HAL
open science

Metals and Neuronal Metal Binding Proteins Implicated in Alzheimer's Disease

Joana S Cristóvão, Renata Santos, Cláudio Gomes

To cite this version:

Joana S Cristóvão, Renata Santos, Cláudio Gomes. Metals and Neuronal Metal Binding Proteins Implicated in Alzheimer's Disease. Oxidative Medicine and Cellular Longevity, 2016, 2016, pp.1-13. 10.1155/2016/9812178 . hal-02328478

HAL Id: hal-02328478

https://hal.science/hal-02328478

Submitted on 23 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Hindawi Publishing Corporation
Oxidative Medicine and Cellular Longevity
Volume 2016, Article ID 9812178, 13 pages
http://dx.doi.org/10.1155/2016/9812178

Review Article

Metals and Neuronal Metal Binding Proteins Implicated in Alzheimer's Disease

Joana S. Cristóvão,[1] Renata Santos,[2] and Cláudio M. Gomes[1]

[1] *Faculdade de Ciências Universidade de Lisboa, Biosystems and Integrative Sciences Institute and Department of Chemistry and Biochemistry, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal*
[2] *Development of the Nervous System, Institut de Biologie de l'Ecole Normale Supérieure (IBENS), INSERM U1024, CNRS UMR8197, 46 rue d'Ulm, 75005 Paris, France*

Correspondence should be addressed to Cláudio M. Gomes; cmgomes@fc.ul.pt

Received 5 November 2015; Accepted 17 December 2015

Academic Editor: Felipe Dal Pizzol

Copyright © 2016 Joana S. Cristóvão et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Alzheimer's disease (AD) is the most prevalent age-related dementia affecting millions of people worldwide. Its main pathological hallmark feature is the formation of insoluble protein deposits of amyloid-β and hyperphosphorylated tau protein into extracellular plaques and intracellular neurofibrillary tangles, respectively. Many of the mechanistic details of this process remain unknown, but a well-established consequence of protein aggregation is synapse dysfunction and neuronal loss in the AD brain. Different pathways including mitochondrial dysfunction, oxidative stress, inflammation, and metal metabolism have been suggested to be implicated in this process. In particular, a body of evidence suggests that neuronal metal ions such as copper, zinc, and iron play important roles in brain function in health and disease states and altered homeostasis and distribution as a common feature across different neurodegenerative diseases and aging. In this focused review, we overview neuronal proteins that are involved in AD and whose metal binding properties may underlie important biochemical and regulatory processes occurring in the brain during the AD pathophysiological process.

1. Alzheimer's Disease: Hallmark Amyloid Aggregation and Neuronal Dysfunction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline. The neuropathology hallmarks are gross atrophy of the cortex and hippocampus, and the accumulation of amyloid-beta (Aβ) into senile plaques and of hyperphosphorylated tau into neurofibrillary tangles. The deposition of Aβ and hyperphosphorylated tau aggregates in the human brain occurs in opposite directions with an orderly neuroanatomical pattern. Amyloid plaques first appear in the neocortex and slowly progress through the striatum, the basal cholinergic nuclei, the brain stem, and finally the cerebellum [1]. The deposition of tangles begins in the brain stem and progresses towards the neocortex [2]. Thus, the common presence of amyloid plaques and tau neurofibrillary tangles in the cortex only happens at late stages of the disease.

AD is heterogeneous and multifactorial with sporadic and familial forms [3–6]. The large majority of patients have the sporadic form or late onset dementia (later than 65 years). The few remaining patients have the familial form with early onset dementia (around 30 years to 65 years) and may present different symptoms. These patients have mutations in one of three genes encoding proteins essential for Aβ formation: the amyloid precursor protein (APP) and presenilins 1 and 2 (PSEN1/2) [7–10]. Presenilins are components of catalytic subunit of γ-secretase multicomplex, responsible for the cleavage of APP and formation of Aβ. The origin of the sporadic form is complex involving multiple genetic and environmental risk factors, for example, the presence of apolipoprotein E-ε4 allele, mitochondrial dysfunction, head injury, or a compromised brain blood barrier [3, 11]. Despite the fact that AD is the most common form of dementia of the elderly and affects millions of people worldwide, the exact cause of this disorder is still unknown. The genetic evidence

obtained from the rare familial form of AD supports the hypothesis that the accumulation of Aβ plaques is at the origin of the disease. This is the foundation for the amyloid-β cascade hypothesis [12] which has been the central theory in AD research for the last three decades. According to this hypothesis, the deposition of Aβ is the initial event and it is sufficient to trigger the cascade of pathological and clinical changes in AD, which are the formation of senile plaques and neurofibrillary tangles and subsequent neuronal death, vascular damage, and dementia [12]. Although senile plaque deposition is an early event in the disease, as observed in postmortem human brains [1], plaque accumulation in the brain does not correlate with dementia [13] implying that other mechanisms are associated with neurodegeneration. Notably, therapies designed until now that aimed at targeting amyloid plaques and APP proved to be largely unsuccessful. An increasing amount of data challenges the amyloid-β cascade hypothesis.

Therefore, efforts to integrate the other pathogenic features of AD and multiple etiology pathways into a more global model are now needed. During the course of AD, tau is hyperphosphorylated and accumulates in the somatodendritic compartment as paired helical filaments and straight filaments [14]. In neurons, tau is the major microtubule associated protein and stabilizes its structure. Tau interacts with tubulin promoting its assembly into microtubules. The level of phosphorylation regulates the activity of tau and hyperphosphorylation suppresses its microtubule assembly activity. In addition, hyperphosphorylated tau sequesters normal tau and other microtubule associated proteins that further contribute to microtubule disassembly [15]. Therefore, the abnormal phosphorylation of tau results in loss of normal function and gain of toxic function in the AD brain. The formation of neurofibrillary tangles does correlate with cognitive decline and with neuronal and synapse loss [13, 16].

Senile plaques are extracellular deposits composed mainly of amyloid peptides ranging from 39 to 43 amino acids, which are natural metabolites of APP generated by sequential cleavage by β-secretase and γ-secretase l [17]. The APP is a transmembrane protein necessary for neurogenesis, for neurite outgrowth and guidance, and for synapse formation and repair [18]. APP is processed in different ways through different enzymes leading to the formation of amyloidogenic and nonamyloidogenic precursors. The processing of APP results in the formation of soluble α- and β-secreted APP (sAPP) which is cleaved by α- and β-secretase, respectively. As a product in the nonamyloidogenic pathway, sAPPα promotes neuronal survival and neurite outgrowth, among other beneficial neuronal functions. Contrarily, sAPPβ is not involved in the beneficial functions of sAPPα, participating in synapse pruning. Aβ is secreted through sequential APP cleavage by β- and γ-secretases, resulting in peptides that can range from 39 to 43 amino acids. The Aβ peptides are catabolized by multiple amyloid degrading enzymes, for example, neprilysin and insulin-degrading enzyme [19]. It is the imbalance between the production and clearance of Aβ that triggers its deposition as amyloid plaques. However, several studies suggest that Aβ has a physiological role in the synapses and its complete removal induces neuronal cell death [20–22]. In addition to the aggregates, Aβ is also present in soluble oligomeric forms in APP-transgenic mice and human diseased brains [20]. Compared to Aβ aggregates, the soluble oligomers are highly neurotoxic [23]. Therefore, it is possible that aggregation of Aβ into plaques is a neuroprotective mechanism that eliminates the toxic oligomeric forms [15].

The normal functions of synapses are impaired during the course of AD. Synapse loss correlates with dementia suggesting that it is important for disease progression and for the degeneration process [24]. Dense plaque deposition causes the surrounding neurites to bend and change trajectory, which can lead to changes in synapse signal transmission. Also, gliosis and oxidative stress are observed in the vicinity of plaques. During normal development of the brain, microglia are involved in synaptic pruning after birth and it is possible that in the diseased AD brain the recruitment of activated microglia around the plaques participates in the synapse loss [24]. In addition to aggregates, the oligomeric forms of Aβ obtained from cultured cells or from human AD brain disturb synapses and lead to cognition impairment in injected mice [25–27]. Comparably, evidence also shows that soluble forms of tau are toxic for synapses [28]. The molecular mechanisms that lead to synapse dysfunction and neuronal loss downstream of Aβ and tau are not completely identified but different pathways are implicated such as mitochondrial dysfunction, oxidative stress, inflammation, and dysregulation of metal homeostasis.

