Copper homeostasis and cuproptosis in Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by neuroinflammation, synaptic dysfunction and neuronal loss. Research has revealed a connection between copper metabolism and the pathophysiology of AD, particularly through a newly identified form of copper-dependent cell death referred to as cuproptosis. Cuproptosis is driven by the aggregation of lipoylated proteins and proteotoxic stress caused by excessive copper accumulation, leading to cellular demise, which is a key event in AD. While studies on copper levels in the brain in AD remain inconclusive, there is mounting evidence suggesting that an imbalance in copper homeostasis, particularly elevated labile copper levels, contributes to oxidative damage and neurodegeneration in patients with AD. The present review examines the role of cuproptosis in AD and discusses how targeting this pathway may provide novel therapeutic opportunities. By investigating the underlying mechanisms and potential clinical implications, the present review highlights that regulation of cuproptosis provides a promising approach for modulating disease progression and developing personalized treatment strategies for AD.

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1. Introduction

Copper is a redox-active transition metal and is essential for brain function, serving as a cofactor in critical enzymatic systems, including the cytochrome *c* oxidase (CCO; Complex IV) system for mitochondrial oxidative phosphorylation (OXPHOS) and the copper/zinc superoxide dismutase 1 (Cu/Zn-SOD1) system for antioxidant defense (1,2). The distribution of copper in the brain, particularly in glutamatergic synapses and locus coeruleus neurons, is tightly regulated by copper transporter 1 (CTR1)-mediated uptake, ATP7A/B-dependent trafficking and metallothionein buffering systems (3). Copper also serves regulatory roles in synaptic plasticity, including in N-methyl-D-aspartate receptor (NMDA-R) endocytosis and aminomethylphosphonic acid receptor trafficking, and modulates >30 central nervous system (CNS) enzymes essential for neuropeptide maturation (4,5).

The disruption of copper homeostasis has increasingly been implicated in the pathogenesis of Alzheimer's disease (AD), a neurodegenerative disorder characterized by amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs) of hyperphosphorylated tau and neuronal loss (6,7). Pathological copper accumulation exerts dual toxicity: i) Catalytic generation of reactive oxygen species (ROS) via Fenton-like reactions; and ii) structural disruption of Aβ peptides, thereby promoting oligomerization and plaque formation (8). In patients with AD, elevated labile copper levels in cerebrospinal fluid (CSF) and cortical regions, particularly within Aβ plaques, exacerbate mitochondrial dysfunction by inhibiting Complex IV and depleting glutathione (GSH), creating a vicious cycle of oxidative damage (9).

Studies have identified cuproptosis, a copper-specific cell death pathway distinct from apoptosis and ferroptosis, as a key mechanism in AD-related neurodegeneration (6,10). Cuproptosis involves copper-induced oligomerization of lipoylated mitochondrial enzymes, particularly those in the tricarboxylic acid (TCA) cycle, resulting in proteotoxic stress and disruption of iron-sulfur (Fe-S) cluster biosynthesis (11). This process not only impairs cellular energy metabolism but also exacerbates oxidative stress, further contributing to neuronal death (12,13). In addition, synaptic copper dysregulation impairs hippocampal function via multiple pathways, including competitive inhibition of NMDA-R at glutamatergic

synapses, suppression of the cAMP response element-binding protein (CREB) pathway via PP1/PP2A phosphatase activation, and impaired activity-dependent brain-derived neurotrophic factor (BDNF) secretion, which is vital for synaptic plasticity and memory formation (14).

Therapeutic strategies targeting copper homeostasis are currently under investigation, with promising approaches including selective copper chelators [such as blood-brain barrier (BBB)-permeable clioquinol (CQ) analogs], zinc-induced metallothionein expression for competitive ion displacement and antioxidant interventions to enhance Cu/Zn-SOD activity (15). Preclinical studies have highlighted the importance of temporal specificity in therapeutic interventions (16-18). Aggressive copper chelation may be beneficial in advanced AD to lower toxic copper pools, while pro-homeostatic approaches (such as copper chaperones) can be more effective during prodromal stages to restore the physiological copper balance (16). However, the U-shaped relationship between copper levels and cognitive decline highlights the need for careful biomarker-guided personalized therapies to avoid the risks of copper deficiency, which can also impair brain function (9).

The present review investigates the dual roles of copper in AD, integrating the emerging concept of cuproptosis with classical Aβ/tau hypotheses, and critically evaluates copper-targeted therapeutic strategies. By synthesizing recent advances in the field, the present review aims to propose a precision medicine framework that addresses the multifactorial pathology of AD and suggests potential therapeutic strategies.

2. Fundamentals of copper metabolism

Copper homeostasis. Copper homeostasis is a tightly regulated process, which is essential for maintaining physiological functions such as mitochondrial respiration, antioxidant defense and neurotransmitter synthesis, while avoiding redox toxicity (19). This balance is achieved through the coordinated actions of copper transporters, metalloreductases, cytosolic chaperones and organelle-specific trafficking proteins (20). Collectively, these components ensure appropriate cellular copper uptake, distribution, utilization, storage and excretion (Fig. 1). In neurons, disruptions in systemic copper transport, such as altered CTR1 expression, ceruloplasmin (CP) dysfunction or hepatic clearance defects, can impair copper delivery and increase the risk of oxidative stress (21-23).

Copper absorption and transport. Dietary copper is primarily obtained from foods such as meat, offal, nuts and cereals (Fig. 1) (24,25). Copper absorption primarily occurs in the duodenum, where dietary Cu^{2+} is reduced to Cu^{+} by metalloreductases such as six-transmembrane epithelial antigen of the prostate 4 and duodenal cytochrome B (26,27). The reduced form is then imported into enterocytes via the high-affinity copper transporter CTR1 (Fig. 1). In enterocytes, copper can either be transiently sequestered by metallothioneins or exported into the portal circulation via ATP7A (28,29). In the circulation, copper binds to human serum albumin and transcuprein and is delivered to the liver, where it is incorporated into metallothionein (MT) or excreted via ATP7B-mediated biliary pathways to maintain the systemic copper balance (30-32) (Fig. 1).

Copper storage and pools. Upon delivery to the liver, circulating copper is taken up by hepatocytes via CTR1 (Fig. 1) (33). Intracellular copper is distributed into two major pools: A stationary enzymatic pool tightly bound to copper-dependent enzymes such as cyclooxygenase (COX) and SOD1 (34-36), and a labile exchangeable pool associated with copper chaperones, including copper chaperone for superoxide dismutase (CCS), COX17 and antioxidant-1 (ATOX1). The enzymatic pool maintains essential bioenergetic and antioxidant functions, while the labile pool regulates dynamic cellular signaling and trafficking (Fig. 1) (37).

Copper chaperones direct intracellular copper to specific organelles. For instance, ATOX1 delivers copper to ATP7A and ATP7B in the trans-Golgi network for enzyme metalation (38,39). In addition, ATOX1 functions as a copper-sensitive transcription factor through interactions with Sp1 and metal regulatory transcription factor 1, thereby affecting genes involved in the oxidative stress response and neuronal plasticity (40,41). COX17 mediates mitochondrial copper delivery, which is critical for CCO assembly and electron transport chain (ETC) integrity (42,43). CCS transfers copper to SOD1, which is essential for superoxide detoxification (44).

To prevent redox toxicity, excess cytosolic copper is sequestered by MT and GSH (Fig. 1) (44). The thioredoxin system further contributes to cellular redox buffering, particularly in neurons where copper dysregulation can induce oxidative injury (45).

Copper excretion. Copper is mainly excreted through bile, a process facilitated by ATP7B, which accounts for ~95% of total copper excretion, with a minor fraction expelled via urine (Fig. 1) (46,47). This efficient ATP7B-mediated biliary excretion system ensures controlled copper levels and can minimize toxicity. The ability of the liver to regulate copper excretion through ATP7B is crucial for maintaining the systemic copper balance and preventing toxic accumulation (47,48).

Regulation of copper homeostasis. The liver exerts a central effect on maintaining the systemic copper balance by regulating intestinal absorption, hepatic storage and biliary excretion (49,50). Under conditions of hepatic copper excess, the high-affinity transporter CTR1 undergoes endocytosis and degradation to reduce further uptake, while ATP7B expression is upregulated to promote copper excretion via bile (29,51). By contrast, during copper deficiency, intestinal copper uptake is enhanced via increased CTR1 activity (52). The gut-liver axis further modulates copper homeostasis. Intestinal peptides such as hepcidin, although classically involved in iron metabolism, have been implicated in copper regulation under overload conditions (53). Furthermore, the gut microbiota influences copper bioavailability by altering intestinal absorption and producing copper-binding metabolites that impact host copper metabolism (54).

