 7.4 changes drastically (Figure 5). In addition, this change affected the capability to catalyze the production of ROS and might be responsible for differences in AD model murine and human AD patients.[31] A similar large change in the coordination sphere (and location) of the main binding sites was observed for other mutations or for pathologically relevant truncations or derivatizations.[5,32]

3.4. Impact on Metal-Based Therapy for AD: 2. Blocking Metal Binding

Another more recent therapeutic approach in order to avoid the detrimental Cu–Aβ interaction is to block the Cu binding to Aβ by occupying the binding site with another kinetically inert and strongly bound metal. This was mainly studied with Pt (or platinoid) compounds.[33] However, our studies showed[34] that binding of a Pt compound does not impede Cu(II)-binding (nor its capability to catalyze ROS production); it just pushes it to another site, in line with the dynamic multisite Cu-binding properties of Aβ (Figure 4, middle panel right).

3.5. Redox Activity of Cu–Aβ Proceeds via Sparsely Populated States

The redox activity of the Cu-center in Cu–Aβ is an important property, because it is the underlying mechanism of the catalysis of ROS production by Cu–Aβ. In vitro studies showed that Cu–Aβ is able to catalyze the production of H_2O_2 and $HO^\bullet$ in the presence of dioxygen (aerobic conditions) and the physiological reducing agent vitamin C. Electrochemical analysis of Cu–Aβ suggested that the redox reaction between the most populated Cu(I) and Cu(II) states (see above) is very sluggish and that all redox occurs via a sparsely populated state (~0.1%) that is very efficient.[35] It is the dynamics of the Cu(I//II)–Aβ that allows the (fast) population of this state. The structure or ligands of this state are not known (but see below) and are difficult to study considering the sparse population. Computational chemistry suggested that this state does not involve amide coordination (as in component II, Figure 3).[36]

Recently, we mapped out the reactive state responsible for the Fenton-type reaction, $H_2O_2 \rightarrow HO^\bullet + HO^-$ (this state is not necessarily the same as the sparsely populated, highly redox active state deduced from electrochemistry, because no substrates were present in the latter case). This was achieved by analyzing the oxidation damage of $HO^\bullet$, supposed to mainly attack the ligands of the redox reactive state. Interestingly, the main damage occurred at Asp1 and His13 and14, but not His6.[37] Further computational studies support the view that only some of the possible Cu(I)–Aβ states are reactive with H_2O_2. The structural characteristics to have a Fenton-type reactive Cu(I)–Aβ states was a coordination of Cu(I) by two ligands (classically His, but also Asp1 possible) with a geometry far from linear (180°) and accessibility of the water-soluble substrate H_2O_2 or HO_2^- to the inner sphere of Cu(I).[38]

3.6. Catalytic Activity of Cu–Aβ: Cu/Zn–Aβ Is Not a Metalloenzyme!

Enzymes are normally selective and efficient. To be that, they have been selected to recognize the proper substrate. In the case of metalloenzymes, the classical way is to have the catalytic metal buried in the ground of a pocket that can bind and properly orient the substrate. This confers the specificity. With this background, it is very difficult to imagine that such a flexible metallopeptide like Cu– or Zn–Aβ in which fast metal exchange between different sites occurs can have a defined and specific enzymatic activity. Nevertheless, this has been claimed in the past, for example, monooxidase activity, but a recent study by Casella and co-workers clearly shows that the activity is not comparable in terms of selectivity and efficiency with an enzymatic function.[39] Thus, it seems clear that there is no physiological enzymatic type function for Zn– or Cu–Aβ.

However, a pathological function based on catalysis for Cu–Aβ is more likely, because metal binding seems adventitious, and hence such a reaction could be the ROS production, which is in line with a more uncontrolled catalytic activity due to the flexible structure of Cu–Aβ.

