Redox Biology 70 (2024) 103048

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Redox changes and cellular senescence in Alzheimer's disease

Nicole Yu [a,b,c,1], Mazhar Pasha [a,b,c,1], John Jia En Chua [a,b,c,d,*]

[a] Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[b] LSI Neurobiology Programme, National University of Singapore, Singapore
[c] Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[d] Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore

ARTICLE INFO

Keywords:
Alzheimer's disease
Oxidative stress
Cellular senescence
Heme
Mitochondrial dysfunction
ER stress

ABSTRACT

The redox process and cellular senescence are involved in a range of essential physiological functions. However, they are also implicated in pathological processes underlying age-related neurodegenerative disorders, including Alzheimer's disease (AD). Elevated levels of reactive oxygen species (ROS) are generated as a result of abnormal accumulation of beta-amyloid peptide (Aβ), tau protein, and heme dyshomeostasis and is further aggravated by mitochondria dysfunction and endoplasmic reticulum (ER) stress. Excessive ROS damages vital cellular components such as proteins, DNA and lipids. Such damage eventually leads to impaired neuronal function and cell death. Heightened oxidative stress can also induce cellular senescence via activation of the senescence-associated secretory phenotype to further exacerbate inflammation and tissue dysfunction. In this review, we focus on how changes in the redox system and cellular senescence contribute to AD and how they are affected by perturbations in heme metabolism and mitochondrial function. While potential therapeutic strategies targeting such changes have received some attention, more research is necessary to bring them into clinical application.

1. Introduction

It has been estimated that the central nervous system (CNS) consumes approximately 20 % of the body's total energy [1]. Of the various cell types present in the brain, neurons expend much of this energy, where it is used to power both electrical activity as well as synaptic transmission [2,3]. The brain is heavily dependent on glycolysis in the cytoplasm and oxidative phosphorylation in mitochondria to generate sufficient amounts of ATP to sustain its energy needs [4,5]. The high metabolic rate makes it particularly susceptible to oxidative damage, with an estimated 1 to 2 % of oxygen used during respiration being converted to superoxide [1]. Moreover, despite its high iron content, the brain possesses lower amounts of antioxidant enzymes as compared to other organs [6]. These properties further exacerbate the potential to generate excessive reactive oxygen species (ROS) that can contribute to neuronal dysfunction and loss underlying neurodegenerative disorders and aging.

In parallel to oxidative stress, cellular senescence also contributes to neuronal dysfunction and neurodegenerative disorders. Cellular senescence describes the process of irreversible growth arrest that can be triggered by various factors, including DNA damage, telomere dysfunction, mitochondrial dysfunction, activation of oncogenes, aging, as well as oxidative stress [7,8]. Furthermore, oxidative stress is one of the major factors that triggers stress-induced premature senescence (SIPS) and the senescence-associated secretory phenotype (SASP), which releases proinflammatory chemokines, cytokines, and metalloproteinases that have the potential to induce age-related pathology [9,10]. Further, in Alzheimer's disease (AD), studies have unveiled an intricate network of molecular pathways connecting abnormal accumulation of amyloid beta peptides (Aβ40 and Aβ42) and/or hyperphosphorylated tau proteins with redox dyshomeostasis, mitochondrial dysfunction, cellular senescence, synaptic impairment, endoplasmic reticulum (ER) stress, calcium imbalance, inflammatory responses, as well as heme/iron dyshomeostasis [11–15]. Indeed, oxidative stress and cellular senescence could be a prominent early event in the pathogenesis of AD [16–21]. In this review, we outline how redox dyshomeostasis and senescence can contribute to neurodegenerative disorders, and also highlight the intricate relationship between redox reactions, cellular senescence, Aβ and Tau proteins, heme dyshomeostasis, ER stress and mitochondrial dysfunction in the context of AD. Finally, we examine some of the therapeutic interventions that are currently being evaluated or being developed.

* Corresponding author. Department of Physiology Yong Loo Lin School of Medicine, National University of Singapore, 28 Medical Drive, 117456, Singapore.
E-mail address: phsjcje@nus.edu.sg (J.J.E. Chua).
[1] Nicole Yu and Mazhar Pasha contributed equally to this review.

https://doi.org/10.1016/j.redox.2024.103048
Received 20 November 2023; Received in revised form 8 January 2024; Accepted 16 January 2024
Available online 17 January 2024

Abbreviations

Aβ, Aβ1-42, Aβ40, Aβ42	Amyloid beta peptide
Ach	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ATP	Adenosine triphosphate
BAX	Bcl-2 Associated X-protein
Bcl-2	B-cell lymphoma 2
CNS	Central nervous system
CSF	Cerebrospinal fluid
D + Q	Dasatinib and quercetin
ER	Endoplasmic reticulum
Fe2+	Ferrous iron
GPX	Glutathione peroxidase
HEBP1	Heme-binding protein 1
MAO	Monoamine oxidase
MB	Methylene blue
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial DNA
Na^+/K^+-ATPase	Sodium–potassium ATPase
OH8dG	8-hydroxy-2′-deoxyguanosine
PP2A	Protein phosphatase 2 A
ROS	Reactive oxygen species
SA-β-gal	Senescence-associated beta-galactosidase
SAMD	Senescence-associated mitochondrial dysfunction
SASP	Senescence-associated secretory phenotype
SIPS	Stress-induced premature senescence