Copper levels are monitored and adjusted via transcriptional and post-translational feedback mechanisms. Changes in intracellular copper concentrations can affect the localization and stability of copper transporters (such as CTR1 and ATP7A/B) and the expression of regulatory genes (47,55,56). Furthermore, copper-inducible kinases, such as unc-51 like autophagy activating kinase 1, serve a role in copper-dependent autophagy, eventually promoting the degradation of

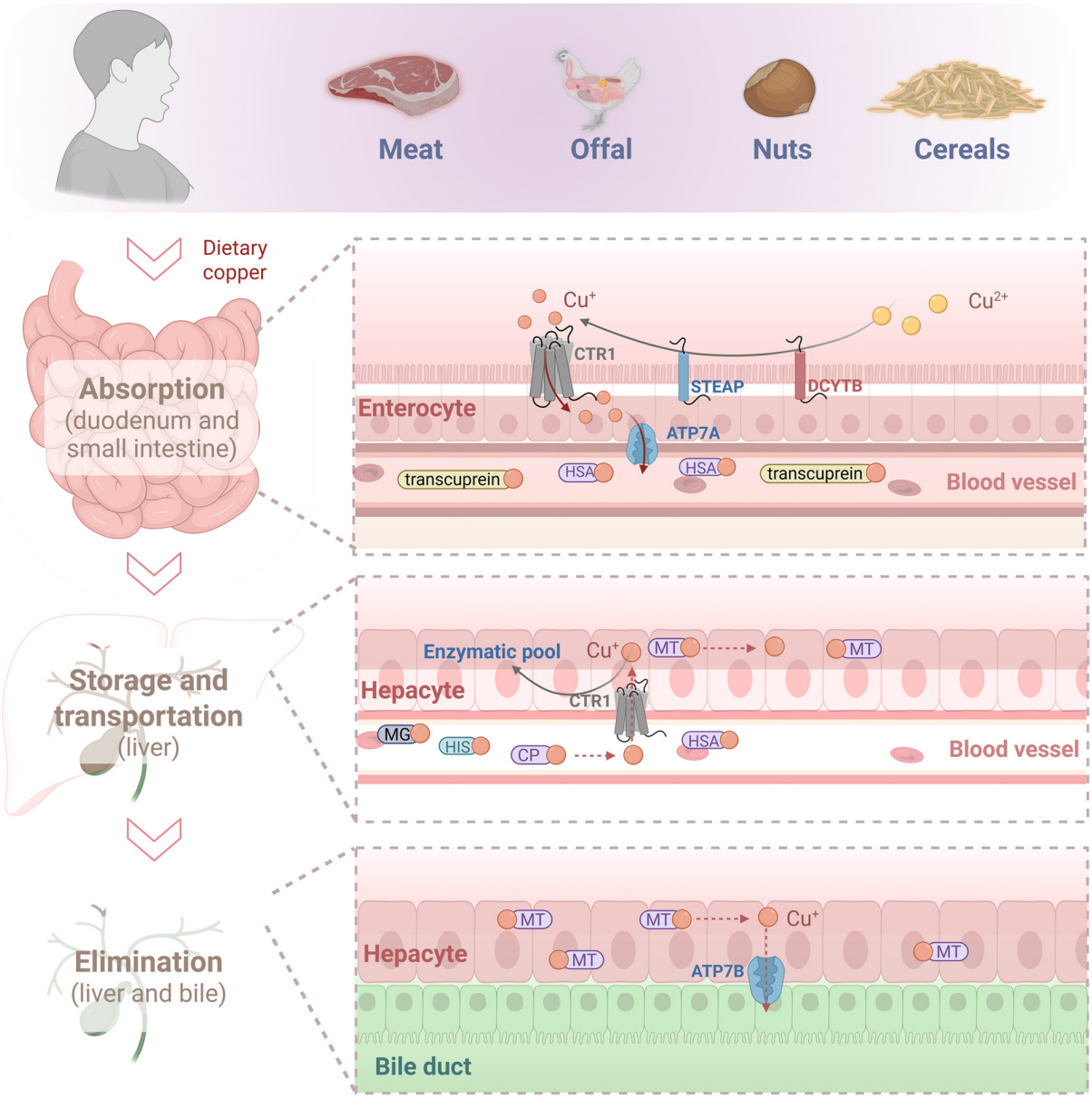

Figure 1. Copper absorption and transport. Dietary copper is primarily absorbed in the duodenum and proximal small intestine via the CTR1 transporter, following reduction of Cu^{2+} to Cu^{+} by STEAP and DCYTB. Once absorbed, copper is either stored in intestinal cells by metallothioneins or transported to the liver via ATP7A. In the liver, copper is distributed and stored, with any excess excreted through bile. This process ensures systemic copper homeostasis and bioavailability. CP, ceruloplasmin; CTR1, copper transporter 1; DCYTB, duodenal cytochrome B; HIS, histidine; HSA, human serum albumin; MG, metal group; MT, metallothionein; STEAP, six-transmembrane epithelial antigen of the prostate.

copper-enriched organelles and maintaining the intracellular copper equilibrium (57,58).

In the CNS, ATP7A facilitates copper transport across the BBB and into synaptic vesicles, while ATP7B contributes to copper efflux into the CSF, thus maintaining the neural copper balance and protecting against redox-induced damage (59,60). Disruptions in these transport pathways have been associated with neurodegenerative diseases, including AD and Wilson's disease (61).

Biological roles of copper in the CNS. Copper is an essential trace element and serves critical physiological roles in the CNS. Considering the high oxidative metabolism and limited regenerative capacity of the CNS, it is particularly sensitive to disturbances in copper homeostasis (62,63). Copper is primarily transported into neurons via CTR1, a high-affinity copper transporter, and functions as a cofactor for several crucial enzymes, including COX, SOD1, dopamine β-hydroxylase (DBH) and peptidylglycine α-amidating monooxygenase (64). It is extensively involved in physiological processes, including synaptic function, energy metabolism, antioxidant defense and neurodevelopment (65,66). This intricate involvement underscores the necessity of precise copper regulation to maintain CNS function and prevent neurodegenerative disorders.

Copper serves a vital role in neurotransmitter synthesis and synaptic signal transmission at the neurochemical level (62). DBH, a copper-dependent enzyme, catalyzes the conversion of dopamine (DA) to norepinephrine (NE) within synaptic vesicles, a key reaction in emotional regulation and stress responses (9). Additionally, peptidylglycine α-amidating

monooxygenase, another copper-dependent enzyme, modifies various neuropeptides, such as oxytocin and Substance P (67,68).

Copper is vital for cellular energy metabolism, particularly in the mitochondrial ETC (69). CCO (Complex IV), a copper-dependent enzyme, catalyzes the reduction of oxygen in a process that couples electron transfer to ATP synthesis, which is essential for maintaining neuronal energy supply (70). A deficiency in copper can diminish the activity of Complex IV, leading to reduced ATP synthesis. This reduction can precipitate an energy crisis in neurons, exacerbating neurodegenerative changes (69).

Due to their high metabolic rate, neurons are particularly susceptible to damage from ROS, and copper serves a crucial role in antioxidant defense (71). Cu/Zn-SOD1, which utilizes copper as a catalytic center, effectively eliminates superoxide radicals, thus preventing oxidative damage to neurons (72). Dysfunctional SOD1 has been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis (73). Additionally, CP, a copper-dependent ferroxidase, catalyzes the oxidation of Fe^{2+} to Fe^{3+}, facilitating transmembrane iron transport and maintaining iron homeostasis (74). Copper deficiency can lead to abnormal intracellular iron accumulation, exacerbating oxidative stress and neuronal damage in the CNS, which may contribute to the development of neurodegenerative diseases (75-77).

During neurodevelopment, copper serves a critical role in myelination. Copper supports the normal function of oligodendrocytes, the cells responsible for myelin production, thereby ensuring efficient neural signal transmission (78,79). Copper deficiency, such as that observed in Menkes disease, can lead to hypomyelination, causing motor disorders and cognitive deficits due to impaired neural system functionality (80,81). Furthermore, copper serves a pivotal role in neurogenesis and synaptic formation. Copper deficiency during pregnancy can result in abnormal neuronal differentiation and reduced synaptic plasticity, severely impacting normal CNS development (82,83). From an epigenetic perspective, copper can also regulate gene expression through histone demethylases such as lysine demethylase 5B, affecting cell differentiation, neural network remodeling and stress responses (84).

3. Copper dysregulation and cuproptosis

Copper dysregulation. Dysregulation of copper metabolism serves a critical role in cellular dysfunction in neurological diseases (85). Therefore, investigating the underlying mechanisms of this dysregulation is necessary to understand disease pathogenesis and develop potential therapeutic strategies.

Copper deficiency. Copper deficiency contributes to a spectrum of neurological impairments through multiple interconnected mechanisms, including disrupted mitochondrial energy metabolism, impaired neurotransmitter synthesis, dysregulated iron homeostasis and heightened oxidative stress (86). Both *in vitro* and *in vivo* studies have consistently demonstrated that inadequate copper availability compromises key neuronal processes involved in maintaining the redox balance and bioenergetic function (Table I) (87-95).

i) Disrupted energy metabolism. Copper is an essential cofactor for CCO, a critical component of the mitochondrial ETC. Deficiency in copper impairs CCO activity, leading to reduced mitochondrial respiration and ATP production, thereby disrupting cellular energy metabolism. The function of oligodendrocytes, which are highly dependent on ATP, may be compromised, leading to hypomyelination and subsequent neurological deficits (96,97). In the spinal cord, copper deficiency can cause degeneration of the dorsal columns, which manifests as sensory ataxia and gait instability (98). Peripheral neuropathy may present with limb numbness and paresthesia, while optic neuropathy can result in visual impairment (99,100). While these manifestations are most apparent in acquired copper deficiency syndromes, they highlight the critical role of copper in maintaining both central and peripheral nervous system integrity, disruption of which may contribute to the complex neurodegenerative features observed in AD.