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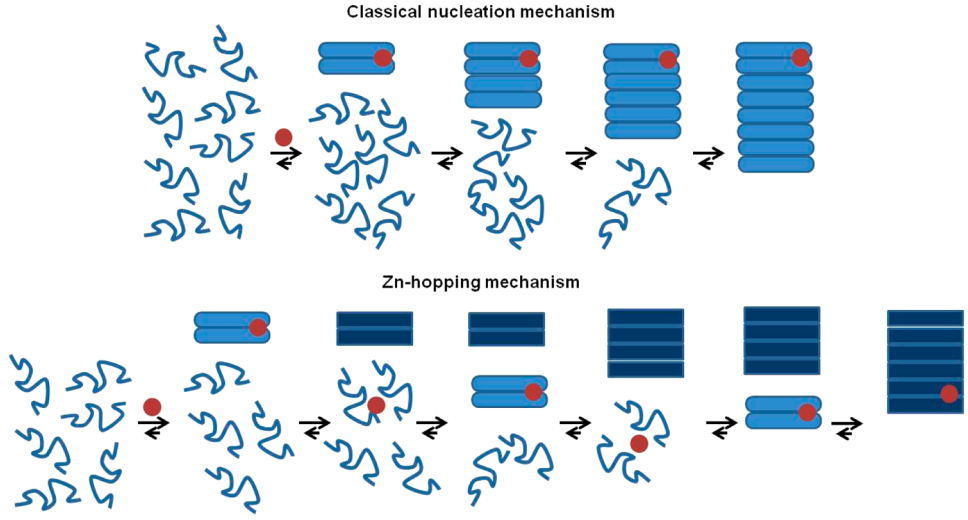

Figure 6. Metal-induced aggregation mechanisms: Difference between mechanism without (top) and with (bottom) fast metal exchange. (top) The metal induces a metal−peptide nucleus, which serves as template to grow amyloids. The structure of the Zn-nucleus is propagated; that is, the nucleus determines the structure (seeding of a strain). (bottom) The metal induces the nucleus but leaves rapidly. The nuclei can rearrange to a nuclei of the apo type. This apo type structure serves as a template for further growth.

Table 2. Comparison of the Binding of Kinetically Labile Metal Ions (Mainly Cu(I/II), Zn(II)) to Intrinsically Disordered Proteins (Intrinsically Disordered Metal-Binding Proteins) to That with the Classical, Well Structured Metalloproteins

	metalloproteins	metals bound to IDPs
metal binding site(s)	one well-defined site for each metal	several sites
kinetics	often kinetically trapped slow k_{off}	fast kinetics, inter and intramolecular (ms or faster)
binding affinity	high	modest
mutations	mutations affect binding property or folding but rarely change the location of the binding site	mutations, even far (2nd or further coordination sphere) from the metal site can change the location of the metal-binding (population shift)
reactivity	well-defined, selective catalysis or inert structural element	not selective, can catalyze different reactions with low selectivity and efficiency, uncontrolled ROS production
protein aggregation (amyloids)	less prone to amyloid formation as a barrier crossing of partial unfolding has to occur first	no or little unfolding necessary to form amyloids
occurrence	throughout the body	only at places or conditions where higher "free" (loosely bound) metal concentrations occur
function	often single and defined function, catalytic center, structural element	pathological interactions? gain of pathological functions?

3.7. Metal Ions and Amyloid Formation

The effect of Cu and Zn ions on Aβ aggregation was recently reviewed by us.[40] Here we just want to discuss the dynamic aspects. For a long time, the aggregation of metal ions coordinated to amyloidogenic peptides was considered with an inert Cu/Zn−peptide complex; that is, the complex Cu/Zn−Aβ formed a building block for aggregation. However, as mentioned above metal ions can exchange on a faster time scale than aggregation occurs. Results on a model peptide showed that the exchange can be very important for the aggregation behavior (Figure 6).[41]

For instance, due to the fast exchange, transient binding occurs. Thus, substoichiometric amounts of a metal ion could transiently interact with an entire pool of a much higher concentration peptide. Indeed, our studies of Zn interaction with an amyloidogenic peptide, Aβ11−28, suggested that transient Zn binding is sufficient to trigger the aggregation of a higher concentration peptide. Hence, Zn could be considered as an aggregation catalyst, only possible due to the fast exchange. Moreover, Zn bound to preaggregated Aβ11−28 was able to trigger aggregation of monomeric Aβ11−28 via metal exchange and not via the classical nucleation as one could expect. Whether the same holds for Aβ or other IDPs is not known, but the potential is there due to the metal-binding properties.