2. Redox dyshomeostasis and cellular senescence in AD

2.1. Redox dyshomeostasis

Redox reactions, involving both reduction and oxidation of relevant biomolecules, are important for a range of physiological functions, including ATP generation, cell signaling, antioxidant defense, embryonic development, wound healing, and cancer prevention [22–25]. Conversely, their perturbations have been implicated in pathological events such as oxidative stress, mitochondrial dysfunction, and cancer promotion [26–28]. As aging occurs, altered redox homeostasis can be observed as levels of hydrogen peroxide or nitric oxide increase but additionally, in advanced aging and neurodegenerative disorders (including AD), other highly reactive molecules such as hydroxyl radicals and superoxide cause further damage like synaptic impairment, mitochondrial dysfunction, and cell death [29]. The involvement of oxidative stress in AD is well documented (Fig. 1). Indeed, studies in transgenic Tg2576 mice [30], SK-N-BE neuroblastoma cells, PS1/PS2-deficient, APP deficient and JNK-deficient mouse embryonic fibroblasts [31], and in the brain of AD patients [32] have showed that oxidative stress increases the accumulation of Aβ and the deposition of neurofibrillary tangles. Upregulation of oxidative stress markers such as F_2-isoprostanes, malondialdehyde, *trans*-4-hydroxy-2-nonenal in brain samples and biological fluids (cerebrospinal fluid, plasma and urine samples) obtained from AD and mild cognitive impairment patients have also been documented [33–35].

Notably, a reduction in the levels of antioxidant enzymes (including glutathione, glutathione S-transferase, and glutathione peroxidase) correlating with disease severity has been observed in the synaptosomal fractions isolated from both Mild Cognitive Impairment (MCI) and AD patients [36,37]. Moreover, immunohistochemical staining of post-mortem AD brain samples showed increased and decreased levels of glutaredoxin-1 and thioredoxin-1 in neurons, respectively [38]. Thus, disrupted redox homeostasis, characterized by heightened oxidative stress, and decreased antioxidant enzymes, can significantly impact the onset and progression of AD.

2.2. Cellular senescence

Cellular senescence has been shown to play a pivotal role in the progression of AD [20,21]. Increased senescence, with high expression of senescence-associated beta-galactosidase (SA-β-gal), p53 (a mediator of cellular senescence), DNA/telomere damage, and SASP have been observed in various types of brain cells, including astrocytes, microglia, and neurons [7,14,39,40]. Accumulation of senescent cells over time releases SASP and can promote inflammation, oxidative stress, synaptic dysfunction, and neuronal cell death [19,39,40]. Studies have shown

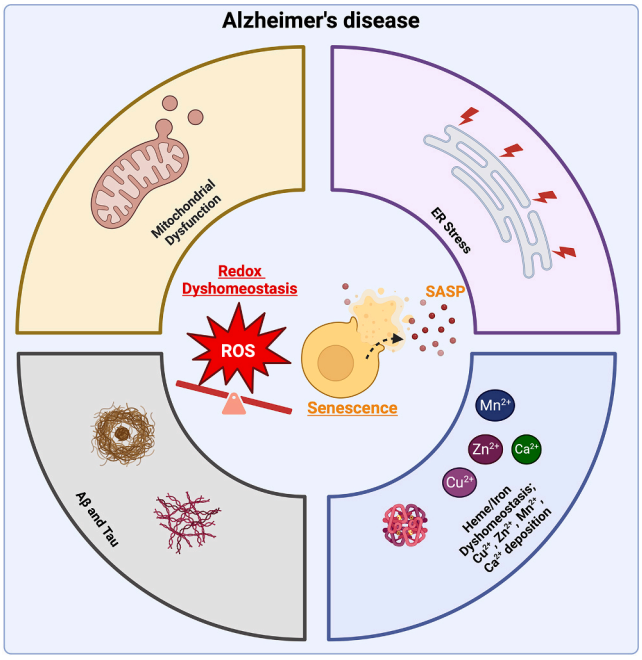

Fig. 1. Schematic representation of the various processes and stimuli that trigger neurodegeneration in AD. Redox dyshomeostasis and cellular senescence accompanied by SASP plays a pivotal role in influencing key pathological processes in AD, including mitochondrial dysfunction, ER stress, increased deposition of metal ions (Fe2+, Cu2+, Zn2+, Mn 2+, Ca2+) as well as Aβ and tau. These processes can also directly contribute to the generation of ROS, thereby exacerbating redox dyshomeostasis. Ultimately, these intricately linked pathways collectively culminate in neurodegeneration observed in AD. (Figure created with BioRender.com).

that removal of senescent cells can slow down aging processes and pathophysiological changes observed in age-related disease models [41,42]. Importantly, terminally differentiated neurons, which are post-mitotic, can also release SASP [39]. Furthermore, excessive ROS, which can be caused for instance by senescence-associated mitochondrial dysfunction (SAMD), originating from a DNA damage response, also triggers cellular senescence [43,44].

2.3. Crosstalk between oxidative stress and cellular senescence

Studies employing a mouse model of AD (APP/PS1) suggested a link between oxidative stress and cellular senescence, wherein, mice exposed

to prolonged oxidative stress exhibited cellular alterations that closely resembled those observed in various senescent states like elevated expression of SA-β-gal, cell cycle arrest, and changes in the shape and structure of cells [45,46]. Zhang et al. demonstrated the upregulation of ROS production and p53 expression in a human astrocyte cell line (U87) upon exposure to Aβ1-40, and this effect was reversed by galantamine pretreatment [47]. Recently, Wang et at. showed that neuronal senescence is triggered by Aβ oligomers, primarily through increased production of ROS in cultured M17 neuronal cells, and Olmesartan mitigates cellular senescence by downregulating p21and p16 through a SIRT1-dependent deacetylation of p53 [48]. In addition, fibroblasts obtained from AD patients showed increased levels of ROS, reduced growth rates, elevated expression of cell cycle regulators like p21, p16, and p53, and exhibited a senescence-like phenotype [49]. Therefore, these findings provide evidence suggesting that oxidative stress associated with cellular senescence plays a pivotal role in mediating pathological processes associated with AD.