In vitro studies using SH-SY5Y neuroblastoma cells have demonstrated that copper deficiency can impair mitochondrial function, leading to increased oxidative stress and reduced ATP production (101,102). These cellular changes may mimic the metabolic dysfunction observed in AD models, suggesting a mechanistic link between disrupted copper homeostasis and neurodegeneration.

ii) Impaired neurotransmitter synthesis. Copper deficiency can reduce the activity of DBH, hindering NE synthesis and affecting sympathetic nervous function (103,104). This may induce hypotension, orthostatic hypotension, arrhythmias and impaired thermoregulation (95). Monoamine oxidase (MAO), another copper-dependent enzyme, is involved in the metabolism of serotonin and DA. Reduced MAO activity may contribute to mood disorders and cognitive dysfunction, and can exacerbate neurological damage (105,106). Experimental evidence from cell culture studies also indicates that copper deficiency decreases DBH activity, thereby reducing NE levels and disrupting catecholamine metabolism, which may explain the autonomic dysfunction observed in neurological conditions (95,103,107-109).

iii) Altered iron homeostasis. CP, a copper-dependent ferroxidase, serves a pivotal role in iron metabolism. Copper deficiency can impair CP synthesis, which leads to inadequate oxidation of Fe^{2+} to Fe^{3+}, disrupts iron mobilization and transport, and results in functional iron deficiency and anemia (53,110). Abnormal iron metabolism may cause iron accumulation in various tissues, including the brain, liver and pancreas, potentially inducing neurodegenerative changes such as neuronal loss, gliosis and mitochondrial dysfunction, which may clinically manifest as ataxia, dystonia and dementia (23). As reported in animal studies, reduced copper availability decreases CP activity, promoting iron accumulation in brain tissues. This disruption has been shown to be associated with increased neuroinflammatory markers and Aβ deposition in transgenic AD mouse models, suggesting that iron dysregulation driven by copper deficiency may exacerbate AD pathology (76,111).

iv) Increased oxidative stress. Cu/Zn-SOD1 is a copper-dependent antioxidant enzyme, and is crucial for scavenging free radicals and mitigating oxidative stress (112). Copper deficiency can decrease Cu/Zn-SOD1 activity, thus diminishing the free radical-scavenging capacity, exacerbating

Table I. Summary of the effects of copper on Alzheimer's disease.

A, *In vitro*

Authors, year	Experimental model	Dose and route	Duration	Findings and pathological features	(Refs.)
Pilozzi *et al*, 2020	SH-SY5Y neuroblastoma cells	$CuCl_2$ (0.01, 0.1 and 1 μM) in culture medium	48 h	Aβ oligomerization ↑; APP translation ↑; APP protein expression ↑	(87)
Kitazawa *et al*, 2009	SH-SY5Y neuroblastoma cells	Copper exposure (10 μM to 1 mM in culture medium)	24 h	APP protein levels ↑ (dose-dependent; ≤0.1 mM); APP protein levels ↓ (at 1 mM; due to toxicity); no change in APP mRNA levels	(88)
Crouch *et al*, 2009	SH-SY5Y neuroblastoma cells	Cu^{2+}(gtsm) and Cu^{2+} (atsm) (25 μM in culture medium)	5 h	GSK3β inhibition ↑; Tau phosphorylation ↓; Aβ oligomer levels ↓	(89)
Xia *et al*, 2024	SH-SY5Y neuroblastoma cells	Aβ1-42 fibrils (1-5 μM) in culture medium	24 h	Cu^{2+} ↓; Cu^{+} ↑ (mitochondria and lysosomes); ROS ↑; mitochondrial damage ↑; GSH ↓; autophagy ↑	(90)

B, *In vivo*

Authors, year	Experimental model	Dose and route	Duration	Findings and pathological features	(Refs.)
Hua *et al*, 2011	*Drosophila* (fruit flies)	Dietary copper supplementation (concentration not specified)	Lifespan	Copper exacerbates Aβ42-induced eye damage; copper chelators or metallothioneins ameliorate neurodegeneration	(91)
Pilozzi *et al*, 2020	APP/PS1 transgenic mice	Dietary copper supplementation (300 mg Cu/kg)	24 days	Aβ1-40 and Aβ1-42 levels ↑; Aβ plaque area ↑; astrogliosis (GFAP) ↑; pro-inflammatory cytokines (MCP-5) ↑; spatial working memory and short-term memory ↓	(87)
Kitazawa *et al*, 2009	3xTg-AD mice	250 ppm $CuSO_4$ in drinking water (with 5% sucrose)	3 months	APP and C99 levels ↑; Aβ40 levels ↑; BACE1 expression ↑; AT8-positive neurons in CA1 ↑; slight increase in tau phosphorylation	(88)
Kitazawa *et al*, 2009			9 months	APP, C99 and C83 levels ↑; Aβ40 and Aβ42 levels ↑; BACE1 and ADAM10 expression ↑; marked increase in tau phosphorylation (AT8, AT180 and PHF-1 ↑); cdk5/ p25 activation ↑	
Yu *et al*, 2015	3xTg-AD mice	250 ppm copper sulfate in drinking water	6 months	Memory impairment ↑; hippocampal protein expression altered (44 proteins differentially expressed); complexin-1 and complexin-2 ↓ (key memory-associated proteins)	(92)
Sparks and Schreurs, 2003	Cholesterol-fed rabbits	0.12 ppm copper sulfate in drinking water	10 weeks	Aβ accumulation ↑; senile plaque-like structures ↑ (hippocampus and temporal lobe); learning deficits ↑ (trace conditioning task); SOD activity ↑; GPX activity ↓	(93)

Table I. Continued.

B, *In vivo*

Authors, year	Experimental model	Dose and route	Duration	Findings and pathological features	(Refs.)
Sparks *et al*, 2006	PS1/APP transgenic mice	0.12 ppm copper sulfate in drinking water	6 weeks	Aβ deposition ↑ (similar plaque number but larger plaque size in copper-treated mice); distilled water reduces plaque size	(94)
Crouch *et al*, 2009	APP/PS1 transgenic mice	Cu^{2+}(gtsm) (10 mg/kg; daily gavage)	6 weeks	Cognitive performance ↑ (Y-maze test); Aβ trimer levels ↓; Tau phosphorylation ↓; GSK3β inhibition ↑ (via Akt activation)	(89)
Xia *et al*, 2024	5xFAD transgenic mice	Endogenous Aβ accumulation (geneticmodel)	12 months	Cu^{2+} ↓; Cu^{+} ↑ (brain tissue); Aβ plaques ↑; mitochondrial dysfunction ↑; Cu transport genes (ATP7A/B) ↑	(90)
Prohaska and Brokate, 1999	Sprague-Dawley and Holtzman rats	Cu-deficient or Cu-adequate diet and water	4 weeks (postweanling); perinatal exposure	Cu deficiency: DBH activity and mRNA ↑; norepinephrine ↓; dopamine ↑; Cu repletion restored DBH mRNA levels	(95)

3xTg-AD, triple transgenic Alzheimer's disease mouse model; 5xFAD, five familial Alzheimer's disease mutations mouse model; Aβ, amyloid-β; ADAM10, ADAM metallopeptidase domain 10; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme 1; Cu^{+}, cuprous ion; Cu^{2+}, cupric ion; Cu^{2+}(gtsm), copper^{2+}-glyoxalbis(N4-methylthiosemicarbazonato); Cu^{2+}(atsm), copper^{2+} diacetylbis(N4-methylthiosemicarbazone); DBH, dopamine β-hydroxylase; GFAP, glial fibrillary acidic protein; GSH, glutathione; GPX, glutathione peroxidase; MCP-5, monocyte chemoattractant protein-5; PHF-1, paired helical filament-1; PS1, presenilin 1; ROS, reactive oxygen species; SOD, superoxide dismutase.

oxidative damage and further impairing neuronal function (Table II) (113-115). However, whether the protein levels of Cu/Zn-SOD1 concurrently decline remains a subject of debate (116). *In vivo* studies using copper-deficient animal models have indicated a reduction in Cu/Zn-SOD1 activity, compared with that in copper-sufficient controls, leading to elevated oxidative marker levels and neuronal damage (117-119). These findings highlight that copper deficiency not only impacts enzyme function but may also increase vulnerability to oxidative stress in AD.

Copper overload. Excessive copper accumulation can cause damage to the nervous system. In copper metabolic disorders, such as Wilson's disease, copper accumulates excessively in neural tissues, particularly in the basal ganglia and other critical brain regions, leading to neurological dysfunction (120-122). These observations indicate that copper overload may serve a crucial role in neurodegenerative diseases.

i) Increased oxidative stress. Copper is a redox-active transition metal, and its excessive accumulation can markedly enhance the generation of ROS. Through Fenton-like reactions, copper facilitates the decomposition of hydrogen peroxide (H_2O_2), producing highly reactive hydroxyl radicals (OH·), thus inducing cellular oxidative damage. Simultaneously, copper overload can impair the cellular antioxidant defense system, exacerbating oxidative injury (123-125). Under normal conditions, antioxidant enzymes such as SOD, GSH peroxidase and catalase eliminate excessive ROS, maintaining the cellular redox balance. However, copper overload can inhibit the activity of these enzymes and deplete GSH, a key non-enzymatic antioxidant, leading to decreased GSH levels and reduced antioxidant enzyme activity (126,127). This imbalance results in ROS accumulation, further aggravating oxidative damage (128,129).

ii) Disrupted energy metabolism. Copper can directly or indirectly damage mitochondrial DNA (mtDNA), especially the D-loop region, which is critical for mtDNA replication and transcription (130). Copper overload can catalyze redox cycling, promoting ROS generation, such as that of OH·. These ROS can induce mtDNA oxidative damage, influencing mitochondrial gene expression and functional stability (70). Additionally, copper overload can inhibit the activities of mitochondrial respiratory chain complexes (Complexes I-IV), leading to reduced ATP production and compromised neuronal energy supply (70). The oxidative environment further disrupts mitochondrial membrane integrity, impairs ETC function and inhibits ATP synthesis, causing neuronal metabolic disorders and functional impairment (70). Additionally, copper overload can promote lipid peroxidation and increase malondialdehyde (MDA) production. As a marker of membrane oxidative damage, MDA can further destabilize mitochondrial membranes, finally accelerating mitochondrial functional failure (131).

iii) Activation of the inflammatory response. Copper can exacerbate inflammatory responses through various mechanisms. Copper overload can lead to excessive ROS accumulation, enhance myeloperoxidase activity and

Table II. Dysfunction of cuproenzymes.