Despite the relatively low affinity of Aβ, metals could have an important impact on the aggregation. Low metal concentration might be enough for initiating aggregation due to transient binding and fast exchange (metal hopping mechanism, Figure 6). Such low concentrations could occur due to leaking by other proteins or by transient release of metal ions in the synaptic cleft (see above).

4. WHAT CAN BE GENERALIZED FROM CU/ZN−Aβ TO METAL ION BINDING TO IDPS?

First the considerations on dynamics summarized in Table 2 are restricted to the relatively kinetically labile metal ions, which include certainly Cu(II), Cu(I), Zn(II), Fe(II), etc. but not metals like Pt(II), Ru(II), or Co(III). Because these labile metals are the ones mostly involved neurodegenerative diseases, the dynamics is crucial. However, kinetically stable metals (Pt, Ru, Ir etc.) might be of importance in this context in a therapeutical approach.[33,42]

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It seems likely and is supported by the literature that kinetically more labile metal ions interact with other IDPs than Aβ, α-synuclein, amylin, etc., in a similar way, that is, they have modest affinity, fast exchange, etc.[30,43] This holds also for the interaction of metal ions with the unstructured part of a protein, like in the prion, that has also a structured part, but in which the octarepeat metal-binding domain is intrinsically disordered.[44]

So far we considered Aβ and other IDPs in their monomeric form. The disorder changes upon aggregation into fibrils, because fibrils contain a high amount of β-sheets. If the metal-binding site would be located in the well structured amyloid region, the metal site could be well structured as well (and hence have properties more like that of the well structured monomeric metalloproteins). In the case of Aβ, this seems not to be the case, because the binding site is in the flexible part of the amyloid aggregates. Perhaps induction of well structured metal sites upon aggregation for Aβ and other IDPs will not be easy to achieve, because the architecture of the amyloid structure is restricted and hence might not easily allow the insertion of a well optimized metal site (little induced fit possible). In a similar direction goes the reflection about the fact that IDPs can obtain a more defined structure upon binding to a partner. There is another biological relevant possibility that this creates a more classical metal-binding site. Indication for such an example has been reported for Cu(I)−α-synuclein by using TFE as membrane mimic.[45]

In conclusion, for IDPs that form disordered complexes with d-block metals (like Cu, Zn, Fe, Mn) with fast exchange between different binding sites, it seems more tempting to assume that this interaction is pathophysiological. The main argument is that the high dynamics of the metal−protein interaction is incompatible with tight control of the reactivity of the metal ions. This is particular dangerous for Cu (or Fe), due to its strong ability to catalyze ROS production.

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Notes

The authors declare no competing financial interest.

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Christelle Hureau studied physical chemistry at the University of Paris XI, where she also did her Ph.D. research on Mn-based inorganic models of photosystem II in the group of Prof. Girerd. She focused on electrochemistry and advanced EPR techniques during her postdoctoral stays. In 2007, she joined the group of Prof. Faller, where she studies fundamental aspects of metal ion interactions with amyloid-β peptide.

Giovanni La Penna has been Researcher of the National research council of Italy since 1997. Born in Firenze (I), he earned his Master degree in chemistry at the University of Firenze (I) and his Ph.D. in chemical sciences at the University of Pisa (I). He has had collaborations, within grants, postdoctoral positions, and exchange programs with IBM-SEMEA (I), Scuola Normale Superiore (Pisa, I), Profs. J. W. Emsley and G. R. Luckhurst (Southampton, UK), Dr. D. Genest (Orleans, F), Prof. Y. Okamoto (Okazaki, Japan), and Prof. M. Solà (Girona, E). The present focus of the research is the role of metal ions in biological and biomimetic processes, investigated by means of molecular models and computational techniques.

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