3. Aβ, tau and redox dyshomeostasis in AD

3.1. Aβ and oxidative stress

Increased levels of ROS can originate from a number of biological processes, including impaired heme metabolism, mitochondrial dysfunction, ER stress. The ability of pathological species of Aβ and tau to affect these processes and also alter others (including changes in mitochondrial function, disruption in synaptic dysfunction, excitotoxicity, altered calcium homeostasis, and oxidative stress with increased production of ROS-like superoxide, hydrogen peroxide, and hydroxyl radicals) have been extensively documented in recent years [16–18,50]. These studies show that excessive Aβ accumulation triggers oxidative stress resulting in lipid peroxidation through the interaction of oxygen-derived free radicals with polyunsaturated fatty acids and subsequent formation of 4-hydroxy-2-nonenal and acrolein (reactive products of lipid peroxidation). This sequence of events disrupts neuronal ion homeostasis including impaired sodium–potassium ATPase (Na^+/K^+-ATPase) activity, increased calcium concentration, increased susceptibility to glutamate toxicity, and causes structural changes in synaptic membranes, eventually resulting in neuronal cell death [51–53]. Paradis et al. showed that neurons exposed to Aβ1–42 exhibited increased susceptibility to oxidative stress, possibly due to the downregulation of anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) and increased levels of pro-apoptotic Bcl-2-Associated X-protein (BAX) [54]. Conversely, high levels of ROS can impact the formation of Aβ by elevating the levels of amyloid precursor protein and modifying the activity of key enzymes involved in its processing, like β-secretase and γ-secretase. Consequently, oxidative stress promotes autophagy, leading to intra-lysosomal accumulation of Aβ, and the release of lysosomal enzymes, ultimately resulting in neuronal death [55–59].

3.2. Tau and Oxidative stress

Pathological tau has also been implicated in causing changes in redox status. Cente et al. demonstrated that the presence of a truncated tau protein in a transgenic rat model of tauopathy results in the accumulation of ROS and sensitizes neurons to stress-induced cell death [60]. Conversely, oxidative stress also induces the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein in neuronal cells via upregulating the activity of tau protein kinase (glycogen synthase kinase-3β) and PP2A-like phosphatase [61,62]. Furthermore, other studies have shown that Aβ triggers the accumulation of hyperphosphorylated tau by activating glycogen synthase kinase-3β and mitogen-activated protein kinase [63–65]. These Aβ- and tau-dependent mechanisms can operate in parallel and reinforce each other, contributing to the pathological changes observed in AD. Nevertheless, the abovementioned findings have mostly been based on preclinical models.

4. The role of heme in causing redox dyshomeostasis in AD

In addition to Aβ and Tau, imbalances in heme and its metabolism have been implicated in redox changes in AD. Heme, a complex of ferrous iron and protoporphyrin IX, is an important iron-containing cofactor that plays a pivotal role in oxygen transport (haemoglobin), electron transfer (mitochondria), storage (myoglobin), and in signal transduction and gene regulation (via the heme response elements) [66–68]. However, an excess of free heme and its cofactor, iron, is detrimental to cells by promoting oxidative stress and lipid peroxidation, eventually resulting in membrane damage and apoptosis. Thus, heme metabolism, its synthesis, transport, utilization and its degradation must be finely balanced [66,69]. Indeed, studies have shown that altered heme homeostasis results in the dysregulation of heme proteins (e.g., heme oxygenase) and affects iron regulation and mitochondrial function in AD [70–72]. Findings also revealed that free heme/iron binds with amyloidogenic and tau proteins leading to the formation of senile plaques and neurofibrillary tangles in AD [73–75].

Atamna et al. showed that heme and Aβ can form a complex, initiating heme deficiency and the generation of oxidants like hydrogen peroxide from mitochondria, which ultimately resulted in oxidative stress and cellular toxicity [76]. Using fast kinetics and freeze-quenching techniques, Pal et al. reported that the Aβ-heme complex generates a highly reactive intermediate, compound I. This compound oxidizes neurotransmitters such as serotonin, reducing their levels, thereby causing abnormalities in neurotransmission—an essential pathological event in AD [77]. Furthermore, heme and Aβ can trigger mitochondrial-dependent apoptotic neuronal cell death via heme-binding protein 1 (HEBP1), which is elevated in a subset of patients diagnosed with rapidly progressing forms of AD [78].

Several studies using brain tissue from the APP/PS1 mouse model, human AD tissue, and isolated amyloid plaque cores have also revealed that iron could be chemically reduced in the presence of Aβ, and this process was implicated as a source of excess free radical generation [79–82]. Interestingly, MRI data from AD subjects have shown elevated levels of iron, transferrin, and ferritin, as well as reduced levels of ferroportin-1 in hippocampus, cortex, and basal ganglia. The imbalance originated from an increase in free Fe^{2+} within cells, ultimately triggering the activation of the ferroptosis pathway, which is a form of cell death that depends on iron [83–86]. In addition to iron, anomalous accumulation of other metal ions such as copper [87], zinc [88], manganese [89], or calcium [90], in various brain regions can potentially contribute to the excessive production of ROS, Aβ and tau proteins, which are closely linked to the development and progression of AD [91,92].