Authors, year	Protein	Role in AD	Copper interaction and effects	Pathological consequences	(Refs.)
Gu *et al*, 2023; Trist *et al*, 2021; Furukawa *et al*, 2004	Cu/Zn-SOD1	Antioxidant enzyme that detoxifies superoxide radicals	Cu^+ is essential for Cu/Zn-SOD1 activity; copper deficiency reduces Cu/Zn-superoxide dismutase 1 activity; oxidative stress can cause misfolding and aggregation	Oxidative stress ↑, neuronal damage ↑ and aggregation-related toxicity ↑	(113-115)
Saporito-Magriñá *et al*, 2018; Ribas *et al*, 2014	GSH	Major antioxidant that protects cells from oxidative stress	Cu^+ binds to GSH, forming a Cu^+-GSH complex, leading to GSH depletion and impaired redox homeostasis	Antioxidant capacity ↓, oxidative stress ↑ and cellular damage ↑	(165,166)
Zhu *et al*, 2024; Yang *et al*, 2024; Ruiz *et al*, 2021; Crouch *et al*, 2005	CCO	Mitochondrial enzyme crucial for electron transport and ATP production	Cu^+ is directly utilized by COX, while Cu^{2+} delivers copper; excessive Cu^+ disrupts mitochondrial function via oxidative stress	Energy metabolism impaired and mitochondrial dysfunction ↑	(8,50,70,167)
Okita *et al*, 2017; Xu *et al*, 2017	MTs	Metal-binding proteins that detoxify excess metals and reduce oxidative stress	Cu^+ binds to MTs with high affinity; however, excessive copper overwhelms MT capacity, impairing detoxification	Oxidative stress ↑, metal toxicity ↑ and metal homeostasis is dysregulated	(168,169)
Ruiz *et al*, 2021; Garza *et al*, 2023; Rossi *et al*, 1998	CCO	Mitochondrial enzyme crucial for electron transport and ATP production	Copper is a critical cofactor for CCO, and is required for its proper function in the electron transport chain	Copper deficiency impairs CCO activity, leading to energy metabolism ↓, mitochondrial dysfunction ↑ and neurological deficits	(70,153,170)
Rahman *et al*, 2009; Xiao *et al*, 2018	Neurotransmitter synthesis enzymes	Enzymes (such as dopamine β-hydroxylase) that synthesize neurotransmitters	Copper is a cofactor for these enzymes, and its deficiency reduces their activity, impairing neurotransmitter synthesis	Neurotransmitter (such as dopamine and norepinephrine) levels ↓, leading to synaptic dysfunction and cognitive deficits	(108,109)

AD, Alzheimer's disease; Cu/Zn-SOD1, copper/zinc superoxide dismutase 1; SOD1, superoxide dismutase 1; Cu^+, cuprous ion (reduced copper ion); Cu^{2+}, cupric ion (oxidized copper ion); GSH, glutathione; CCO, cytochrome c oxidase; COX, cyclooxygenase; MTs, metallothioneins.

activate the NF-κB signaling pathway, promoting the release of pro-inflammatory cytokines (such as IL-1α and TNF-β) while inhibiting anti-inflammatory cytokines, resulting in a chronic inflammatory state (132,133). Additionally, copper can activate the innate immune system via the α kinase 1-dependent pathway, further amplifying inflammatory signals (132). Copper can also activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome, promoting IL-1β production and exacerbating inflammatory damage (132,134).

iv) Activation of other forms of programmed cell death. Copper overload can induce other forms of programmed cell death, notably ferroptosis and apoptosis, through distinct molecular mechanisms. Classical ferroptosis is an iron-dependent process characterized primarily by lipid peroxidation and subsequent cell membrane damage, and is predominantly mediated by iron-catalyzed Fenton reactions (135). In this classical pathway, depletion of intracellular GSH and subsequent inactivation of GSH peroxidase 4 (GPX4) lead to the accumulation of lipid hydroperoxides, resulting in extensive membrane disruption and cell death (136). By contrast, copper-induced ferroptosis follows a unique pathway distinct from the classical iron-dependent mechanism. Specifically, copper directly interacts with GPX4 to facilitate its aggregation and subsequent autophagic degradation (137). This copper-mediated GPX4 degradation disrupts cellular antioxidant defenses, indirectly amplifying lipid peroxidation and

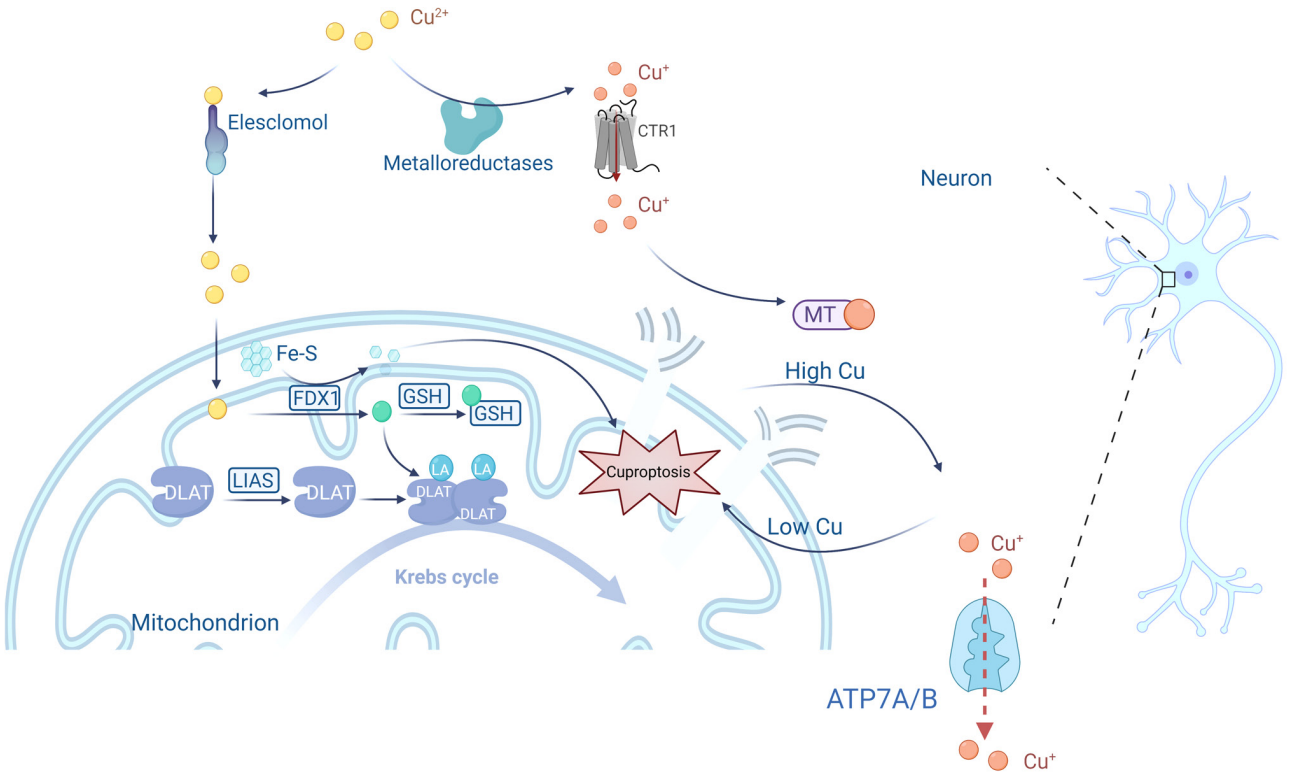

Figure 2. Mechanism of cuproptosis in neurons. Excessive copper [Cu^{2+}] is transported into cells via elesclomol. The accumulation of Cu^{2+} disrupts Fe-S cluster proteins and lipoic acid-dependent enzymes such as DLAT. Copper-induced stress depletes GSH, an antioxidant that protects cells from oxidative damage. Additionally, some extracellular Cu^{2+} is reduced to Cu^{+} by metalloreductases and transported into cells via CTR1. This Cu^{+} in mitochondria can directly trigger cuproptosis. Cu^{+}/Cu^{2+}, reduced/oxidized copper ion; CTR1, copper transporter 1; DLAT, dihydrolipoamide S-acetyltransferase; FDX1, ferredoxin 1; Fe-S, iron-sulfur; GSH, glutathione; LA, lipoic acid; LIAS, lipoic acid synthase; MT, metallothionein.

promoting ferroptosis. Additionally, copper ions themselves catalyze Fenton-like reactions to generate ROS, exacerbating oxidative stress either independently or synergistically with iron (138).