2. Metals and Metal Binding Proteins Implicated in AD

Metal ions play essential roles in the brain and there is solid evidence pointing to their homeostatic dysfunction across different neurodegenerative diseases (e.g., [29–31]). This includes the first row transition metals, iron, copper, and zinc and also calcium, whose homeostasis is important for neuronal function and during aging [32–34]. One major hypothesis for this cross talk, which has been put forward since a number of years and which has been elegantly reviewed in [35], proposes that AD is as much as a metallopathy as a proteinopathy. Indeed, age-related metal ion dysfunction altered levels of neuronal metal ions in AD-affected areas including accumulation in protein deposits, and the interplay between metal ions and AD pathological proteins indicates a close relationship between protein misfolding, aggregation, and metal ion homeostasis. In AD patients, it has been shown that Cu^{2+}, Zn^{2+}, and Fe^{2+} are found in the core and rims of senile plaques [36, 37] and colocalize with Aβ [38]. This has led to the suggestion that metal ion sequestration into plaques could lead to deficient distribution of these metals in the neighbouring regions [39]. Moreover, it is described that in AD patients Zn^{2+} is decreased in serum and blood but increased in the cerebrospinal fluid and neocortical tissue [40–42]. In addition, Zn^{2+}, Cu^{2+}, and Fe^{2+} are increased in the neuropil of AD patients [36, 43]. In agreement with a role of metal ions in pathology, molecules designed to chelate Zn^{2+} and Cu^{2+} from amyloid-beta aggregates [44, 45] were

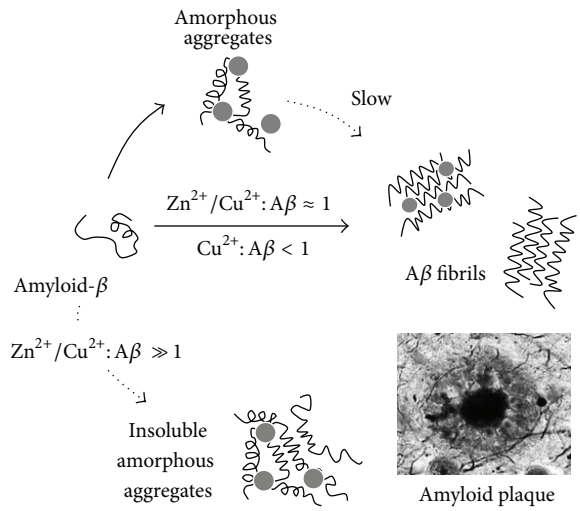


Figure 1: Modulation of amyloid-β aggregation by Cu^{2+} and Zn^{2+} binding. Aβ aggregation into fibrils is a complex pathway that involves multiple intermediate precursor species. The scheme is a simplification depicting direct effects of Cu^{2+} and Zn^{2+} on Aβ aggregation. Superstoichiometric levels of Cu^{2+} and Zn^{2+} (Zn^{2+}/Cu^{2+}: A$\beta \gg 1$) result in insoluble and amorphous aggregates rather than organized fibrils, while equimolar Cu^{2+} and Zn^{2+} (Zn^{2+}/Cu^{2+}: A$\beta \approx 1$) induce amorphous aggregates, which slowly convert to fibrils. At subequimolar Cu^{2+} levels (Cu^{2+}: A$\beta < 1$), the kinetics of fibril formation are accelerated. The AD amyloid plaques, depicted in a representation at the bottom right corner of the figure, contain high levels of Zn (1055 μM), Fe (940 μM), and Cu (390 μM), as reviewed in [35]. See text for details.

found to decrease Aβ deposits in mice models due to Aβ solubilisation [45]. Here, as a contribution for a broader molecular and biochemical analysis of protein-metal cross talks in neurodegeneration, we undertake an overview of proteins with metal binding properties which are implicated in AD (Table 1).

2.1. Amyloid-β. Metal ions have been acknowledged as important players of the pathological effects of Aβ aggregation in AD and have been considered as possible modulators of Aβ misfolding and aggregation due to their binding to the Aβ peptide [46–49] and to amyloid fibrils [50, 51]. Cu^{2+}, Zn^{2+}, and Fe^{2+} bind to Aβ influencing its aggregation pathway and are found in and nearby extracellular senile plaques [29, 36]. The binding of metal ions to Aβ invariably results in aggregation which may either be into amyloid fibers or into amorphous aggregates, depending on the metal ion, stoichiometry, and environmental conditions [49]. In spite of contradictory findings, there seems to be a consensus that (a) superstoichiometric levels of Cu^{2+} and Zn^{2+} result in insoluble and amorphous aggregates rather than organized fibrils [49, 52–55]; (b) equimolar Zn^{2+} and Cu^{2+} induce amorphous aggregates, which slowly convert to fibrils [56, 57]; and (c) at subequimolar Cu^{2+} levels, the kinetics of fibril formation are accelerated [52, 58, 59] (Figure 1). The observation that high levels of Zn^{2+} and Cu^{2+} seem to shift aggregation into oligomeric precursors rather than organized fibrils has important consequences in brain function, as these Aβ precursors are now known to be the neurotoxic self-propagating species causing neurodegeneration. Furthermore, Cu^{2+} and Fe^{2+} participate in ROS production causing oxidative stress and neuronal damage, thus being one of the causes that potentiate Aβ toxicity [60–62]. Indeed, the formation of H_2O_2 as a product of the interaction between Aβ and Cu^{2+} can generate hydroxyl radicals, which are related to AD pathology [63]. Superoxide has also been recently shown to be an intermediate of the reaction leading to the production of H_2O_2 by Cu^{+}-Aβ and O_2 [64]. Zinc and copper chelators inhibit Aβ plaque deposition in AD patients [44, 65, 66], further suggesting that amyloid pathology may arise from the dysregulation of these metal ions. Excess of iron increases Aβ production [67] and leads to the formation of annular protofibrils [68] and slows down the formation of ordered cross-β fibrils [69] towards the formation of shorter and less ordered aggregates [53, 69] which are potentially more toxic.

2.2. Tau. Tau is a disordered cytosolic protein involved in microtubule assembly and stability whose aggregation and toxic deposition are triggered by hyperphosphorylation. This results in the formation of intracellular tau paired helical filaments (PHF), which ultimately gather to form the characteristic neurofibrillary tangles (NFT) [70, 71], a process which is modulated by metal ions [30] (Figure 2). Zn^{2+} binds tau and promotes its hyperphosphorylation [72]; however, low concentrations of zinc induce fibril formation whereas high concentrations induce granular aggregates [73]. Fe^{3+} also binds to hyperphosphorylated tau and induces its aggregation [74, 75], mostly into PHF [75]; however, reduction to Fe^{2+} can reverse aggregation of tau [75]. Excess of iron is accumulated in NTF [76, 77] generating oxidative stress due to the Fenton reaction and perpetuating tau hyperphosphorylation [78]. The role of Cu^{2+} in tauopathies is controversial. Some studies suggest that tau binds Cu^{2+} [79], inhibiting its aggregation

Table 1: Effect of metal ions on selected metal-binding proteins implicated in AD.

Protein	Metal	Effect	Model	Reference
Aβ	Cu^{2+}	Modulates aggregation. Presence of Cu^{2+} in Aβ aggregates decreases toxicity; however, presence of Cu^{2+} in soluble Aβ accelerates cell death. Substoichiometric levels of Cu^{2+} render Aβ aggregates more toxic.	Synthetic Aβ, HEK cells, primary hippocampal cells, and PC12 cells	[49, 52–55, 57–59]
		Increases oxidative stress and neurotoxicity.	Synthetic Aβ, primary neuronal cells	[60, 63, 126, 127]
	Zn^{2+}	Modulates aggregation. Zn^{2+} leads to less toxic Aβ aggregates.	Synthetic Aβ, HEK cells, and primary cortical cells	[49, 53, 54, 57]
	Fe^{2+}	Modulates aggregation promoting the formation of annular protofibrils.	Synthetic Aβ	[49, 68, 69]
		Increases protein levels by disruption of APP processing.	Primary cortical neurons, APP/PS1 mice model, and HEK cells	[67]
		Increases oxidative stress.	M17 neuroblastoma cells, *Drosophila* model	[61, 62]
Tau	Cu^{2+}	Modulates phosphorylation.	Tg-AD mice model, SH-SY5Y cells, and AD mice model	[81, 82]
		Modulates aggregation.	Peptide from tau first microtubule-binding repeat	[80]
	Zn^{2+}	Induces phosphorylation through Zn^{2+} PP2A inhibition.	Rat brain slice cultures, primary neuronal cells	[72]
		Induces fibril formation via disulfide cross-linking.	Recombinant tau protein	[73]
	Fe^{2+}	Modulates aggregation.	Recombinant tau protein, isolated hyperphosphorylated tau from human AD brain tissue	[74, 75]
		Induces imbalance in Cdk5/p25 function that causes a decrease in tau phosphorylation and an increase in oxidative stress.	Primary hippocampal cells	[78, 128]
APP	Cu^{2+}	Increases APP expression levels and Aβ secretion. Promotes APP trafficking and its redistribution.	SH-SY5Y cells, polarized epithelial cells, MDCK-APP-cherry cells, primary cortical neurons, N2a cells, and APP/PS1 mouse model	[81, 83, 85, 86]
		Increases oxidative stress. Cu^{2+}-metalated APP ectodomain promotes neuronal cell death.	Recombinant APP protein and mutants, primary neuronal cells	[90, 91]
	Zn^{2+}	Inhibits ferroxidase activity.	Human brain tissue	[92]
		Increases APP expression levels and amyloidogenic cleavage that leads to accumulation of Aβ.	SH-SY5Y cells, APP/PS1 mice model	[84]
	Fe^{2+}	APP interacts with ferroportin and promotes iron export.	Human brain tissue, HEK293 cells	[92, 93]
Presenilin	Ca^{2+}	Overexpression of PS1 decreases Ca^{2+} release from ER and downregulates Ca^{2+}-dependent mitochondrial transport proteins. Expression of PPS1 M146V causes inhibition of Ca^{2+} channels.	HEK293 cells, human brain tissue, SH-SY5Y cells, SK-N-SH cells, and APPswe/PS1dE9 mice model	[95–97]
MT3	Cu^{2+} Zn^{2+}	Decreases protein levels.	Human brain tissue, Tg2576 mouse model	[100, 101]
		MT3 interacts with Aβ inhibiting/modulating Aβ aggregation and cytotoxicity.	Recombinant MT3 protein and synthetic Aβ, SH-SY5Y cells, primary cortical cells, and Tg2576 mouse model	[104–107]
		Metal swapping between MT3 and Aβ lowers ROS production and decreases neurotoxicity.	Recombinant MT3 protein and synthetic Aβ, SH-SY5Y cells	[109]
		MT3 increases sAPPα levels and reduces Aβ production.	N2a Swedish APP cells	[102]
ZnTs	Zn^{2+}	Increases expression levels and colocalization with amyloid plaques.	APP/PS1 mouse model, human brain tissue	[110–112, 129]

Table 1: Continued.