5. Mitochondrial dysfunction, redox changes, and cellular senescence in AD

The mitochondrial electron transport chain is one of the primary intracellular sources of ROS. Ironically, heightened oxidative stress negatively impacts mitochondrial integrity and function [93,94]. In turn, damaged mitochondria, characterized by decreased mitochondrial membrane potential and reduced respiratory capacity, further exacerbates ROS levels and trigger cellular senescence, marked by telomere shortening [95–97]. Using long-term hippocampal neuronal cultures, Dong et al. demonstrated that decrease in mitochondrial membrane potential follows an increase in the proportion of senescent cells (as indicated by SA-β-gal), and is accompanied by increased levels of ROS [98].

Mitochondrial dysfunction with elevated levels of ROS appears to be a prominent and early characteristic of AD. Calkins et al. reported that neurons from an APP transgenic AD mouse model exhibited abnormal mitochondrial structure with reduced membrane potential and

increased levels of ROS [99]. Mecocci et al. observed a significant increase in oxidized nucleoside, 8-hydroxy-2′-deoxyguanosine (OH8dG) within mitochondrial DNA (mtDNA) extracted from AD patients compared to controls [100]. Similarly, Wang et al. observed higher levels of multiple oxidized bases in both nuclear and mitochondrial DNA in individuals with AD as compared to control subjects [101]. Collectively, these studies highlight that oxidative stress, senescence, and mitochondria dysfunction work in synergy, reinforcing each other to contribute to AD pathology, with oxidative stress playing a central role. Thus, gaining a comprehensive understanding of these interconnected pathways could assist in identifying additional potential therapeutic approaches for AD.

6. ER and oxidative stress in AD

ER stress is characterised by the accumulation of misfolded or unfolded proteins within the ER, leading to the disturbance of cellular homeostasis. ER and oxidative stress are closely linked, given that protein folding in the ER requires a tightly controlled redox environment and excess ROS generation can severely affect ER homeostasis [102,103]. Excessive and prolonged perturbation of ER stress enhances γ-secretase activity and Aβ secretion, which could eventually lead to the aggregation and accumulation of misfolded/unfolded proteins (e.g., oligomerized Aβ) that can contribute to the progression of AD [104–106]. Increased expression of various ER stress markers, including phospho-PERK phospho-IRE1α, phospho-eIF2α, XBP1, and CHOP, have been documented in post-mortem brain tissues obtained from AD patients [107–109].

Of note, the ER and mitochondria are closely interconnected physically and functionally, at multiple contact sites (ER-mitochondrial contact sites) [110]. These sites regulate a range of cellular functions, including oxidative stress, inflammatory response, metabolite exchange (phospholipids), iron, and calcium homeostasis [111–114]. Area-Gomez et al. observed increased accumulation of presenilin 1 and 2 (presenilins are the catalytic components of the γ-secretase complex) in a subcompartment of the ER-mitochondria associated membranes, thus, corresponds to enhance γ-secretase activity, leading to the accumulation of Aß [115]. Schreiner et al. demonstrated the generation of Aβ at mitochondria-ER contact sites, including mitochondria-associated ER membranes and outer mitochondrial membrane in the brains of C57BL6/J mice [116]. Similarly, studies have showed that Aβ modulates ER-mitochondrial contact sites and alters calcium homeostasis in the human AD brain and different AD mouse models ($App^{Swe/Lon}$ mice, App^{NL-F}, and App^{NL-G-F}) [117,118]. Consequently, accumulation of Aβ could affect the signaling and metabolic pathways at ER-mitochondrial contact sites. Moreover, as mentioned earlier, the aggregation of Aβ leads to an increase production of ROS. Thus, ER stress in AD has the potential to extend to the mitochondria, subsequently amplifying the release of ROS. Therefore, directing therapeutic interventions towards these cellular sources of oxidative stress may provide robust outcomes in the treatment AD.

7. Treatments and interventions targeting redox in AD

There are only a limited number of approved drugs currently available for the treatment of AD. In the United States, FDA-approved drugs targeting disease progression and cognitive symptoms only include anti-amyloid treatments such as Aducanumab and Lecanemab, cholinesterase inhibitors, and glutamate regulators [119]. Although most of these drugs do not directly target oxidative stress, there are efforts to identify and develop strategies targeting components of redox and oxidative stress for clinical treatment of AD. An overview of the therapeutic interventions for AD discussed in this review is presented in Fig. 2.

7.1. Treatments targeting heme-related dyshomeostasis

As heme dyshomeostasis and the occurrence of heme deficiency can lead to mitochondrial decay observed in AD [120,121], some efforts have been made to identify therapeutic strategies targeting heme (Fig. 2). Studies have indicated that neuroglobins such as apoNeuroglobin can sequester heme from the heme(II)-Aβ complex, which reduces ROS production by heme-Aβ and heme-IAPP complexes. This can, in turn, reduce heme-induced cytotoxicity observed in AD [122]. Although identified, these have yet to be tested clinically. Another drug of interest that could be associated with heme in AD is methylene blue (MB), which has been implicated in senescence [123], and has been suggested as a possible therapeutic [124]. However, there have been reported adverse effects of MB including CNS-related symptoms like confusion, dizziness, and headaches, as well as some increased tone in limbs, sweating, and agitation [125]. Clinical trial findings also found mixed results of MB administration in AD patients, in that the effects of MB could be dependent on dose; moderate doses (138 mg) showed cognitive benefits but there were no effects at higher (228 mg) or lower doses (69 mg) [126].