Copper can displace zinc ions at p53 binding sites, causing p53 protein misfolding and weakening its DNA-binding ability, thereby disrupting the p53-mediated DNA damage response and cell cycle regulation (139). This mechanism may reduce the capacity of cells to repair DNA damage, increasing genomic instability and promoting apoptosis. Simultaneously, copper overload can lead to loss of mitochondrial membrane potential ($\Delta\Psi m$), which triggers cytochrome *c* release, further activates the intrinsic apoptosis pathway, accelerates cell death and causes tissue damage (140,141).

Cuproptosis. Research has indicated that copper overload can trigger cuproptosis, a unique form of cell death induced by excessive accumulation of copper within mitochondria (142) (Fig. 2). This mechanism offers a novel pathological perspective on the role of copper in neurodegenerative disorders.

Cuproptosis is a copper-dependent form of programmed cell death first described by Tsvetkov *et al* (12) in 2022, who identified a distinct mechanism by which copper induces cell death through mitochondrial metabolic disruption. Unlike classical forms of cell death such as apoptosis, ferroptosis and necroptosis, cuproptosis does not involve traditional cell death markers. Subsequent research has demonstrated that interventions aiming at inhibiting apoptosis, necroptosis, pyroptosis and ferroptosis do not prevent copper-induced cell death, confirming that cuproptosis represents a unique and independent cell death pathway (12,143).

Mitochondrial dependence. Cuproptosis, a form of mitochondrial-dependent programmed cell death, is contingent upon mitochondrial copper overload. This cell death pathway is particularly toxic to cells that rely on OXPHOS for energy metabolism, such as neurons, whereas cells primarily dependent on glycolysis exhibit greater tolerance (140,144). Under physiological conditions, mitochondria not only serve as the central site for cellular respiration and ATP production but also serve a critical role in the regulation of copper metabolism (70,145).

Excessive copper can enter neurons in the form of either Cu^{2+} or Cu^{+} (60). Cu^{2+} may enter cells through specialized copper-ionophore complexes such as elesclomol, or alternatively, it can be reduced extracellularly to Cu^{+} by metalloreductases (146,147). Following this reduction, Cu^{+} is primarily transported into the cytoplasm via the high-affinity copper transporter CTR1 (148) (Fig. 2). The mechanisms of copper entry into mitochondria remain only partially understood. It has been proposed that copper may enter as anionic copper ligands (CuL) or complexed with GSH (70), possibly passing through the outer mitochondrial membrane into the intermembrane space (IMS). In the IMS, copper is delivered to the active sites Cu_A and Cu_B of CCO by copper chaperones COX17, synthesis of cytochrome *c* oxidase (SCO)1 and SCO2, ensuring catalytic function (69,149). CCO, as the Complex IV of the ETC, transfers electrons from cytochrome *c* to oxygen, facilitating ATP synthesis (69). Transport across

the inner mitochondrial membrane likely involves transporters such as solute carrier family 25 member 3 and mitoferrin-1, where copper is stored in a CuL-bound form to support copper-dependent enzymes (150).

Proper assembly of CCO requires SCO1 and SCO2, which help maintain copper homeostasis and enzymatic function (151). Additionally, copper-binding proteins COX23 and COX19 also participate in the assembly of CCO, where COX19 may influence copper transport to COX11 by regulating the redox status, although the specific role of COX23 in copper transport remains unclear (152). The correct assembly and function of CCO serve a crucial role in ensuring proper copper distribution and maintaining the normal function of copper-dependent enzymes in mitochondria (152,153).

Mitochondria contain Cu/Zn-SOD1, the copper metalation of which is mediated by the copper chaperone CCS (154). Apo-SOD1 is first imported into the IMS, where it binds to CCS for metalation, ultimately forming mature SOD1 that performs antioxidative functions by scavenging superoxide radicals (155,156). As a result, the precise regulation and supply of copper are vital for the normal functions of CCO and SOD1, thus ensuring efficient oxidative phosphorylation and robust antioxidant protection.

Mechanistic process. Cuproptosis is characterized by three core processes: Copper ion delivery and acylation modification, abnormal aggregation of acylated proteins, and proteotoxic stress leading to mitochondrial dysfunction (122,157) (Fig. 2).

The process is initiated by ferredoxin 1 (FDX1), which mediates the reduction of Cu^{2+} to Cu^{+}, allowing copper to bind to lipoylated sites on mitochondrial enzymes (158). Lipoylation, a critical post-translational modification for TCA cycle enzymes, including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain α-ketoacid dehydrogenase and the glycine decarboxylase complex, enhances their catalytic activity under normal conditions (159).

However, when copper binds to these lipoylated proteins, it triggers their aggregation, particularly affecting critical TCA cycle enzymes such as dihydrolipoamide S-acetyltransferase (DLAT) and dihydrolipoamide branched-chain transacylase E2 (DBT) (Fig. 2) (158). This aggregation inhibits the TCA cycle and OXPHOS, reducing the production of acetyl-CoA and reduced form of NADH, disrupting the ETC, and leading to metabolic dysregulation (12). Whole-genome CRISPR screening has further validated that lipoylation modifications are central to copper-induced cell death (cuproptosis), with DLAT aggregation serving as a crucial molecular hallmark (159,160).

The aggregation of copper-bound mitochondrial proteins triggers proteotoxic stress, leading to the destabilization and breakdown of Fe-S clusters. These Fe-S clusters are essential cofactors for several critical enzymes involved in the TCA cycle and ETC complexes I-III (8). The loss or disruption of Fe-S clusters subsequently impairs ETC function, resulting in a decreased $\Delta\Psi m$ and augmented oxidative stress.

The protein aggregation and subsequent Fe-S cluster disruption induced by copper overload activate cellular protein quality control pathways, including the increased expression of molecular chaperones such as heat shock protein 70 (HSP70), which attempts to mitigate the proteotoxic burden (8,160). Nevertheless, when the proteotoxic and oxidative stresses exceed the cellular regulatory and compensatory capacities, the resulting protein homeostasis imbalance further deteriorates mitochondrial function (161). This dysfunction can trigger the intrinsic apoptotic pathway, marked by mitochondrial outer membrane permeabilization and subsequent caspase activation (162). Mitochondrial dysfunction serves as a pivotal convergence point connecting cuproptosis and ferroptosis (163). Specifically, copper-induced destabilization of mitochondrial Fe-S clusters may exacerbate the release or redistribution of labile iron, thereby potentiating the iron-dependent lipid peroxidation characteristic of ferroptosis (164).

4. Copper dysregulation in AD

Copper serves a dual role in AD pathology. As an essential trace element, it supports mitochondrial respiration, antioxidant defense and neurotransmitter synthesis (Table II) (8,50, 70,108,109,113-115,153,165-170). However, dysregulation of copper homeostasis, either deficiency or overload, can exacerbate neurodegeneration (171). Copper deficiency impairs CCO activity and antioxidant capacity, while copper overload promotes Aβ aggregation, tau phosphorylation, oxidative stress and mitochondrial dysfunction (8,50,70,167). Experimental studies have suggested that low-to-moderate copper exposure enhances amyloidogenic processing, whereas excessive copper induces cytotoxicity (87,88). In transgenic AD mouse models, dietary copper supplementation increased Aβ deposition, β-secretase [β-site APP cleaving enzyme 1 (BACE1)] expression, neuroinflammation and cognitive deficits. Conversely, controlled copper delivery via copper complexes alleviated AD-related pathological parameters, including reductions in Aβ accumulation, decreased tau phosphorylation, attenuation of oxidative stress and neuroinflammation, and improvement in cognitive performance (87-94). These findings highlight the importance of maintaining copper balance, as both excess and deficiency can independently drive AD progression.

Copper overload and cuproptosis in AD. Some studies have demonstrated that brain tissue copper concentrations in patients with AD can reach levels as high as 400 μM, compared with ~70 μM in age-matched healthy individuals (172-174). Excessive copper accumulation in the brain is increasingly being recognized as a critical pathogenic factor driving the progression of AD (175,176). Elevated copper levels detected in the serum and CSF have been closely associated with accelerated neurodegeneration and atrophy in specific brain regions, including the entorhinal cortex and hippocampal CA1 area (177,178). Furthermore, copper overload promotes Aβ aggregation, tau phosphorylation, oxidative stress and neuroinflammation (88,179) (Fig. 3).