Protein	Metal	Effect	Model	Reference
ProSAP/Shank scaffold proteins	Zn^{2+}	Zn^{2+} sequestering by Aβ decreases Shank1 and ProSAP27Shank3 protein levels and promotes synapse loss by disruption of Homer1b and Shank1 scaffold.	Primary hippocampal cells, human brain tissue, and Cos7 cells	[115–117]
	Ca^{2+}	Homers 2 and 3 interact with APP inhibiting APP processing and consequently reducing Aβ secretion.	HEK293 cells, C57/Black6 mouse model	[130, 131]
Ferritin	Fe^{2+}	Increases protein levels. Present within and around amyloid plaques and neurofibrillary tangles.	Human brain tissue	[119–121]
S100B	Ca^{2+}	Increased expression of S100B contributes to overexpressing βAPP in diffuse amyloid deposits.	Primary neuron cells	[132]
	Zn^{2+} Ca^{2+}	S100B interacts with tau resulting in the inhibition of tau phosphorylation via Ca^{2+}/calmodulin-dependent kinase II.	Bovine S100B, SH-SY5Y cells	[133, 134]
S100A9	Ca^{2+}	Increases protein levels. Present near amyloid plaques. Interacts with Aβ *In vitro* and forms linear and annular aggregates. Knockout of the S100A9 gene reduces neuropathology due to reduced Aβ and APP C-terminal levels.	Human brain tissues, Tg2576 mice model, SH-SY5Y cells, and S100A9 recombinant protein	[135–139]
S100A7	Ca^{2+}	Expression of exogenous S100A7 inhibits Aβ production and promotes α-secretase activity.	Primary corticohippocampal cells	[140]

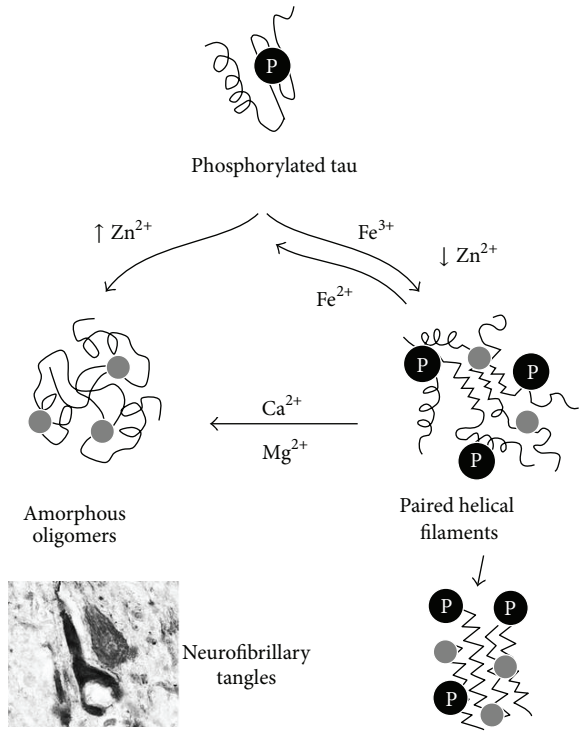


Figure 2: Modulation of tau aggregation by metal ions. Hyperphosphorylated (P) tau undergoes aggregation, which is influenced by metal ion binding. Tau phosphorylation facilitates Fe^{3+} binding that promotes the formation of paired helical filaments (PHF) and further tau fibrillation. The reduction of Fe^{3+} to Fe^{2+} reverts PHF formation. Zn^{2+} binding at high ratios promotes the formation of amorphous tau oligomers, whereas, at low ratios, PHF are formed. Both Ca^{2+} and Mg^{2+} binding to PHF favour the conversion into amorphous off-pathway aggregates. A neurofibrillary tangle is depicted in a representation at the bottom left corner of the figure. See text for details. Adapted from [30].

in vitro [80] while promoting tau hyperphosphorylation in hippocampal neurons [81]. Other studies however suggest that addition of copper-bis(thiosemicarbazone) complexes that increase intracellular copper in AD mice brains inhibits tau phosphorylation [82].

2.3. Amyloid-Beta Precursor Protein. Abnormal processing of the amyloid precursor protein leads to neurotoxic Aβ production. The proteolytic processing of APP is influenced by metal ions, by protein ligands, and by the APP oligomerization state. Cu^{2+} and Zn^{2+} promote APP expression [83–85] and possibly interfere with Aβ metabolism. Cu^{2+} enhances APP dimerization and increases extracellular release of Aβ [86]; yet, other studies suggest that high copper concentrations modulate APP processing leading to reduced Aβ production [87]. Interestingly, APP contains a copper binding domain and a site that favours Cu^{+} coordination, which has led to the suggestion that it could act as a neuronal metallotransporter [87]. Recent structural and biochemical studies have uncovered a high-affinity binding site within the E2 domain that binds competitively Cu^{2+} and Zn^{2+} at physiological concentrations [88]. Metal binding results in large conformational changes and in different structural states that regulate the function of APP and Aβ metabolism [89]. Indeed, APP can be a mediator of Cu neurotoxicity since it was shown that in primary neuronal cultures APP loaded with Cu^{2+} induces cell death [90]. This may possibly involve catalytic reduction of Cu^{2+} to Cu^{+} leading to an increase in oxidative stress in neurons [91]. The links between APP and metal metabolism are further emphasized by the interaction of APP with ferroportin, to promote iron export and its ferroxidase activity [92, 93]. APP ferroxidase activity is inhibited by Zn^{2+} binding contributing to Fe^{2+} accumulation in AD brains [92].

2.4. Presenilin-1. Presenilin-1 (PS-1) is a component of the γ-secretase multicomplex, responsible for the cleavage of APP. Presenilins have an activity as low-conductance passive ER Ca^{2+} leak channels which is independent of γ-secretase activity [94]. Overexpression of presenilin results in increased Ca^{2+} release whose levels are restored by γ-secretase inhibitors [95]. Mutations in presenilins as in familial AD forms result in downregulation of Ca^{2+} channels and Ca^{2+}-dependent mitochondrial transport proteins, strengthening the relationship between Ca^{2+} homeostasis and presenilin [94, 96, 97]. A recent study based on the effects of metal chelators on γ-secretase suggests that Ca^{2+} and Mg^{2+} stabilize γ-secretase and enhance its activity [98].

2.5. Metallothionein 3. Metallothioneins are a family of ubiquitous proteins with metal binding properties and antioxidant

activity [99]. Neuronal metallothionein 3 (MT3), which is involved in the transport and homeostasis of Zn^{2+} and Cu^{2+}, plays an important role in several AD related pathways. MT3 is decreased in AD patients [100] and in Tg2576 mice [101], which can lead to aberrant neuritic sprouting [100]. Additionally, MT3 increases sAPPα (soluble amyloid precursor protein α) levels and reduces Aβ production [102], through an increase in ADAM10 (a disintegrin and metallopeptidase 10). ADAM10 is a protein responsible for the cleavage of APP-derived peptides and activation of the nonamyloidogenic pathway [103]. Mechanistically, it has been reported that the β-domain of MT3 interacts with Aβ, abolishing Cu^{2+} mediated aggregation [104, 105] and ROS production [104]. It has also been suggested that rapid metal exchange between Zn^{2+}-MT3 and Cu^{2+}-Aβ [106] or Zn^{2+} release by MT3 [107] promotes structural changes in Aβ aggregates. In agreement with this, in primary neuron cultures, MT3 inhibits the formation of toxic Aβ aggregates alleviating their neurotoxic effects [105, 108]. One possible mechanism for this effect may be related to the observed metal swapping between MT3 and soluble and aggregated Aβ, which abolishes the production of Cu-induced ROS [104, 109].

2.6. Zinc Transporter 3. Zinc transporter 3 (ZnT3) is a synaptic Zn^{2+} transporter responsible for loading zinc into presynaptic vesicles. This protein is highly expressed in the brains of AD transgenic mice, in which it colocalizes with amyloid plaques [110–112], where zinc is also found at high concentrations. Zinc sequestering within amyloid plaques has been suggested to provoke an imbalance in the cellular environment with concurrent effects on overall metal metabolism and protein homeostasis [35]. ZnT3 has been shown to decrease with aging and AD, contributing to the aggravation of zinc-mediated cognitive decline [113]. In the AD Tg2576 transgenic mouse model with a ZnT3 knockout, cerebral Aβ deposition was nearly abolished by the lack of synaptic Zn^{2+} [58, 59]. ZnT3 and other zinc transporters, such as ZnTs 1, 4, 5, 6, and 7, are also found upregulated in amyloid plaques of human AD brains near Zn^{2+} enriched terminals [60], revealing a cross talk between zinc induced amyloid plaques and zinc transporters. In ZnT3 knockout mice, the addition of metal chaperones results in restoration of expression of the synaptic proteins PSD-95, AMPAR, and NMDAR2b, due to the restitution of hippocampal zinc content [113].

2.7. ProSAP/Shank Scaffold Proteins. ProSAPs/Shanks are zinc-regulated multidomain proteins that are important scaffolding molecules of the postsynaptic density (PSD), a protein dense structure composed of both membranous and cytoplasmic proteins localized at the postsynaptic plasma membrane of excitatory synapses [114]. Deregulation of ProSAP/Shank has been reported in AD: in patients brains and in transgenic mice models, the accumulation of Aβ oligomers is accompanied by reduction of synaptic scaffold protein levels, such as Shank1 and ProSAP2/Shank3 [115], and disruption of the Homer1b and Shank1 scaffolds [116]. Interestingly, sequestration of Zn^{2+} by Aβ leads to less mature synapses by decreasing Shank1 protein levels at the postsynaptic density in hippocampal neurons [117]. Future studies will further elucidate the mechanistic cross-links between the presence of Aβ, zinc levels, and the scaffolding PSD proteins in the context of AD [118].