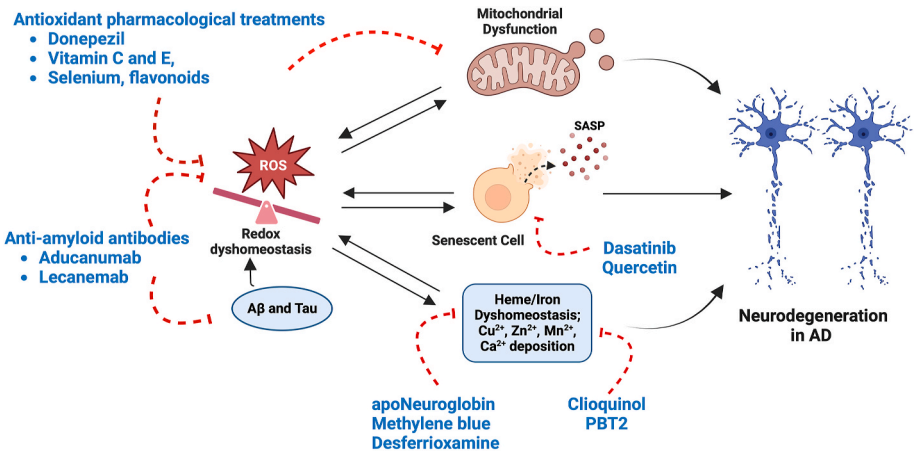

Fig. 2. An overview of the therapeutic interventions for AD. *Redox dyshomeostasis, cellular senescence, mitochondrial dysfunction, and heme dyshomeostasis are major contributors to the pathogenesis of AD. Various current and proposed interventions to mitigate neurodegeneration include antioxidant treatments targeting oxidative stress and mitochondrial dysfunction (such as donepezil, vitamin C and E, selenium, and flavonoids), heme/iron (such as apoNeuroglobin and desferrioxamine), metal ions (clioquinol and PBT2), anti-amyloid antibodies that reduce the accumulation of Aβ and tau proteins (such as Aducanumab and Lecanemab) and senolytic agents (such as Dasatinib and Quercetin) (Figure created with BioRender.com).*

7.2. Treatments targeting metal dyshomeostasis

Aside from heme dyshomeostasis, metal dyshomeostasis and subsequent elevated ROS activity have been also implicated in AD. Accordingly, improving metal homeostasis could be another possible therapeutic strategy. Specifically, the chelation of metals such as iron, zinc, and copper has been suggested as a treatment option in order to reduce the accumulation of these metals. A clinical study using desferrioxamine (a chelator of free iron) was found to slow down AD progression [127]. Clioquinol, a chelator of zinc and copper that is able to cross the blood-brain barrier, was also introduced as a drug candidate for AD but had conflicting data [128]. The successor to clioquinol, PBT2, was developed as another drug candidate for AD by targeting metal-induced Aβ oligomers. Patients treated with the drug demonstrated improved executive function components on tests as well as a significantly reduced Aβ42 concentration in their cerebrospinal fluids (CSF) [129]. However, metal chelation therapies can come with side effects [130], resulting from the sequestration of healthy functional metal ions and redistribution of other metal ions [131], and hence these therapies are no longer being clinically pursued [132].

7.3. Treatments using acetylcholinesterase inhibitors

Acetylcholinesterase (AChE), the enzyme that degrades acetylcholine (ACh), has been identified as an important target for AD intervention and AChE inhibitors have since been approved for clinical use. Lower levels of ACh have been observed in AD patients [133,134] and AChE has been suggested to play a role in Aβ-aggregation during plaque formation by increasing the neurotoxicity of Aβ aggregates [135]. It has been found that AChE inhibitors can exert therapeutic effects by increasing acetylcholine levels, which can then lead to increased cholinergic neurotransmission and improved cognitive functions in patients [136]. Preclinical findings have also shown that AChE inhibitors may suppress oxidative stress, as treatment using AChE inhibitors mitigated streptozotocin-induced oxidative stress in mice [137]. Moreover, AD patients treated with the AChE inhibitor, donepezil, showed reduced levels of proteins linked to impaired redox homeostasis as compared to untreated patients [138]. Donepezil has been frequently used in FDA-approved clinical treatment of AD and recently, there have been efforts to develop metal directed donepezil, through modifying the drug with copper [139]. Additionally, the development of novel donepezil-related compounds has led to the discovery of compounds that can modulate Aβ misfolding coupled with antioxidant properties [140], as well as those that are multi-functional anti-AD agents that can inhibit both cholinesterase and monoamine oxidase (MAO) activity [141].

7.4. Antioxidant treatments

Other antioxidant treatments for AD - primarily involving Vitamin E, Vitamin C, and selenium - have had mixed results regarding their effectiveness, however. Some findings on Vitamin E have indicated that its combination with Vitamin C could be associated with reduced prevalence of AD [142] and slowing of functional decline [143], whereas other findings suggested only modest reductions in long-term AD risk [144] or no association with AD [145] in participants. Another antioxidant supplement that also has anti-inflammatory properties is selenium, which is a trace element that is found in selenoproteins [146]. One of these proteins, selenoprotein P, has been found to be increased in the CSF of AD patients [147], which made selenium a possible therapeutic target for AD. Nevertheless, although meta-analytical findings suggest that it could alleviate certain AD and MCI symptoms such as glutathione peroxidase (GPX) activity and cognitive deficits, its long-term effects have yet to be ascertained [148]. Altogether, these natural antioxidants that have been approved for clinical trials may come with limitations and results that are not yet conclusive.