Aβ plaques. Aβ is a 39- to 42-amino acid polypeptide derived from the amyloid precursor protein (APP) through proteolytic processing involving BACE1 and the γ-secretase complex (180,181). In aqueous environments, Aβ exhibits a hydrophilic N-terminus and a hydrophobic C-terminus, with both termini being unstructured (182). Residues His13 to Asp23 form an α-helix, a structure that predisposes Aβ to

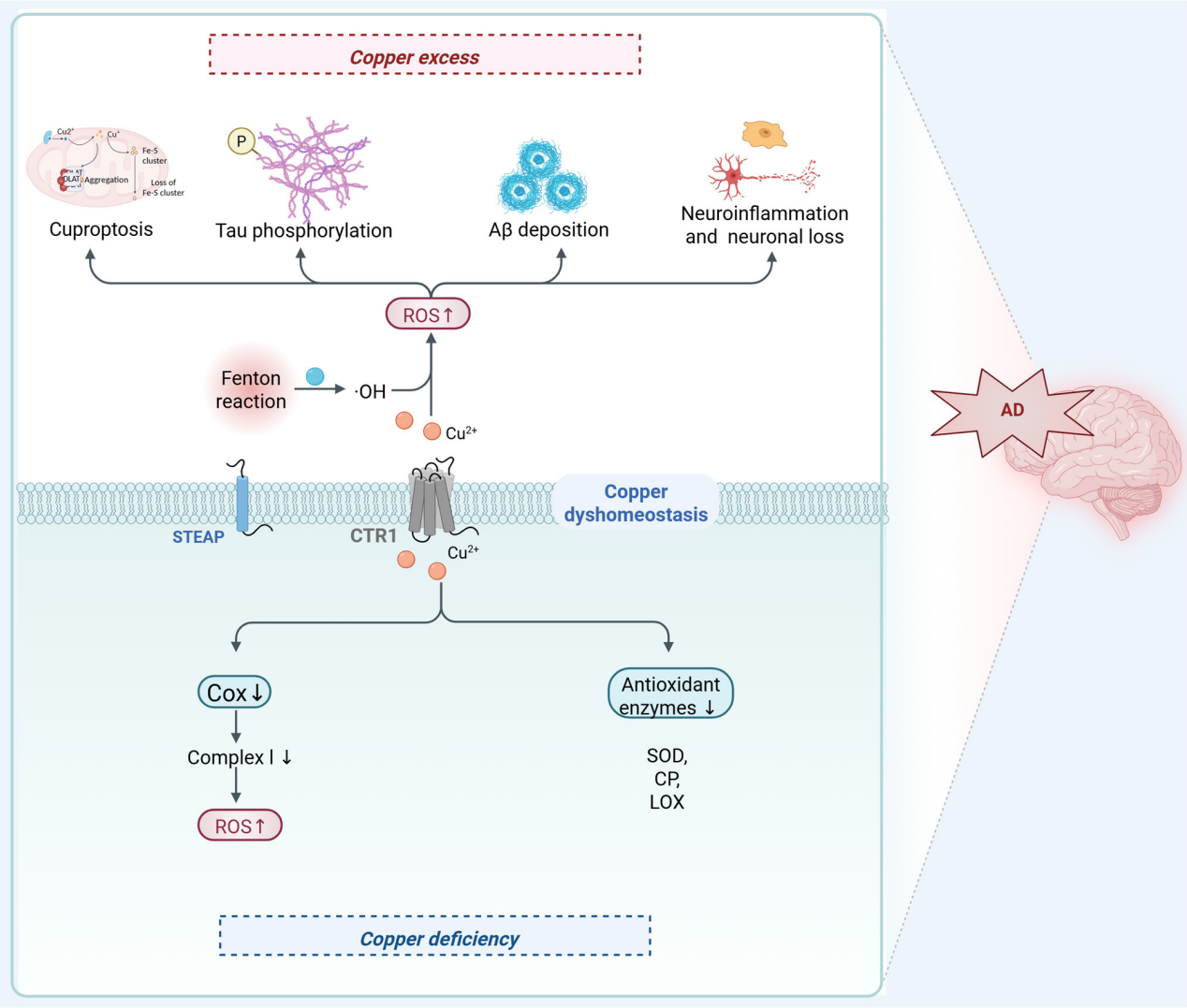

Figure 3. Copper dyshomeostasis and its dual impact on AD. Both copper excess and deficiency contribute to AD pathogenesis. Copper overload induces Aβ aggregation, Tau phosphorylation, oxidative stress (via the Fenton reaction) and neuroinflammation with neuronal loss. Conversely, copper deficiency reduces antioxidant enzymes (such as SOD, CP and LOX) and Cox activity, leading to impaired mitochondrial function and elevated ROS levels. These disruptions in copper homeostasis accelerate neurodegeneration. Aβ, amyloid-β; AD, Alzheimer's disease; CP, ceruloplasmin; Cox, cyclooxygenase; CTR1, copper transporter 1; DLAT, dihydrolipoamide S-acetyltransferase; Fe-S, iron-sulfur; LOX, lysyl oxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; STEAP, six-transmembrane epithelial antigen of the prostate.

aggregate into β-sheet-rich assemblies, leading to the deposition of senile plaques, a hallmark of AD (183,184).

At the molecular level, copper directly interacts with Aβ and tau proteins, facilitating their abnormal aggregation, enhancing neurotoxicity, and promoting both Aβ deposition and tau hyperphosphorylation, ultimately leading to neuronal dysfunction and injury (185). Copper ions [Cu^{2+}/Cu^{+}] serve a role in Aβ aggregation and neurotoxicity (186,187). Cu^{2+} binds to histidine residues at the N-terminus of Aβ (His6, His13 and His14), promoting the formation of β-sheet-rich oligomers that are resistant to proteolytic degradation, thereby accelerating Aβ deposition (188). Under physiological pH conditions, two primary coordination modes exist for Cu^{2+} binding to Aβ monomers: Mode I involves the NH_2 group, one oxygen atom and two histidine residues (His6 and either His13 or His14); mode II involves the substitution of one histidine by a deprotonated amide (189). Aβ exhibits a higher affinity for Cu^{+} than for Cu^{2+}, suggesting that Cu^{+} may be the more biologically relevant oxidation state; however, the specific role of Cu^{+} in Aβ aggregation remains controversial. Some studies suggest that Cu^{+} may stabilize Aβ monomers and inhibit aggregation by occupying critical histidine residues, thereby reducing fibrillization (190,191). By contrast, other evidence indicates that Cu^{+} may promote the formation of soluble toxic oligomers or redox cycling with Cu^{2+}, contributing to oxidative stress and aggregation (192,193). The inconsistency likely arises from differences in experimental conditions, such as pH, Cu^{+}/Cu^{2+} ratio, Aβ isoform, and the presence of reducing agents or cofactors (190). Additional cellular studies using mouse hippocampal HT-22 cells exposed to Aβ1-42 oligomers have demonstrated that copper overload can promote Aβ-induced neuronal damage via the NLRP3/caspase-1/Gasdermin D pathway (179,194). In addition, these experiments revealed that copper chloride treatment exacerbated the toxic effects of Aβ, suggesting a synergistic relationship between copper accumulation and AD pathology (179). Research on aging

mice has demonstrated that copper accumulation in brain capillaries is associated with reduced low-density lipoprotein receptor-related protein 1 (LRP1) expression and higher brain Aβ levels (195).

Aβ can bind Cu^{2+}/Cu^{+} to facilitate aggregation. Additionally, Aβ may reduce Cu^{2+} to Cu^{+}, which can subsequently participate in Fenton-like reactions with H_2O_2 to produce OH·, thereby inducing oxidative stress (196). Oxidation of the Met35 residue in Aβ to methionine sulfoxide increases Aβ hydrophobicity, promoting cross-β stacking and further accelerating Aβ deposition (197). Studies have indicated that Cu^{2+} can influence Aβ metabolism and tau phosphorylation (198,199). In SH-SY5Y neuroblastoma cells, treatment with $CuCl_2$ for 48 h increased Aβ oligomerization, and upregulated APP translation and protein expression (198). Notably, the use of the cell-permeable copper complex $Copper^{2+}$-glyoxalbis(N4-methylthiosemicarbazonato) [Cu^{2+}(gtsm)] mitigated AD-like changes by promoting GSK3β inhibition, reducing tau phosphorylation and decreasing Aβ oligomers, highlighting its potential as a therapeutic strategy for safe and bioavailable copper supplementation (89). Furthermore, copper redistribution induced by Aβ1-42 fibrils shifts Cu^{2+} to Cu^{+} in mitochondria and lysosomes, triggering ROS accumulation, mitochondrial dysfunction and autophagy, which are the key features of AD neurodegeneration (90).

Copper influences AD pathology through its interaction with key proteins involved in disease progression (Table II). Cu^{2+} binding to APP has been shown to promote Aβ oligomerization and plaque formation, thereby exacerbating neurotoxicity. Additionally, the interaction of copper with BACE1 via Cu^{+} binding can alter APP processing, linking copper dysregulation to increased Aβ production (24). Copper also impacts antioxidant defenses by modulating SOD1 activity, where reduced copper availability decreases the free radical-scavenging capacity of SOD1, leading to oxidative stress. Furthermore, copper can modulate tau pathology by inhibiting GSK3β via Akt signaling, reducing tau phosphorylation and potentially mitigating NFT formation. Animal studies have indicated that cholesterol intake combined with copper exposure may synergistically promote AD-related pathological changes (93,200). In rabbits fed a cholesterol-rich diet, supplementation with trace amounts of copper (0.12 ppm) in drinking water markedly increased Aβ deposition, leading to the formation of senile plaque-like structures in the hippocampus and temporal lobe. This combination also markedly impaired the ability of rabbits to perform complex learning tasks, suggesting that elevated copper levels may interact with altered lipid metabolism to exacerbate AD pathology (93).

Copper modulates LRP1-mediated Aβ clearance across the BBB. In healthy individuals, this mechanism maintains Aβ homeostasis; however, in aging patients or patients with AD, elevated vascular copper levels may impair LRP1-mediated Aβ clearance, leading to Aβ accumulation in the brain and exacerbating AD pathology (195).