2.8. Ferritin. Ferritin is the major intracellular iron storage protein in the body. It has elevated levels in AD brain tissue [119–121] and is found in the vicinity of AD plaques [120], suggesting that ferritin trapped within the plaque inclusions may block the transport of iron between cells. The loss of integrity of hippocampus tissue of AD patients is linked with the increase of ferritin [122] and with a reduction of ferroportin protein levels [123]. Effectively, the impact of iron on AD outcomes is not fully explored but a recent longitudinal study has shown that ferritin is strongly associated with cerebrospinal fluid apolipoprotein E levels; in turn, ferritin is elevated by the Alzheimer's risk allele, APOE-ε4 [124]. This study speculates that the APOE-ε4 genotype raises the baseline iron load in the AD brain, lowering the threshold for iron-mediated neuronal loss, a hypothesis that remains to be experimentally addressed.

2.9. S100 Proteins. S100 proteins are a family of at least 21 different vertebrate-specific proteins with two Ca^{2+}-binding EF-hand type sites and in some cases additional sites for Zn^{2+} and Cu^{2+} [125]. S100 proteins are part of the inflammatory response and a number of these proinflammatory cytokines (S100B, S100A6, S100A7, S100A1, S100A9, and S100A12) have been implicated in neurodegenerative disorders, such as AD.

S100B is a proinflammatory cytokine that triggers glial cell proliferation in a RAGE-dependent manner [141]. RAGE is an immunoglobulin-like cell surface receptor that is upregulated in AD and triggers the expression of proinflammatory cytokines and mediates Aβ transport across the blood-brain barrier [142–144]. At high micromolar concentrations, S100B promotes neuroinflammatory processes and neuronal apoptosis [145]. Increased expression of S100B by plaque-associated astrocytes in AD contributes to the appearance of dystrophic neurites overexpressing βAPP in diffuse amyloid deposits [132]. Astrocytic overexpression of S100B is correlated with the degree of neurite pathology in Aβ aggregates and is induced by interleukin-1 (IL-1), which is secreted by activated microglia present in the plaques [146]. TNFα, a cytokine with high levels in AD, decreases S100B expression in astrocytes but increases its extracellular levels which can lead to RAGE activation [147]. Furthermore, studies demonstrated increased susceptibility to neuroinflammation and neuronal dysfunction after infusion of Aβ in transgenic mice overexpressing S100B [148]. Interestingly, S100B interacts with tau in a Zn^{2+} dependent fashion that could be responsible for neurite outgrowth [133]. Other studies, however, suggest that the S100B:tau interaction is mediated by Ca^{2+}/calmodulin-dependent kinase II and results in the inhibition of tau phosphorylation [134].

S100A6, S100A9, and S100A12 also have consistently high levels in samples of AD patients [135, 149]. In particular, S100A9 is found near neuritic plaques [136, 137] and was

found to coaggregate with Aβ *in vitro* and form toxic aggregates [136, 138]. Knockout of S100A9 in a transgenic mouse resulted in reduced Aβ levels in the brain and the animals presented an improved spatial reference memory [139]. In agreement with these observations, knockdown of S100A9 in the AD Tg2576 mice model reduced Aβ and APP C-terminal levels and decreased BACE activity [137]. Induction of S100A9 levels increased intracellular Ca^{2+} levels, which in turn upregulated secretion of the inflammatory cytokines IL-1β and TNFα [150]. On the opposite, expression of exogenous S100A7 in primary corticohippocampal neuron cultures derived from Tg2576 transgenic embryos inhibits the generation of Aβ and promotes the activity of α-secretase [140]. Interestingly, S100 proteins have been found to have amyloidogenic properties [151–155]. This feature, along with the high abundance of S100 proteins in protein deposits, their metal binding properties, dysregulation of Ca^{2+} signalling, and the high levels of Cu^{2+} and Zn^{2+} in the plaques, will certainly translate into the elucidation of new functions of S100 proteins in AD pathomechanisms.

3. Conclusion

Metal homeostasis and balance depend on a number of biochemical processes and proteins, many of which operate in the neuronal environment and in the extracellular synaptic space or at its interface. The biochemistry of this particular cellular moiety is deeply altered upon aging and under neurodegeneration, with wide changes in protein levels, signalling molecules, and metal ion concentrations. Changes in protein and metal ion homeostasis are hallmark features across amyloid-forming neurodegenerative diseases and as we have here overviewed, a number of proteins implicated in AD are directly regulated by metal-protein interactions; in some cases, metal ions are even directly involved as modulators of aggregation pathways. Uncovering the mechanistic details of this cross talk at the biochemical levels in respect to effects on synaptic protein networks, Aβ metabolism and intra- and extracellular protein aggregation in the context of concurrent affected processes such as oxidative stress and neuroinflammation are thus among the major challenges in modern molecular neurosciences.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by the Bial Foundation through grant PT/FB/BL-2014-343 (to CMG), by the Fundação para a Ciência e a Tecnologia through grant PTDC/QUI-BIQ/117789/2010 (to CMG), PhD fellowship SFRH/BD/101171/2014 (to JSC), and grant UID/MULTI/04046/2013 from FCT/MCTES/PIDDAC (to BioISI). CMG is a recipient of a Consolidation Level Investigator FCT, also from the Fundação para a Ciência e a Tecnologia (IF/01046/2014).

References

[1] D. R. Thal, U. Rüb, M. Orantes, and H. Braak, "Phases of Aβ-deposition in the human brain and its relevance for the development of AD," *Neurology*, vol. 58, no. 12, pp. 1791–1800, 2002.

[2] R. J. Castellani and G. Perry, "The complexities of the pathology–pathogenesis relationship in Alzheimer disease," *Biochemical Pharmacology*, vol. 88, no. 4, pp. 671–676, 2014.

[3] R. A. Armstrong, "What causes Alzheimer's disease?" *Folia Neuropathologica*, vol. 51, no. 3, pp. 169–188, 2013.

[4] C. M. Karch, C. Cruchaga, and A. M. Goate, "Alzheimer's disease genetics: from the bench to the clinic," *Neuron*, vol. 83, no. 1, pp. 11–26, 2014.

[5] D. H. Kim, S. H. Yeo, J.-M. Park et al., "Genetic markers for diagnosis and pathogenesis of Alzheimer's disease," *Gene*, vol. 545, no. 2, pp. 185–193, 2014.

[6] I. Piaceri, B. Nacmias, and S. Sorbi, "Genetics of familial and sporadic Alzheimer's disease," *Frontiers in Bioscience*, vol. 5, no. 1, pp. 167–177, 2013.

[7] A. Goate, M.-C. Chartier-Harlin, M. Mullan et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," *Nature*, vol. 349, no. 6311, pp. 704–706, 1991.

[8] E. Levy-Lahad, W. Wasco, P. Poorkaj et al., "Candidate gene for the chromosome 1 familial Alzheimer's disease locus," *Science*, vol. 269, no. 5226, pp. 973–977, 1995.

[9] E. I. Rogaev, R. Sherrington, E. A. Rogaeva et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene," *Nature*, vol. 376, no. 6543, pp. 775–778, 1995.

[10] R. Sherrington, E. I. Rogaev, Y. Liang et al., "Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease," *Nature*, vol. 375, no. 6534, pp. 754–760, 1995.

[11] W. J. Strittmatter, K. H. Weisgraber, D. Y. Huang et al., "Binding of human apolipoprotein E to synthetic amyloid β peptide: isoform-specific effects and implications for late-onset Alzheimer disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 17, pp. 8098–8102, 1993.

[12] J. A. Hardy and G. A. Higgins, "Alzheimer's disease: the amyloid cascade hypothesis," *Science*, vol. 256, no. 5054, pp. 184–185, 1992.

[13] P. Giannakopoulos, F. R. Herrmann, T. Bussière et al., "Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease," *Neurology*, vol. 60, no. 9, pp. 1495–1500, 2003.

[14] H. Zempel and E. Mandelkow, "Lost after translation: missorting of Tau protein and consequences for Alzheimer disease," *Trends in Neurosciences*, vol. 37, no. 12, pp. 721–732, 2014.

[15] K. Iqbal, F. Liu, and C.-X. Gong, "Alzheimer disease therapeutics: focus on the disease and not just plaques and tangles," *Biochemical Pharmacology*, vol. 88, no. 4, pp. 631–639, 2014.

[16] M. Ingelsson, H. Fukumoto, K. L. Newell et al., "Early Aβ accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain," *Neurology*, vol. 62, no. 6, pp. 925–931, 2004.

[17] Y. Ling, K. Morgan, and N. Kalsheker, "Amyloid precursor protein (APP) and the biology of proteolytic processing: relevance to Alzheimer's disease," *The International Journal of Biochemistry & Cell Biology*, vol. 35, no. 11, pp. 1505–1535, 2003.

[18] M. Nicolas and B. A. Hassan, "Amyloid precursor protein and neural development," *Development*, vol. 141, no. 13, pp. 2543–2548, 2014.

[19] N. N. Nalivaeva, C. Beckett, N. D. Belyaev, and A. J. Turner, "Are amyloid-degrading enzymes viable therapeutic targets in Alzheimer's disease?" *Journal of Neurochemistry*, vol. 120, no. 1, pp. 167–185, 2012.

[20] L. Mucke and D. J. Selkoe, "Neurotoxicity of amyloid β-protein: synaptic and network dysfunction," *Cold Spring Harbor Perspectives in Medicine*, vol. 2, no. 7, Article ID a006338, 2012.

[21] H. A. Pearson and C. Peers, "Physiological roles for amyloid β peptides," *The Journal of Physiology*, vol. 575, no. 1, pp. 5–10, 2006.