Other potential treatments targeting redox mechanisms for AD include redox enzymes such as peroxiredoxins, glutaredoxins, and thioredoxins [149], herbal medicines such as Ginkgo biloba that can increase the activity of antioxidant enzymes like catalase and superoxide dismutase [150,151] as well as induce heme oxygenase-1 (HO-1) resulting in a neuroprotective effect [152], and flavonoids that can have antioxidative neuronal effects [153]. Further efforts to develop treatments targeting redox-related mechanisms are important, given the strong evidence that these mechanisms contribute an important role in the pathophysiology of AD.

7.5. Treatments targeting cellular senescence

In addition to redox-related therapies, interventions targeting senescence, specifically the clearance of senescent cells in AD, by senolytic agents have also been explored. These include dasatinib, an FDA-approved Src/tyrosine kinase inhibitor, and flavonoids such as quercetin and fisetin. Studies have indicated that compared to no senolytic treatment, a combination of dasatinib and quercetin (D + Q) senolytic treatment can help to remove senescent cells and mitigate age-dependent degeneration [154]. Further, in AD, it has been found that D + Q treatment reduced levels of Aβ40 and Aβ42 in the hippocampus and entorhinal cortex of AD mice, as well as alleviated Aβ-plaque associated inflammation and cognitive deficits [155]. Many clinical trials involving senolytic therapeutic interventions are ongoing [156], with a recently completed D + Q trial (NCT04063124) that has focused on AD [157,158]. However, the short- and long-term side effects of senolytic administration in humans remain undetermined [159] and further clinical trials involving senolytics are required.

8. Conclusion and future directions

There is strong evidence that dyshomeostasis and imbalances in redox play a critical role in neurodegenerative diseases like AD. Oxidative stress and senescence-related processes, triggered and/or modulated by heavy metals, primarily heme and iron, together with Aβ and tau proteins, contribute to the pathophysiology of AD. Therapeutic interventions have been approved for use in patients and there are ongoing clinical trials with novel interventions targeting redox based on preclinical evidence. However, the limitations to these still persist. Additional research and clinical trials are required before effective treatment with minimal side effects can be achieved and applied on a wider scale.

CRediT authorship contribution statement

Nicole Yu: Investigation, Visualization, Writing – original draft, Writing – review & editing. **Mazhar Pasha:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **John Jia En Chua:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was supported by a Tier 2 grant from the Singapore Ministry of Education (MOE-Q2 T2EP30122-0006).