Tau tangles. Tau is a microtubule-associated protein that, under normal physiological conditions, stabilizes microtubules to maintain neuronal structural integrity and facilitate axonal transport (201). In AD, tau undergoes hyperphosphorylation, leading to the loss of its microtubule-stabilizing function. This dysfunction impairs axonal transport and synaptic activity (201). Hyperphosphorylated tau aggregates into paired helical filaments, which further assemble into NFTs (202,203). The accumulation of NFTs disrupts neuronal function and is associated with cognitive decline in patients with AD (204).

Cu^{2+} can directly bind to tau, influencing its conformation and promoting aggregation. Each tau monomer can bind to one Cu^{2+} ion, with a dissociation constant in the micromolar range (205). This interaction may facilitate the formation of β-sheet-rich tau fibrils, contributing to synaptic failure, neuronal death and cognitive decline observed in patients with AD (199). In addition, copper-induced oxidative stress can activate kinases responsible for tau phosphorylation, thereby enhancing the propensity of tau to form toxic aggregates. This process is driven by GSK-3β activation and PP2A inhibition (206). When Cu^{2+} binds to Aβ, it also produces ROS, which leads to neuronal damage (207). Oligomers isolated from postmortem brains of patients with AD have been found to potently induce AD-type tau phosphorylation (208,209).

Cuproptosis. In addition to the classical pathological hallmarks of AD, including extracellular Aβ plaque deposition and phosphorylated tau, studies have suggested that cuproptosis may also contribute to AD pathogenesis (10,210) (Fig. 3). This pathway is defined by the aggregation of lipoylated mitochondrial proteins and destabilization of Fe-S clusters, ultimately leading to proteotoxic stress and mitochondrial dysfunction. Postmortem analyses of patients with AD have revealed the abnormal accumulation of DLAT within hippocampal neurons, where it colocalizes with phosphorylated tau (10,211).

Transcriptomic and proteomic analyses in AD-like models further demonstrate the dysregulation of core cuproptosis-related enzymes. Specifically, dihydrolipoamide dehydrogenase, FDX1, glutaminase and pyruvate dehydrogenase E1 subunit β are markedly downregulated, while DBT is markedly upregulated under AD-mimicking conditions (212). Complementary bioinformatics analyses of clinical datasets have revealed upregulation of multiple cuproptosis-associated genes in patients with AD, including MAP2K1 and solute carrier family 31 member 1, the latter of which encodes CTR1 (213,214). Predictive models based on these gene signatures exhibit moderate diagnostic performance in distinguishing patients with AD from healthy controls (215). *In vitro* experiments using SH-SY5Y neuronal cells treated with $A\beta_{(25-35)}$ oligomers have demonstrated the robust upregulation of FDX1 compared with untreated controls, further supporting the activation of cuproptosis pathways in AD-like conditions (213). In one study, C57BL/6 mice exposed to polystyrene nanoplastics (an environmental vector for copper) exhibited increased cerebral copper accumulation, DLAT lipid acylation and dysregulation of cuproptosis regulators [such as FDX1, lipoic acid synthase (LIAS) and HSP70]. These molecular disturbances were accompanied by mitochondrial damage, synaptic dysfunction and behavioral impairments, including memory deficits (216). Furthermore, FDX1, a central mediator of copper reduction and lipoylated protein regulation, has been found to be markedly upregulated in both AD animal models and human subjects, particularly in individuals carrying the apolipoprotein E ε4/ε4 genotype (213).

Neuroinflammation and neuronal loss. Copper ion overload can directly cause neuronal damage or death, accelerating the pathological process of AD (9). In AD mouse models, low-dose copper exposure exacerbates neuroinflammation, further impairing neuronal function (195). In the brains of patients with AD, microglia enhance intracellular copper accumulation by upregulating the copper transporter CTR1, triggering microglial cuproptosis. Dying microglia release pro-inflammatory factors (such as IL-1β and TNF-α) and mtDNA, further activating the NLRP3 inflammasome in astrocytes and promoting chronic neuroinflammation (9,217). Additionally, prolonged high copper exposure can lead to astrocyte dysfunction and apoptosis, further exacerbating neuronal damage. Astrocytes surrounding Aβ plaques exhibit mitochondrial copper overload and DLAT protein accumulation, both of which are closely associated with local synaptic loss (10,211). Copper overload can also cause synaptic injury, disrupting synaptic plasticity. This is manifested by the downregulation of synaptophysin, affecting synaptic vesicle cycling; the loss of postsynaptic density protein 95, disrupting NMDA-R clustering; and the inhibited phosphorylation of CREB, leading to reduced secretion of BDNF and inhibition of the tropomyosin receptor kinase B receptor signaling pathway, ultimately impairing synaptic plasticity and accelerating the progression of AD (218,219).

Copper deficiency in AD. Despite seeming contradictory, the 'copper deficiency vs. overload' scenarios are two sides of the same coin; both imply a breakdown of normal copper homeostasis. Both conditions can lead to pathogenic outcomes; in particular, neuronal copper deficiency may impair essential cuproenzymes and antioxidant defenses (220). Multiple post-mortem studies have demonstrated that brain copper levels are markedly reduced in AD (221-223). For example, a 2017 metallomic analysis of human brain tissues reveled that copper concentrations in AD were only 53-70% of those in age-matched controls across all examined regions, suggesting a widespread 'pan-cerebral' copper deficiency (221). The magnitude of this drop is notable; brain copper levels in AD are lowered to levels approaching those observed in Menkes disease, a genetic disorder of severe copper deficiency. These findings are consistent with earlier observations such as those by Deibel *et al* (224) and were confirmed by a meta-analysis (225). A quantitative meta-analysis compiling data from prior studies concluded that copper was significantly depleted in the AD neocortex (P=0.0003), although some other metals (such as iron) exhibited no uniform increase (222). Previous reviews have reinforced that most studies since 2015 have reported reduced brain copper levels in patients with AD (226,227). For example, a 2021 review noted that AD brains tended to exhibit decreased copper levels, with only a few contradictory reports of normal or elevated copper levels (223).

While copper overload has been traditionally emphasized in AD pathology, it is equally important to recognize that copper deficiency may also contribute to disease progression. Copper is a cofactor for enzymes such as CCO (Complex IV of mitochondria), Cu/Zn-SOD1, SOD3 and CP, which protect against oxidative damage and support energy metabolism. According to previous studies, decreased brain copper levels can impair antioxidant defenses and increase susceptibility to oxidative stress, suggesting that both excess and deficiency warrant careful consideration when evaluating the role of copper in AD (9,228,229). Copper deficiency impairs the activity of copper-dependent enzymes such as CCO and SOD1, resulting in mitochondrial dysfunction and compromised antioxidant defense (118,170). This leads to increased oxidative stress, impaired nitric oxide (NO) clearance and accumulation of peroxynitrite, further damaging neuronal structures. Both extremes disrupt NO signaling, leading to synaptic dysfunction and neuroinflammation (230). These findings underscore the bidirectional impact of copper imbalance on AD and support a therapeutic strategy aiming at restoring copper homeostasis (Fig. 3). Research has indicated that copper deficiency may serve a paradoxical role in the pathogenesis of AD, affecting Aβ metabolism, iron homeostasis and neuronal energy metabolism (195). A meta-analysis and subsequent studies have demonstrated a decrease in total brain copper levels in patients with AD (222,231,232). Copper deficiency is associated with increased activity of BACE1, and excessive activation of BACE1 enhances the amyloidogenic pathway, leading to increased production of Aβ (233). Additionally, copper serves a critical role in the transcription and processing of APP (234). Physiological levels of copper activate the Sp1 transcription factor, which binds to the APP promoter, maintaining basal APP expression essential for synaptic plasticity (8,234). Dietary treatment of APP23 transgenic mice with Cu sulfate for a 3-month interval extended the lifetime of the mice considerably and restored SOD1 activity back to normal levels (235). In agreement with the benefit of Cu treatment, Cu supplementation may prevent the premature death observed in APP transgenic mice treated with CQ (236). However, copper deficiency can downregulate APP expression and, by reducing competition for non-amyloidogenic processing, shift APP processing toward the amyloidogenic pathway (237). Additionally, disturbances in iron homeostasis are a notable link between copper deficiency and AD pathology. In a state of copper deficiency, CP loses its ferroxidase activity, impairing the oxidation of Fe^{2+} to Fe^{3+}, which leads to iron deposition in the basal ganglia and cortical areas of patients with AD, enhances ferroptosis and oxidative stress through the Fenton reaction, and further exacerbates Aβ-mediated neurotoxicity (238,239).