[22] L. D. Plant, J. P. Boyle, I. F. Smith, C. Peers, and H. A. Pearson, "The production of amyloid β peptide is a critical requirement for the viability of central neurons," *The Journal of Neuroscience*, vol. 23, no. 13, pp. 5531–5535, 2003.

[23] M. P. Lambert, A. K. Barlow, B. A. Chromy et al., "Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 11, pp. 6448–6453, 1998.

[24] T. L. Spires-Jones and B. T. Hyman, "The intersection of amyloid beta and Tau at synapses in Alzheimer's disease," *Neuron*, vol. 82, no. 4, pp. 756–771, 2014.

[25] J. P. Cleary, D. M. Walsh, J. J. Hofmeister et al., "Natural oligomers of the amyloid-β protein specifically disrupt cognitive function," *Nature Neuroscience*, vol. 8, no. 1, pp. 79–84, 2005.

[26] G. M. Shankar, B. L. Bloodgood, M. Townsend, D. M. Walsh, D. J. Selkoe, and B. L. Sabatini, "Natural oligomers of the Alzheimer amyloid-β protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway," *The Journal of Neuroscience*, vol. 27, no. 11, pp. 2866–2875, 2007.

[27] D. M. Walsh, I. Klyubin, J. V. Fadeeva et al., "Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo," *Nature*, vol. 416, no. 6880, pp. 535–539, 2002.

[28] A. M. Pooler, W. Noble, and D. P. Hanger, "A role for tau at the synapse in Alzheimer's disease pathogenesis," *Neuropharmacology*, vol. 76, pp. 1–8, 2014.

[29] A. I. Bush, "The metallobiology of Alzheimer's disease," *Trends in Neurosciences*, vol. 26, no. 4, pp. 207–214, 2003.

[30] S. S. Leal, H. M. Botelho, and C. M. Gomes, "Metal ions as modulators of protein conformation and misfolding in neurodegeneration," *Coordination Chemistry Reviews*, vol. 256, no. 19-20, pp. 2253–2270, 2012.

[31] S. Pfaender and A. M. Grabrucker, "Characterization of biometal profiles in neurological disorders," *Metallomics*, vol. 6, no. 5, pp. 960–977, 2014.

[32] S. Smaili, H. Hirata, R. Ureshino et al., "Calcium and cell death signaling in neurodegeneration and aging," *Anais da Academia Brasileira de Ciencias*, vol. 81, no. 3, pp. 467–475, 2009.

[33] P. Egorova, E. Popugaeva, and I. Bezprozvanny, "Disturbed calcium signaling in spinocerebellar ataxias and Alzheimer's disease," *Seminars in Cell & Developmental Biology*, vol. 40, pp. 127–133, 2015.

[34] S. S. Leal and C. M. Gomes, "Calcium dysregulation links ALS defective proteins and motor neuron selective vulnerability," *Frontiers in Cellular Neuroscience*, vol. 9, article 225, 2015.

[35] K. J. Barnham and A. I. Bush, "Biological metals and metal-targeting compounds in major neurodegenerative diseases," *Chemical Society Reviews*, vol. 43, no. 19, pp. 6727–6749, 2014.

[36] M. A. Lovell, J. D. Robertson, W. J. Teesdale, J. L. Campbell, and W. R. Markesbery, "Copper, iron and zinc in Alzheimer's disease senile plaques," *Journal of the Neurological Sciences*, vol. 158, no. 1, pp. 47–52, 1998.

[37] P. Zatta, D. Drago, S. Bolognin, and S. L. Sensi, "Alzheimer's disease, metal ions and metal homeostatic therapy," *Trends in Pharmacological Sciences*, vol. 30, no. 7, pp. 346–355, 2009.

[38] L. M. Miller, Q. Wang, T. P. Telivala, R. J. Smith, A. Lanzirotti, and J. Miklossy, "Synchrotron-based infrared and X-ray imaging shows focalized accumulation of Cu and Zn co-localized with β-amyloid deposits in Alzheimer's disease," *Journal of Structural Biology*, vol. 155, no. 1, pp. 30–37, 2006.

[39] B. R. Roberts, T. M. Ryan, A. I. Bush, C. L. Masters, and J. A. Duce, "The role of metallobiology and amyloid-β peptides in Alzheimer's disease," *Journal of Neurochemistry*, vol. 120, supplement 1, pp. 149–166, 2012.

[40] H. Basun, L. G. Forssell, L. Wetterberg, and B. Winblad, "Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease," *Journal of Neural Transmission—Parkinson's Disease and Dementia Section*, vol. 3, no. 4, pp. 231–258, 1991.

[41] L. Baum, I. H. S. Chan, S. K.-K. Cheung et al., "Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability," *BioMetals*, vol. 23, no. 1, pp. 173–179, 2010.

[42] D. Religa, D. Strozyk, R. A. Cherny et al., "Elevated cortical zinc in Alzheimer disease," *Neurology*, vol. 67, no. 1, pp. 69–75, 2006.

[43] G. M. Bishop, S. R. Robinson, Q. Liu, G. Perry, C. S. Atwood, and M. A. Smith, "Iron: a pathological mediator of Alzheimer disease?" *Developmental Neuroscience*, vol. 24, no. 2-3, pp. 184–187, 2002.

[44] M. Nguyen, A. Robert, A. Sournia-Saquet, L. Vendier, and B. Meunier, "Characterization of new specific copper chelators as potential drugs for the treatment of alzheimer's disease," *Chemistry—A European Journal*, vol. 20, no. 22, pp. 6771–6785, 2014.

[45] R. A. Cherny, C. S. Atwood, M. E. Xilinas et al., "Treatment with a copper-zinc chelator markedly and rapidly inhibits β-amyloid accumulation in Alzheimer's disease transgenic mice," *Neuron*, vol. 30, no. 3, pp. 665–676, 2001.

[46] C. S. Atwood, R. C. Scarpa, X. Huang et al., "Characterization of copper interactions with Alzheimer amyloid β peptides: identification of an attomolar-affinity copper binding site on amyloid β1–42," *Journal of Neurochemistry*, vol. 75, no. 3, pp. 1219–1233, 2000.

[47] D. Noy, I. Solomonov, O. Sinkevich, T. Arad, K. Kjaer, and I. Sagi, "Zinc-amyloid β interactions on a millisecond time-scale stabilize non-fibrillar Alzheimer-related species," *Journal of the American Chemical Society*, vol. 130, no. 4, pp. 1376–1383, 2008.

[48] J. Danielsson, R. Pierattelli, L. Banci, and A. Gräslund, "High-resolution NMR studies of the zinc-binding site of the Alzheimer's amyloid beta-peptide," *The FEBS Journal*, vol. 274, no. 1, pp. 46–59, 2007.

[49] W.-T. Chen, Y.-H. Liao, H.-M. Yu, I. H. Cheng, and Y.-R. Chen, "Distinct effects of Zn^{2+}, Cu^{2+}, Fe^{3+}, and Al^{3+} on amyloid-β stability, oligomerization, and aggregation: amyloid-β destabilization promotes annular protofibril formation," *The Journal of Biological Chemistry*, vol. 286, no. 11, pp. 9646–9656, 2011.

[50] C. Talmard, A. Bouzan, and P. Faller, "Zinc binding to amyloid-β: isothermal titration calorimetry and Zn competition experiments with Zn sensors," *Biochemistry*, vol. 46, no. 47, pp. 13658–13666, 2007.

[51] S. Parthasarathy, F. Long, Y. Miller et al., "Molecular-level examination of Cu^{2+} binding structure for amyloid fibrils of 40-residue Alzheimer's beta by solid-state NMR spectroscopy," *Journal of the American Chemical Society*, vol. 133, no. 10, pp. 3390–3400, 2011.

[52] D. P. Smith, G. D. Ciccotosto, D. J. Tew et al., "Concentration dependent Cu^{2+} induced aggregation and dityrosine formation of the Alzheimer's disease amyloid-β peptide," *Biochemistry*, vol. 46, no. 10, pp. 2881–2891, 2007.

[53] C. Ha, J. Ryu, and B. P. Chan, "Metal ions differentially influence the aggregation and deposition of Alzheimer's β-amyloid on a solid template," *Biochemistry*, vol. 46, no. 20, pp. 6118–6125, 2007.

[54] Y. Yoshiike, K. Tanemura, O. Murayama et al., "New insights on how metals disrupt amyloid beta-aggregation and their effects on amyloid-beta cytotoxicity," *The Journal of Biological Chemistry*, vol. 276, no. 34, pp. 32293–32299, 2001.

[55] M. Mold, L. Ouro-Gnao, B. M. Wieckowski, and C. Exley, "Copper prevents amyloid-beta(1–42) from forming amyloid fibrils under near-physiological conditions in vitro," *Scientific Reports*, vol. 3, article 1256, 2013.

[56] A. M. Mancino, S. S. Hindo, A. Kochi, and M. H. Lim, "Effects of clioquinol on metal-triggered amyloid-β aggregation revisited," *Inorganic Chemistry*, vol. 48, no. 20, pp. 9596–9598, 2009.

[57] V. Tõugu, A. Karafin, K. Zovo et al., "Zn(II)- and Cu(II)-induced non-fibrillar aggregates of amyloid-β (1–42) peptide are transformed to amyloid fibrils, both spontaneously and under the influence of metal chelators," *Journal of Neurochemistry*, vol. 110, no. 6, pp. 1784–1795, 2009.

[58] C. J. Sarell, S. R. Wilkinson, and J. H. Viles, "Substoichiometric levels of Cu^{2+} ions accelerate the kinetics of fiber formation and promote cell toxicity of amyloid-β from Alzheimer disease," *The Journal of Biological Chemistry*, vol. 285, no. 53, pp. 41533–41540, 2010.