References

[1] R. Franco, M.R. Vargas, Redox biology in neurological function, dysfunction, and aging, Antioxidants Redox Signal. 28 (18) (2018) 1583–1586.
[2] J.J. Harris, R. Jolivet, D. Attwell, Synaptic energy use and supply, Neuron 75 (5) (2012) 762–777.
[3] J.W. Deitmer, Strategies for metabolic exchange between glial cells and neurons, Respir. Physiol. 129 (1–2) (2001) 71–81.
[4] G.W. Davis, Not fade away: mechanisms of neuronal ATP homeostasis, Neuron 105 (4) (2020) 591–593.
[5] D.A. Butterfield, B. Halliwell, Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease, Nat. Rev. Neurosci. 20 (3) (2019) 148–160.
[6] R. von Bernhardi, J. Eugenín, Alzheimer's disease: redox dysregulation as a common denominator for diverse pathogenic mechanisms, Antioxidants Redox Signal. 16 (9) (2012) 974–1031.
[7] C. Martinez-Cue, N. Rueda, Cellular senescence in neurodegenerative diseases, Front. Cell. Neurosci. 14 (2020) 16.
[8] A. Chandrasekaran, M. Idelchik, J.A. Melendez, Redox control of senescence and age-related disease, Redox Biol. 11 (2017) 91–102.
[9] S.J. Chinta, G. Woods, A. Rane, M. Demaria, J. Campisi, J.K. Andersen, Cellular senescence and the aging brain, Exp. Gerontol. 68 (2015) 3–7.
[10] R. Terao, T. Ahmed, A. Suzumura, H. Terasaki, Oxidative stress-induced cellular senescence in aging retina and age-related macular degeneration, Antioxidants 11 (11) (2022).
[11] D.A. Butterfield, A.M. Swomley, R. Sultana, Amyloid beta-peptide (1-42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression, Antioxidants Redox Signal. 19 (8) (2013) 823–835.
[12] M. Manczak, M.J. Calkins, P.H. Reddy, Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: implications for neuronal damage, Hum. Mol. Genet. 20 (13) (2011) 2495–2509.
[13] S. Tu, S. Okamoto, S.A. Lipton, H. Xu, Oligomeric Abeta-induced synaptic dysfunction in Alzheimer's disease, Mol. Neurodegener. 9 (2014) 48.
[14] N. He, W.L. Jin, K.H. Lok, Y. Wang, M. Yin, Z.J. Wang, Amyloid-beta(1-42) oligomer accelerates senescence in adult hippocampal neural stem/progenitor cells via formylpeptide receptor 2, Cell Death Dis. 4 (11) (2013) e924.
[15] M.O. Iliyasu, S.A. Musa, S.B. Oladele, A.I. Iliya, Amyloid-beta aggregation implicates multiple pathways in Alzheimer's disease: understanding the mechanisms, Front. Neurosci. 17 (2023) 1081938.
[16] A. Singh, R. Kukreti, L. Saso, S. Kukreti, Oxidative stress: a key modulator in neurodegenerative diseases, Molecules 24 (8) (2019).
[17] R. Bou Khalil, E. Khoury, S. Koussa, Linking multiple pathogenic pathways in Alzheimer's disease, World J. Psychiatr. 6 (2) (2016) 208–214.
[18] Y. Zhao, B. Zhao, Oxidative stress and the pathogenesis of Alzheimer's disease, Oxid. Med. Cell. Longev. 2013 (2013) 316523.
[19] N.Y.L. Ngoi, A.Q.X. Liew, S.J.F. Chong, M.S. Davids, M.-V. Clement, S. Pervaiz, The redox-senescence axis and its therapeutic targeting, Redox Biol. 45 (2021) 102032.
[20] R. Bhat, E.P. Crowe, A. Bitto, M. Moh, C.D. Katsetos, F.U. Garcia, et al., Astrocyte senescence as a component of Alzheimer's disease, PLoS One 7 (9) (2012) e45069.
[21] V. Boccardi, L. Pelini, S. Ercolani, C. Ruggiero, P. Mecocci, From cellular senescence to Alzheimer's disease: the role of telomere shortening, Ageing Res. Rev. 22 (2015) 1–8.
[22] J. Santolini, S.A. Wootton, A.A. Jackson, M. Feelisch, The Redox architecture of physiological function, Curr Opin Physiol 9 (2019) 34–47.
[23] M. Demaria, N. Ohtani, S.A. Youssef, F. Rodier, W. Toussaint, J.R. Mitchell, et al., An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA, Dev. Cell 31 (6) (2014) 722–733.
[24] R.M. Laberge, P. Awad, J. Campisi, P.Y. Desprez, Epithelial-mesenchymal transition induced by senescent fibroblasts, Cancer Microenviron 5 (1) (2012) 39–44.
[25] D. Munoz-Espin, M. Canamero, A. Maraver, G. Gomez-Lopez, J. Contreras, S. Murillo-Cuesta, et al., Programmed cell senescence during mammalian embryonic development, Cell 155 (5) (2013) 1104–1118.
[26] J. Checa, J.M. Aran, Reactive oxygen species: drivers of physiological and pathological processes, J. Inflamm. Res. 13 (2020) 1057–1073.
[27] L. Nousis, P. Kanavaros, A. Barbouti, Oxidative stress-induced cellular senescence: is labile iron the connecting link? Antioxidants 12 (6) (2023).
[28] H. Cui, Y. Kong, H. Zhang, Oxidative stress, mitochondrial dysfunction, and aging, J Signal Transduct 2012 (2012) 646354.
[29] A. Kumar, B. Yegla, T.C. Foster, Redox signaling in neurotransmission and cognition during aging, Antioxidants Redox Signal. 28 (18) (2018) 1724–1745.
[30] J. Apelt, M. Bigl, P. Wunderlich, R. Schliebs, Aging-related increase in oxidative stress correlates with developmental pattern of beta-secretase activity and beta-amyloid plaque formation in transgenic Tg2576 mice with Alzheimer-like pathology, Int. J. Dev. Neurosci. 22 (7) (2004) 475–484.
[31] E. Tamagno, M. Guglielmotto, M. Aragno, R. Borghi, R. Autelli, L. Giliberto, et al., Oxidative stress activates a positive feedback between the gamma- and beta-secretase cleavages of the beta-amyloid precursor protein, J. Neurochem. 104 (3) (2008) 683–695.
[32] Y. Tong, W. Zhou, V. Fung, M.A. Christensen, H. Qing, X. Sun, et al., Oxidative stress potentiates BACE1 gene expression and Abeta generation, J. Neural. Transm. 112 (3) (2005) 455–469.
[33] D. Pratico, V. MYL, J.Q. Trojanowski, J. Rokach, G.A. Fitzgerald, Increased F2-isoprostanes in Alzheimer's disease: evidence for enhanced lipid peroxidation in vivo, Faseb. J. 12 (15) (1998) 1777–1783.
[34] E.E. Reich, W.R. Markesbery, L.J. Roberts 2nd, L.L. Swift, J.D. Morrow, T. J. Montine, Brain regional quantification of F-ring and D-/E-ring isoprostanes and neuroprostanes in Alzheimer's disease, Am. J. Pathol. 158 (1) (2001) 293–297.