5. Therapeutic advances, limitations and future directions

Advances. Copper chelation has emerged as a potential therapeutic strategy for AD, aiming to reduce copper-mediated oxidative stress and protein toxicity while preserving essential physiological copper-dependent enzyme activity (22). First-generation copper chelators, including the 8-hydroxyquinoline derivative CQ, have shown efficacy in preclinical models by redistributing metal ions within Aβ plaques, reducing Aβ-induced neurotoxicity and improving cognitive performance in transgenic mouse models of AD (240). However, the limited BBB permeability and potential off-target effects associated with CQ restrict its further clinical application, prompting the development of second-generation chelators (241). Among these second-generation chelators, PBT2, a hydroxylquinoline-derived compound designed to

modulate metal-protein interactions, exhibits superior BBB permeability, optimized pharmacokinetic properties and improved specificity (242). Preclinical studies have indicated that PBT2 can effectively restore neuronal copper homeostasis and decreased Aβ oligomer formation (8,243,244). In a phase II clinical trial, treatment with PBT2 resulted in a 25% improvement in cognitive scores relative to placebo controls and restored copper availability to critical copper-dependent enzymes such as SOD1 and CCO, thereby potentially reducing oxidative stress and mitochondrial dysfunction (245). However, in a subsequent phase II trial (IMAGINE), PBT2 failed to demonstrate significant improvements in cognitive function or reductions in Aβ burden compared with placebo after 12 months of treatment. Despite promising early results, the trial did not meet its primary endpoints, raising questions regarding the long-term efficacy and clinical applicability of PBT2 in AD management (246,247). Another study indicated that treatment with the copper complex Cu^{2+}(gtsm) for 24 h enhanced inhibition of GSK-3β, lowering tau hyperphosphorylation and decreasing Aβ oligomer formation. These findings suggested that modulating copper homeostasis may simultaneously influence multiple pathological pathways implicated in AD, including Aβ aggregation, tau pathology and oxidative stress. Treatment with the antioxidant N-acetylcysteine alleviated these adverse effects by reducing oxidative stress and restoring cuproptosis-related oxidative mechanisms, providing therapeutic validation of the cuproptosis pathway (216).

However, it is important to critically assess the therapeutic window of copper chelation, as both insufficient and excessive copper levels can adversely affect neuronal health. Some studies have reported that brain copper levels may actually decrease in AD, raising concerns that over-chelation may potentially impair essential copper-dependent functions (14,248). This underscores the need for a more nuanced therapeutic approach, balancing the reduction of copper toxicity with the preservation of physiological functions, and highlights the importance of reliable biomarkers to monitor copper levels during treatment.

Limitations. Copper chelation strategies have exhibited potential in the treatment of AD. However, balancing the reduction of copper toxicity with the maintenance of physiological copper functions remains a critical challenge in optimizing therapeutic approaches (122,245,249).

First-generation copper chelators, such as CQ, have exhibited limited efficacy in clinical trials, primarily due to their low BBB permeability (<5% penetration into brain tissue), thereby restricting their ability to modulate neuronal copper homeostasis effectively (8,9,250). Additionally, their non-selective metal-binding properties can disrupt iron and zinc homeostasis, potentially exacerbating conditions such as anemia, underscoring the need for precise copper regulation (251,252).

Second-generation chelators, such as PBT2, have exhibited dose-dependent effects in clinical studies. While a low dose (30 mg/day) improves synaptic function, a higher dose (250 mg/day) induces copper-deficiency encephalopathy, increasing the risks associated with excessive chelation (9,242). Prolonged copper deprivation may lead to depletion of intracellular copper reserves, impair NMDA-R trafficking, disrupt mitochondrial retrograde signaling and ultimately exacerbate neuronal energy metabolism disorders (253,254). Furthermore, clinical trials of PBT2 have raised concerns regarding its clinical efficacy, as some studies report no significant differences in cognitive outcomes compared with placebo (241,247). These findings suggest that while PBT2 shows potential in preclinical settings, it remains challenging to translate these benefits into clinical improvements, emphasizing the need for more comprehensive and targeted clinical trials.

Genetic factors add complexity to copper-targeted interventions: Polymorphisms in the ATP7B gene may impair hepatic copper excretion, leading to systemic copper overload, and mutations in APP can alter the copper-binding affinity of Aβ, thus influencing plaque formation and its neurotoxicity (255).

The U-shaped dose-response curve refers to the phenomenon where both copper deficiency and copper excess result in neurotoxicity, while only a narrow intermediate range supports neuronal health (256-259). At low concentrations, insufficient copper impairs the activity of critical cuproenzymes such as CCO and SOD1, leading to mitochondrial dysfunction and oxidative stress. Conversely, excessive copper promotes Aβ aggregation, tau hyperphosphorylation and ROS generation, thereby accelerating neurodegenerative processes (256,257,260). This biphasic response has been observed in both *in vitro* and *in vivo* studies, highlighting the therapeutic challenge of achieving optimal copper levels without tipping the balance toward deficiency or overload (140,261).

Future directions

Selective inhibition of cuproptosis. Selective inhibition of cuproptosis is a pivotal research focus, aiming to mitigate copper-induced cytotoxicity while preserving the physiological functions of essential cuproenzymes. One promising strategy involves targeting FDX1, a critical regulator in the cuproptosis pathway (262). Previous studies have identified disulfiram, traditionally used for alcohol aversion therapy, as an agent that downregulates FDX1 expression (263,264). This modulation of copper levels has been shown to lower the infarct volume in experimental cerebral ischemia models, suggesting that FDX1 may serve as an effective target for selectively inhibiting cuproptosis (263). Another avenue of research focuses on dietary modulation of α-lipoic acid, the synthesis of which depends on LIAS and requires FDX1 as a cofactor (150,265). Studies have demonstrated that lipoic acid can improve mitochondrial respiratory function in $Atp7a^{-/-}$ cells, thereby alleviating key pathological processes associated with cuproptosis (266,267). Collectively, these findings highlight the potential of precisely modulating molecular pathways to selectively inhibit cuproptosis, offering novel therapeutic insights for diseases associated with copper dyshomeostasis. The differential expression patterns observed in human datasets refer to alterations in the expression of key cuproptosis-related genes, such as FDX1, LIAS, DLAT, pyruvate dehydrogenase E1 subunit α1 and ATP7B, in the brains of patients with AD compared with age-matched healthy controls (213,268,269). These expression changes are predominantly detected in regions vulnerable to neurodegeneration (such as the hippocampus and temporal cortex), and in some cases associated with disease severity (213,268,269). These human findings mirror

alterations observed in AD mouse models subjected to copper overload or deficiency, supporting the translational relevance of cuproptosis as a contributing mechanism in copper-related neurodegeneration (245,214).

Targeted interventions. Traditional copper chelators often lack specificity, potentially disrupting essential copper-dependent enzymatic functions and exacerbating systemic deficiencies (270). To address the existing issues, innovative strategies are under investigation. Copper bis-choline complexes are engineered to facilitate CP-independent copper transport, aiming to deliver copper directly to neuronal tissues (220,271). Through bypassing traditional copper-binding proteins, they may restore copper homeostasis within the CNS without affecting systemic copper levels. This targeted approach seeks to mitigate neuronal deficits associated with copper imbalance while minimizing peripheral side effects (272). For instance, bis-choline tetrathiomolybdate has exhibited efficacy in reducing systemic free copper levels by forming stable tripartite complexes with copper and albumin, although its specific effects in AD remain under investigation (NCT04573309).

Advancements in nanotechnology have led to the development of nanoparticles designed to interact specifically with Aβ plaques (273). These nanoparticles can bind to Aβ aggregates, potentially altering their conformation and reducing their neurotoxicity. By sequestering excess copper ions within the brain, they may prevent copper-induced oxidative stress and subsequent neuronal damage (274). This method offers a dual therapeutic effect, namely, modulating Aβ plaque toxicity and correcting local copper dyshomeostasis (275). For example, gold nanocages functionalized with phenylboronic acid have been utilized to encapsulate CQ, a metal chelator. Upon exposure to the elevated H_2O_2 levels associated with Aβ aggregation, these nanocages release CQ, which chelates Cu^{2+} ions and inhibits further amyloid fibrillation and oxidative stress (276). It is essential to develop reliable biomarkers for labile copper levels. Techniques such as positron emission tomography imaging with copper-specific radiotracers and CSF labile copper assays are promising approaches (277-279). These methods can provide real-time monitoring of copper dynamics in the brain, guiding targeted interventions and helping to personalize copper-targeted therapies (280). Implementing biomarkers such as serum or CSF levels of copper-binding proteins (such as ceruloplasmin, ATP7B and SOD1) and expression profiles of cuproptosis-related genes (such as FDX1, DLAT and LIAS) will enable clinicians to assess the efficacy of copper modulation strategies and optimize treatment protocols for individual patients (8,279,281). These innovative approaches aim to enhance the specificity and efficacy of copper-targeted therapies in neurodegenerative diseases such as AD, potentially overcoming the limitations associated with traditional chelation strategies. These innovative approaches aim to enhance the specificity and efficacy of copper-targeted therapies in neurodegenerative diseases such as AD, potentially overcoming the limitations associated with traditional chelation strategies.

6. Conclusions

Copper dyshomeostasis serves a multifaceted role in the pathogenesis of AD, contributing to amyloid-β aggregation, tau hyperphosphorylation, oxidative stress and neuroinflammation. Both copper deficiency and overload are detrimental, emphasizing the need for finely tuned copper regulation. The emerging concept of cuproptosis, a copper-dependent form of cell death, provides novel mechanistic insights into copper-related neurotoxicity. Preclinical studies suggest that targeted modulation of copper levels via chelators, copper-delivery compounds or antioxidants may attenuate AD pathology (282-284). However, clinical translation remains limited. Future efforts should focus on identifying reliable biomarkers of copper status and cuproptosis activity to enable personalized, copper-based therapeutic strategies for AD and related neurodegenerative diseases.

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Competing interests

The authors declare that they have no competing interests.

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