[59] J. W. Karr and V. A. Szalai, "Cu(II) binding to monomeric, oligomeric, and fibrillar forms of the Alzheimer's disease amyloid-β peptide," *Biochemistry*, vol. 47, no. 17, pp. 5006–5016, 2008.

[60] G. Eskici and P. H. Axelsen, "Copper and oxidative stress in the pathogenesis of Alzheimer's disease," *Biochemistry*, vol. 51, no. 32, pp. 6289–6311, 2012.

[61] C. A. Rottkamp, A. K. Raina, X. Zhu et al., "Redox-active iron mediates amyloid-β toxicity," *Free Radical Biology and Medicine*, vol. 30, no. 4, pp. 447–450, 2001.

[62] T. Rival, R. M. Page, D. S. Chandraratna et al., "Fenton chemistry and oxidative stress mediate the toxicity of the β-amyloid peptide in a *Drosophila* model of Alzheimer's disease," *European Journal of Neuroscience*, vol. 29, no. 7, pp. 1335–1347, 2009.

[63] D. Jiang, L. Men, J. Wang et al., "Redox reactions of copper complexes formed with different β-amyloid peptides and their neuropathalogical relevance," *Biochemistry*, vol. 46, no. 32, pp. 9270–9282, 2007.

[64] K. Reybier, S. Ayala, B. Alies et al., "Free superoxide is an intermediate in the production of H_2O_2 by Cu(I)-amyloid-β and O_2," *Angewandte Chemie*, 2015.

[65] C. W. Ritchie, A. I. Bush, A. Mackinnon et al., "Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial," *Archives of Neurology*, vol. 60, no. 12, pp. 1685–1691, 2003.

[66] N. G. Faux, C. W. Ritchie, A. Gunn et al., "PBT2 rapidly improves cognition in alzheimer's disease: additional phase II analyses," *Journal of Alzheimer's Disease*, vol. 20, no. 2, pp. 509–516, 2010.

[67] J. Becerril-Ortega, K. Bordji, T. Fréret, T. Rush, and A. Buisson, "Iron overload accelerates neuronal amyloid-β production and cognitive impairment in transgenic mice model of Alzheimer's disease," *Neurobiology of Aging*, vol. 35, no. 10, pp. 2288–2301, 2014.

[68] S. Bolognin, L. Messori, D. Drago, C. Gabbiani, L. Cendron, and P. Zatta, "Aluminum, copper, iron and zinc differentially alter amyloid-Aβ_{1-42} aggregation and toxicity," *The International Journal of Biochemistry & Cell Biology*, vol. 43, no. 6, pp. 877–885, 2011.

[69] B. Liu, A. Moloney, S. Meehan et al., "Iron promotes the toxicity of amyloid β peptide by impeding its ordered aggregation," *The Journal of Biological Chemistry*, vol. 286, no. 6, pp. 4248–4256, 2011.

[70] S. Maeda, N. Sahara, Y. Saito et al., "Granular tau oligomers as intermediates of tau filaments," *Biochemistry*, vol. 46, no. 12, pp. 3856–3861, 2007.

[71] H. Braak and E. Braak, "Neuropathological stageing of Alzheimer-related changes," *Acta Neuropathologica*, vol. 82, no. 4, pp. 239–259, 1991.

[72] X.-Y. Sun, Y.-P. Wei, Y. Xiong et al., "Synaptic released zinc promotes tau hyperphosphorylation by inhibition of Protein Phosphatase 2A (PP2A)," *The Journal of Biological Chemistry*, vol. 287, no. 14, pp. 11174–11182, 2012.

[73] Z.-Y. Mo, Y.-Z. Zhu, H.-L. Zhu, J.-B. Fan, J. Chen, and Y. Liang, "Low micromolar zinc accelerates the fibrillization of human Tau via bridging of Cys-291 and Cys-322," *The Journal of Biological Chemistry*, vol. 284, no. 50, pp. 34648–34657, 2009.

[74] B. Bader, G. Nübling, A. Mehle, S. Nobile, H. Kretzschmar, and A. Giese, "Single particle analysis of tau oligomer formation induced by metal ions and organic solvents," *Biochemical and Biophysical Research Communications*, vol. 411, no. 1, pp. 190–196, 2011.

[75] A. Yamamoto, R. W. Shin, K. Hasegawa et al., "Iron (III) induces aggregation of hyperphosphorylated tau and its reduction to iron (II) reverses the aggregation: implications in the formation of neurofibrillary tangles of Alzheimer's disease," *Journal of Neurochemistry*, vol. 82, no. 5, pp. 1137–1147, 2002.

[76] D. P. Perl and P. F. Good, "Comparative techniques for determining cellular iron distribution in brain tissues," *Annals of Neurology*, vol. 32, supplement 1, pp. S76–S81, 1992.

[77] M. A. Smith, P. L. R. Harris, L. M. Sayre, and G. Perry, "Iron accumulation in Alzheimer disease is a source of redox-generated free radicals," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 18, pp. 9866–9868, 1997.

[78] R. B. Maccioni, G. Farías, I. Morales, and L. Navarrete, "The revitalized tau hypothesis on Alzheimer's disease," *Archives of Medical Research*, vol. 41, no. 3, pp. 226–231, 2010.

[79] Q. Ma, Y. Li, J. Du et al., "Copper binding properties of a tau peptide associated with Alzheimer's disease studied by CD, NMR, and MALDI-TOF MS," *Peptides*, vol. 27, no. 4, pp. 841–849, 2006.

[80] L.-X. Zhou, J.-T. Du, Z.-Y. Zeng et al., "Copper (II) modulates in vitro aggregation of a tau peptide," *Peptides*, vol. 28, no. 11, pp. 2229–2234, 2007.

[81] M. Kitazawa, D. Cheng, and F. M. Laferla, "Chronic copper exposure exacerbates both amyloid and tau pathology and selectively dysregulates cdk5 in a mouse model of AD," *Journal of Neurochemistry*, vol. 108, no. 6, pp. 1550–1560, 2009.

[82] P. J. Crouch, W. H. Lin, P. A. Adlard et al., "Increasing Cu bioavailability inhibits Aβ oligomers and tau phosphorylation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 2, pp. 381–386, 2009.

[83] K. M. Acevedo, Y. H. Hung, A. H. Dalziel et al., "Copper promotes the trafficking of the amyloid precursor protein," *The Journal of Biological Chemistry*, vol. 286, no. 10, pp. 8252–8262, 2011.

[84] C.-Y. Wang, T. Wang, W. Zheng et al., "Zinc overload enhances APP cleavage and Aβ deposition in the Alzheimer mouse brain," *PLoS ONE*, vol. 5, no. 12, Article ID e15349, 2010.

[85] P. Hou, G. Liu, Y. Zhao et al., "The role of copper and the copper-related protein CUTA in mediating APP processing and Abeta generation," *Neurobiology of Aging*, vol. 36, no. 3, pp. 1310–1315, 2015.

[86] Y. Noda, M. Asada, M. Kubota et al., "Copper enhances APP dimerization and promotes Aβ production," *Neuroscience letters*, vol. 547, pp. 10–15, 2013.

[87] K. J. Barnham, W. J. McKinstry, G. Multhaup et al., "Structure of the Alzheimer's disease amyloid precursor protein copper binding domain. A regulator of neuronal copper homeostasis," *The Journal of Biological Chemistry*, vol. 278, no. 19, pp. 17401–17407, 2003.

[88] L. Spoerri, L. J. Vella, C. L. L. Pham, K. J. Barnham, and R. Cappai, "The amyloid precursor protein copper binding domain histidine residues 149 and 151 mediate APP stability and metabolism," *The Journal of Biological Chemistry*, vol. 287, no. 32, pp. 26840–26853, 2012.

[89] S. O. Dahms, I. Könnig, D. Roeser et al., "Metal binding dictates conformation and function of the amyloid precursor protein (APP) E2 domain," *Journal of Molecular Biology*, vol. 416, no. 3, pp. 438–452, 2012.

[90] A. R. White, G. Multhaup, D. Galatis et al., "Contrasting, species-dependent modulation of copper-mediated neurotoxicity by the Alzheimer's disease amyloid precursor protein," *The Journal of Neuroscience*, vol. 22, no. 2, pp. 365–376, 2002.

[91] A. R. White, G. Multhaup, F. Maher et al., "The Alzheimer's disease amyloid precursor protein modulates copper-induced toxicity and oxidative stress in primary neuronal cultures," *The Journal of Neuroscience*, vol. 19, no. 21, pp. 9170–9179, 1999.

[92] J. A. Duce, A. Tsatsanis, M. A. Cater et al., "Iron-export ferroxidase activity of β-amyloid precursor protein is inhibited by zinc in Alzheimer's disease," *Cell*, vol. 142, no. 6, pp. 857–867, 2010.

[93] R. C. McCarthy, Y.-H. Park, and D. J. Kosman, "sAPP modulates iron efflux from brain microvascular endothelial cells by stabilizing the ferrous iron exporter ferroportin," *EMBO Reports*, vol. 15, no. 7, pp. 809–815, 2014.

[94] C. Supnet and I. Bezprozvanny, "Presenilins function in ER calcium leak and Alzheimer's disease pathogenesis," *Cell Calcium*, vol. 50, no. 3, pp. 303–309, 2011.

[95] K. Honarnejad, C. K. E. Jung, S. Lammich, T. Arzberger, H. Kretzschmar, and J. Herms, "Involvement of presenilin holoprotein upregulation in calcium dyshomeostasis of Alzheimer's disease," *Journal of Cellular and Molecular Medicine*, vol. 17, no. 2, pp. 293–302, 2013.

[96] D. Sepulveda-Falla, A. Barrera-Ocampo, C. Hagel et al., "Familial Alzheimer's disease-associated presenilin-1 alters cerebellar activity and calcium homeostasis," *The Journal of Clinical Investigation*, vol. 124, no. 4, pp. 1552–1567, 2014.

[97] M. Ryazantseva, K. Skobeleva, and E. Kaznacheyeva, "Familial Alzheimer's disease-linked presenilin-1 mutation M146V affects store-operated calcium entry: does gain look like loss?" *Biochimie*, vol. 95, no. 7, pp. 1506–1509, 2013.

[98] M. Ho, D. E. Hoke, Y. J. Chua et al., "Effect of metal chelators on γ-secretase indicates that calcium and magnesium ions facilitate cleavage of Alzheimer amyloid precursor substrate," *International Journal of Alzheimer's Disease*, vol. 2011, Article ID 950932, 10 pages, 2011.

[99] P. Babula, M. Masarik, V. Adam et al., "Mammalian metallothioneins: properties and functions," *Metallomics*, vol. 4, no. 8, pp. 739–750, 2012.

[100] W. H. Yu, W. J. Lukiw, C. Bergeron, H. B. Niznik, and P. E. Fraser, "Metallothionein III is reduced in Alzheimer's disease," *Brain Research*, vol. 894, no. 1, pp. 37–45, 2001.

[101] B. L. Martin, A. M. Tokheim, P. T. McCarthy, B. S. Doms, A. A. Davis, and I. M. Armitage, "Metallothionein-3 and neuronal nitric oxide synthase levels in brains from the Tg2576 mouse model of Alzheimer's disease," *Molecular and Cellular Biochemistry*, vol. 283, no. 1-2, pp. 129–137, 2006.

[102] B. H. Park, H. G. Kim, S. W. Jin, S.-G. Song, and H. G. Jeong, "Metallothionein-III increases ADAM10 activity in association with furin, PC7, and PKCα during non-amyloidogenic processing," *FEBS Letters*, vol. 588, no. 14, pp. 2294–2300, 2014.

[103] K. Endres and F. Fahrenholz, "The role of the anti-amyloidogenic secretase ADAM10 in shedding the APP-like proteins," *Current Alzheimer Research*, vol. 9, no. 2, pp. 157–164, 2012.

[104] Y. Luo, Y. Xu, Q. Bao et al., "The molecular mechanism for human metallothionein-3 to protect against the neuronal cytotoxicity of Abeta(1–42) with Cu ions," *JBIC Journal of Biological Inorganic Chemistry*, vol. 18, no. 1, pp. 39–47, 2013.

[105] Y. Irie and W. M. Keung, "Metallothionein-III antagonizes the neurotoxic and neurotrophic effects of amyloid β peptides," *Biochemical and Biophysical Research Communications*, vol. 282, no. 2, pp. 416–420, 2001.

[106] J. T. Pedersen, C. Hureau, L. Hemmingsen et al., "Rapid exchange of metal between Zn_7-metallothionein-3 and amyloid-β peptide promotes amyloid-related structural changes," *Biochemistry*, vol. 51, no. 8, pp. 1697–1706, 2012.

[107] J. Durand, G. Meloni, C. Talmard, M. Vašák, and P. Faller, "Zinc release of Zn_7-metallothionein-3 induces fibrillar type amyloid-β aggregates," *Metallomics*, vol. 2, no. 11, pp. 741–744, 2010.

[108] J.-H. Kim, Y.-P. Nam, S.-M. Jeon, H.-S. Han, and K. Suk, "Amyloid neurotoxicity is attenuated by metallothionein: dual mechanisms at work," *Journal of Neurochemistry*, vol. 121, no. 5, pp. 751–762, 2012.

[109] G. Meloni, V. Sonois, T. Delaine et al., "Metal swap between Zn7-metallothionein-3 and amyloid-β-Cu protects against amyloid-β toxicity," *Nature Chemical Biology*, vol. 4, no. 6, pp. 366–372, 2008.

[110] W. Zheng, T. Wang, D. Yu et al., "Elevation of zinc transporter ZnT3 protein in the cerebellar cortex of the AβPP/PS1 transgenic mouse," *Journal of Alzheimer's Disease*, vol. 20, no. 1, pp. 323–331, 2010.

[111] L.-H. Zhang, X. Wang, Z.-H. Zheng et al., "Altered expression and distribution of zinc transporters in APP/PS1 transgenic mouse brain," *Neurobiology of Aging*, vol. 31, no. 1, pp. 74–87, 2010.

[112] J.-Y. Lee, E. Cho, J.-W. Seo, J. J. Hwang, and J.-Y. Koh, "Alteration of the cerebral zinc pool in a mouse model of Alzheimer disease," *Journal of Neuropathology and Experimental Neurology*, vol. 71, no. 3, pp. 211–222, 2012.

[113] P. A. Adlard, J. Parncutt, V. Lal et al., "Metal chaperones prevent zinc-mediated cognitive decline," *Neurobiology of Disease*, vol. 81, pp. 196–202, 2015.

[114] S. Okabe, "Molecular anatomy of the postsynaptic density," *Molecular and Cellular Neuroscience*, vol. 34, no. 4, pp. 503–518, 2007.

[115] E. Pham, L. Crews, K. Ubhi et al., "Progressive accumulation of amyloid-β oligomers in Alzheimer's disease and in amyloid precursor protein transgenic mice is accompanied by selective alterations in synaptic scaffold proteins," *FEBS Journal*, vol. 277, no. 14, pp. 3051–3067, 2010.

[116] F. Roselli, P. Hutzler, Y. Wegerich, P. Livrea, and O. F. X. Almeida, "Disassembly of shank and homer synaptic clusters is driven by soluble b-amyloid 1–40 through divergent NMDAR-dependent signalling pathways," *PLoS ONE*, vol. 4, no. 6, Article ID e6011, 2009.

[117] A. M. Grabrucker, M. J. Schmeisser, P. T. Udvardi et al., "Amyloid beta protein-induced zinc sequestration leads to synaptic loss via dysregulation of the ProSAP2/Shank3 scaffold," *Molecular Neurodegeneration*, vol. 6, article 65, 2011.

[118] S. Grabrucker, L. Jannetti, M. Eckert et al., "Zinc deficiency dysregulates the synaptic ProSAP/Shank scaffold and might contribute to autism spectrum disorders," *Brain*, vol. 137, no. 1, pp. 137–152, 2014.

[119] K. Jellinger, W. Paulus, I. Grundke-Iqbal, P. Riederer, and M. B. H. Youdim, "Brain iron and ferritin in Parkinson's and Alzheimer's diseases," *Journal of Neural Transmission—Parkinson's Disease and Dementia Section*, vol. 2, no. 4, pp. 327–340, 1990.

[120] J. R. Connor, S. L. Menzies, S. M. St Martin, and E. J. Mufson, "A histochemical study of iron, transferrin, and ferritin in Alzheimer's diseased brains," *Journal of Neuroscience Research*, vol. 31, no. 1, pp. 75–83, 1992.

[121] C. Quintana, S. Bellefqih, J. Y. Laval et al., "Study of the localization of iron, ferritin, and hemosiderin in Alzheimer's disease hippocampus by analytical microscopy at the subcellular level," *Journal of Structural Biology*, vol. 153, no. 1, pp. 42–54, 2006.

[122] E. P. Raven, P. H. Lu, T. A. Tishler, P. Heydari, and G. Bartzokis, "Increased iron levels and decreased tissue integrity in hippocampus of Alzheimer's disease detected in vivo with magnetic resonance imaging," *Journal of Alzheimer's Disease*, vol. 37, no. 1, pp. 127–136, 2013.

[123] A. A. Raha, R. A. Vaishnav, R. P. Friedland, A. Bomford, and R. Raha-Chowdhury, "The systemic iron-regulatory proteins hepcidin and ferroportin are reduced in the brain in Alzheimer's disease," *Acta Neuropathologica Communications*, vol. 1, article 55, 2013.

[124] S. Ayton, N. G. Faux, and A. I. Bush, "Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE," *Nature Communications*, vol. 6, article 6760, 2015.

[125] R. Donato, B. R. Cannon, G. Sorci et al., "Functions of S100 proteins," *Current Molecular Medicine*, vol. 13, no. 1, pp. 24–57, 2013.

[126] X. Huang, M. P. Cuajungco, C. S. Atwood et al., "Cu(II) potentiation of Alzheimer aβ neurotoxicity. Correlation with cell-free hydrogen peroxide production and metal reduction," *The Journal of Biological Chemistry*, vol. 274, no. 52, pp. 37111–37116, 1999.

[127] X. Huang, C. S. Atwood, M. A. Hartshorn et al., "The Aβ peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction," *Biochemistry*, vol. 38, no. 24, pp. 7609–7616, 1999.

[128] J. T. Egaña, C. Zambrano, M. T. Nuñez, C. Gonzalez-Billault, and R. B. Maccioni, "Iron-induced oxidative stress modify tau phosphorylation patterns in hippocampal cell cultures," *BioMetals*, vol. 16, no. 1, pp. 215–223, 2003.

[129] L.-H. Zhang, X. Wang, M. Stoltenberg, G. Danscher, L. Huang, and Z.-Y. Wang, "Abundant expression of zinc transporters in the amyloid plaques of Alzheimer's disease brain," *Brain Research Bulletin*, vol. 77, no. 1, pp. 55–60, 2008.

[130] E. Kyratzi and S. Efthimiopoulos, "Calcium regulates the interaction of amyloid precursor protein with Homer3 protein," *Neurobiology of Aging*, vol. 35, no. 9, pp. 2053–2063, 2014.

[131] L. Parisiadou, I. Bethani, V. Michaki, K. Krousti, G. Rapti, and S. Efthimiopoulos, "Homer2 and Homer3 interact with amyloid precursor protein and inhibit Aβ production," *Neurobiology of Disease*, vol. 30, no. 3, pp. 353–364, 2008.

[132] Y. Li, J. Wang, J. G. Sheng et al., "S100β increases levels of β-amyloid precursor protein and its encoding mRNA in rat neuronal cultures," *Journal of Neurochemistry*, vol. 71, no. 4, pp. 1421–1428, 1998.

[133] W. H. Yu and P. E. Fraser, "S100β interaction with tau is promoted by zinc and inhibited by hyperphosphorylation in Alzheimer's disease," *Journal of Neuroscience*, vol. 21, no. 7, pp. 2240–2246, 2001.

[134] J. Baudier and R. D. Cole, "Interactions between the microtubule-associated tau proteins and S100b regulate tau phosphorylation by the Ca2+/calmodulin-dependent protein kinase II," *The Journal of Biological Chemistry*, vol. 263, no. 12, pp. 5876–5883, 1988.

[135] C. E. Shepherd, J. Goyette, V. Utter et al., "Inflammatory S100A9 and S100A12 proteins in Alzheimer's disease," *Neurobiology of Aging*, vol. 27, no. 11, pp. 1554–1563, 2006.

[136] C. Wang, A. G. Klechikov, A. L. Gharibyan et al., "The role of pro-inflammatory S100A9 in Alzheimer's disease amyloid-neuroinflammatory cascade," *Acta Neuropathologica*, vol. 127, no. 4, pp. 507–522, 2014.

[137] K.-A. Chang, H. J. Kim, and Y.-H. Suh, "The role of S100a9 in the pathogenesis of Alzheimer's disease: the therapeutic effects of S100a9 knockdown or knockout," *Neurodegenerative Diseases*, vol. 10, no. 1–4, pp. 27–29, 2012.

[138] C. Zhang, Y. Liu, J. Gilthorpe, and J. R. C. van der Maarel, "MRP14 (S100A9) protein interacts with Alzheimer beta-amyloid peptide and induces its fibrillization," *PLoS ONE*, vol. 7, no. 3, Article ID e32953, 2012.

[139] H. J. Kim, K.-A. Chang, T.-Y. Ha et al., "S100A9 knockout decreases the memory impairment and neuropathology in crossbreed mice of Tg2576 and S100A9 knockout mice model," *PLoS ONE*, vol. 9, no. 2, Article ID e88924, 2014.

[140] W. Qin, L. Ho, J. Wang, E. Peskind, and G. M. Pasinetti, "S100A7, a novel Alzheimer's disease biomarker with non-amyloidogenic α-secretase activity acts via selective promotion of ADAM-10," *PLoS ONE*, vol. 4, no. 1, Article ID e4183, 2009.

[141] R. H. Selinfreund, S. W. Barger, W. J. Pledger, and L. J. Van Eldik, "Neurotrophic protein S100β stimulates glial cell proliferation,"

Proceedings of the National Academy of Sciences of the United States of America, vol. 88, no. 9, pp. 3554–3558, 1991.

[142] Z. Cai, N. Liu, C. Wang et al., "Role of RAGE in Alzheimer's Disease," *Cellular and Molecular Neurobiology*, 2015.

[143] S. D. Yan, X. Chen, J. Fu et al., "RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease," *Nature*, vol. 382, no. 6593, pp. 685–691, 1996.

[144] R. Deane, S. D. Yan, R. K. Submamaryan et al., "RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain," *Nature Medicine*, vol. 9, no. 7, pp. 907–913, 2003.

[145] L. J. Van Eldik and M. S. Wainwright, "The Janus face of glial-derived S100B: beneficial and detrimental functions in the brain," *Restorative Neurology and Neuroscience*, vol. 21, no. 3-4, pp. 97–108, 2003.

[146] R. E. Mrak and W. S. T. Griffin, "The role of activated astrocytes and of the neurotrophic cytokine S100B in the pathogenesis of Alzheimer's disease," *Neurobiology of Aging*, vol. 22, no. 6, pp. 915–922, 2001.

[147] M. M. Edwards and S. R. Robinson, "TNF alpha affects the expression of GFAP and S100B: implications for Alzheimer's disease," *Journal of Neural Transmission*, vol. 113, no. 11, pp. 1709–1715, 2006.

[148] J. M. Craft, D. M. Watterson, A. Marks, and L. J. Van Eldik, "Enhanced susceptibility of S-100B transgenic mice to neuroinflammation and neuronal dysfunction induced by intracerebroventricular infusion of human β-amyloid," *Glia*, vol. 51, no. 3, pp. 209–216, 2005.

[149] A. Boom, R. Pochet, M. Authelet et al., "Astrocytic calcium/zinc binding protein S100A6 over expression in Alzheimer's disease and in PS1/APP transgenic mice models," *Biochimica et Biophysica Acta (BBA)—Molecular Cell Research*, vol. 1742, no. 1–3, pp. 161–168, 2004.

[150] T.-Y. Ha, K.-A. Chang, J. A. Kim et al., "S100a9 knockdown decreases the memory impairment and the neuropathology in Tg2576 mice, AD animal model," *PLoS ONE*, vol. 5, no. 1, Article ID e8840, 2010.

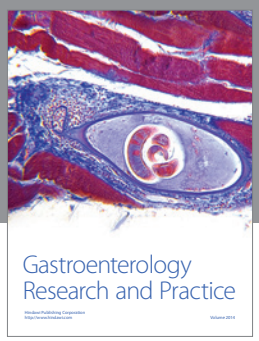
[151] T. Vogl, A. L. Gharibyan, and L. A. Morozova-Roche, "Pro-inflammatory S100A8 and S100A9 proteins: Self-assembly into multifunctional native and amyloid complexes," *International Journal of Molecular Sciences*, vol. 13, no. 3, pp. 2893–2917, 2012.

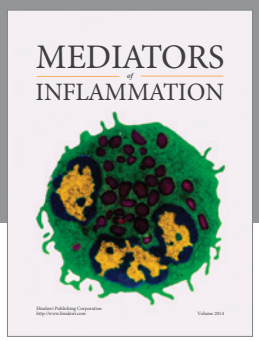
[152] S. B. Carvalho, H. M. Botelho, S. S. Leal, I. Cardoso, G. Fritz, and C. M. Gomes, "Intrinsically disordered and aggregation prone regions underlie β-aggregation in S100 proteins," *PLoS ONE*, vol. 8, no. 10, Article ID e76629, 2013.

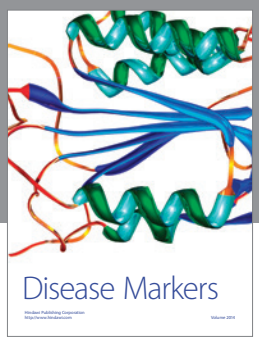
[153] S. B. Carvalho, I. Cardoso, H. M. Botelho et al., "Structural heterogeneity and bioimaging of S100 amyloid assemblies," in *Bio-Nanoimaging*, chapter 18, pp. 197–212, Academic Press, Boston, Mass, USA, 2014.

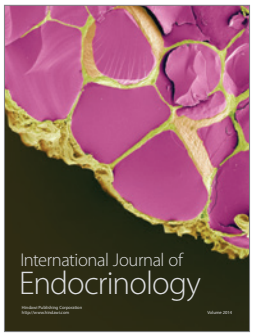
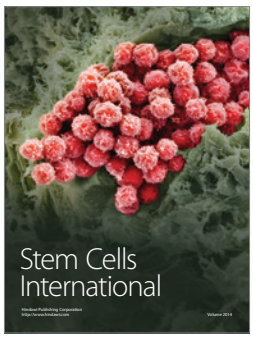
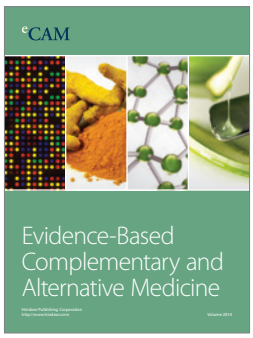
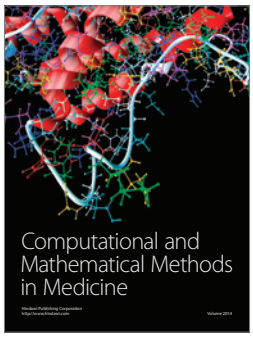
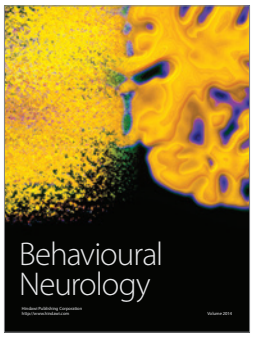
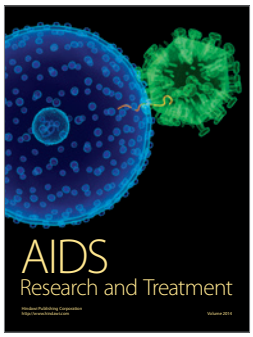
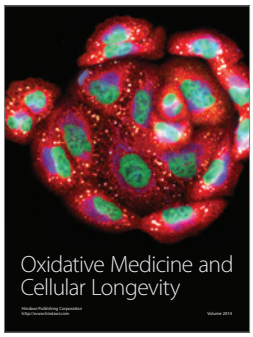
[154] G. Fritz, H. M. Botelho, L. A. Morozova-Roche, and C. M. Gomes, "Natural and amyloid self-assembly of S100 proteins: structural basis of functional diversity," *The FEBS Journal*, vol. 277, no. 22, pp. 4578–4590, 2010.

[155] K. Yanamandra, O. Alexeyev, V. Zamotin et al., "Amyloid formation by the pro-inflammatory S100A8/A9 proteins in the ageing prostate," *PLoS ONE*, vol. 4, no. 5, Article ID e5562, 2009.







Hindawi

Submit your manuscripts at
http://www.hindawi.com