[35] T.I. Williams, B.C. Lynn, W.R. Markesbery, M.A. Lovell, Increased levels of 4-hydroxynonenal and acrolein, neurotoxic markers of lipid peroxidation, in the brain in Mild Cognitive Impairment and early Alzheimer's disease, Neurobiol. Aging 27 (8) (2006) 1094–1099.
[36] M.A. Ansari, S.W. Scheff, Oxidative stress in the progression of Alzheimer disease in the frontal cortex, J. Neuropathol. Exp. Neurol. 69 (2) (2010) 155–167.
[37] P.K. Mandal, S. Saharan, M. Tripathi, G. Murari, Brain glutathione levels–a novel biomarker for mild cognitive impairment and Alzheimer's disease, Biol. Psychiatr. 78 (10) (2015) 702–710.
[38] S. Akterin, R.F. Cowburn, A. Miranda-Vizuete, A. Jimenez, N. Bogdanovic, B. Winblad, et al., Involvement of glutaredoxin-1 and thioredoxin-1 in beta-amyloid toxicity and Alzheimer's disease, Cell Death Differ. 13 (9) (2006) 1454–1465.
[39] E. Sah, S. Krishnamurthy, M.Y. Ahmidouch, G.J. Gillispie, C. Milligan, M.E. Orr, The cellular senescence stress response in post-mitotic brain cells: cell survival at the expense of tissue degeneration, Life 11 (3) (2021) 229.
[40] S. Gaikwad, S. Senapati, M.A. Haque, R. Kayed, Senescence, brain inflammation, and oligomeric tau drive cognitive decline in Alzheimer's disease: evidence from clinical and preclinical studies, Alzheimers Dement 20 (2024) 709–727.
[41] R.-M. Liu, Aging, cellular senescence, and Alzheimer's disease, Int. J. Mol. Sci. 23 (4) (2022) 1989.
[42] R.J. Pignolo, J.F. Passos, S. Khosla, T. Tchkonia, J.L. Kirkland, Reducing senescent cell burden in aging and disease, Trends Mol. Med. 26 (7) (2020) 630–638.
[43] N.Y. Ngoi, A.Q. Liew, S.J.F. Chong, M.S. Davids, M.V. Clement, S. Pervaiz, The redox-senescence axis and its therapeutic targeting, Redox Biol. 45 (2021) 102032.
[44] R. Di Micco, V. Krizhanovsky, D. Baker, F. d'Adda di Fagagna, Cellular senescence in ageing: from mechanisms to therapeutic opportunities, Nat. Rev. Mol. Cell Biol. 22 (2) (2021) 75–95.
[45] M.A. Meraz-Rios, D. Franco-Bocanegra, D. Toral Rios, V. Campos-Pena, Early onset Alzheimer's disease and oxidative stress, Oxid. Med. Cell. Longev. 2014 (2014) 375968.
[46] N. Suelves, S. Saleki, T. Ibrahim, D. Palomares, S. Moonen, M.J. Koper, et al., Senescence-related impairment of autophagy induces toxic intraneuronal amyloid-beta accumulation in a mouse model of amyloid pathology, Acta Neuropathol Commun 11 (1) (2023) 82.
[47] Y. Zhang, L. Zhao, Z. Wu, X. Chen, T. Ma, Galantamine alleviates senescence of U87 cells induced by beta-amyloid through decreasing ROS production, Neurosci. Lett. 653 (2017) 183–188.
[48] J. Wang, B. Zheng, S. Yang, D. Zhou, J. Wang, Olmesartan prevents oligomerized amyloid beta (Abeta)-Induced cellular senescence in neuronal cells, ACS Chem. Neurosci. 12 (7) (2021) 1162–1169.
[49] J. Naderi, C. Lopez, S. Pandey, Chronically increased oxidative stress in fibroblasts from Alzheimer's disease patients causes early senescence and renders resistance to apoptosis by oxidative stress, Mech. Ageing Dev. 127 (1) (2006) 25–35.
[50] F. Cioffi, R.H.I. Adam, K. Broersen, Molecular mechanisms and genetics of oxidative stress in Alzheimer's disease, J Alzheimers Dis 72 (4) (2019) 981–1017.
[51] R.J. Mark, M.A. Lovell, W.R. Markesbery, K. Uchida, M.P. Mattson, A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid beta-peptide, J. Neurochem. 68 (1) (1997) 255–264.
[52] C.B. Pocernich, A.L. Cardin, C.L. Racine, C.M. Lauderback, D.A. Butterfield, Glutathione elevation and its protective role in acrolein-induced protein damage in synaptosomal membranes: relevance to brain lipid peroxidation in neurodegenerative disease, Neurochem. Int. 39 (2) (2001) 141–149.
[53] D.A. Butterfield, C.M. Lauderback, Lipid peroxidation and protein oxidation in Alzheimer's disease brain: potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress, Free Radic. Biol. Med. 32 (11) (2002) 1050–1060.
[54] E. Paradis, H. Douillard, M. Koutroumanis, C. Goodyer, A. LeBlanc, Amyloid beta peptide of Alzheimer's disease downregulates Bcl-2 and upregulates bax expression in human neurons, J. Neurosci. 16 (23) (1996) 7533–7539.
[55] L. Zheng, K. Roberg, F. Jerhammar, J. Marcusson, A. Terman, Oxidative stress induces intralysosomal accumulation of Alzheimer amyloid beta-protein in cultured neuroblastoma cells, Ann. N. Y. Acad. Sci. 1067 (2006) 248–251.
[56] L. Zheng, K. Roberg, F. Jerhammar, J. Marcusson, A. Terman, Autophagy of amyloid beta-protein in differentiated neuroblastoma cells exposed to oxidative stress, Neurosci. Lett. 394 (3) (2006) 184–189.
[57] L. Zheng, K. Kagedal, N. Dehvari, E. Benedikz, R. Cowburn, J. Marcusson, et al., Oxidative stress induces macroautophagy of amyloid beta-protein and ensuing apoptosis, Free Radic. Biol. Med. 46 (3) (2009) 422–429.
[58] L. Zheng, A. Cedazo-Minguez, M. Hallbeck, F. Jerhammar, J. Marcusson, A. Terman, Intracellular distribution of amyloid beta peptide and its relationship to the lysosomal system, Transl. Neurodegener. 1 (1) (2012) 19.
[59] D.A. Butterfield, D. Boyd-Kimball, Oxidative stress, amyloid-beta peptide, and altered key molecular pathways in the pathogenesis and progression of Alzheimer's disease, J Alzheimers Dis 62 (3) (2018) 1345–1367.

[60] M. Cente, P. Filipcik, M. Pevalova, M. Novak, Expression of a truncated tau protein induces oxidative stress in a rodent model of tauopathy, Eur. J. Neurosci. 24 (4) (2006) 1085–1090.
[61] S. Mondragon-Rodriguez, E. Trillaud-Doppia, A. Dudilot, C. Bourgeois, M. Lauzon, N. Leclerc, et al., Interaction of endogenous tau protein with synaptic proteins is regulated by N-methyl-D-aspartate receptor-dependent tau phosphorylation, J. Biol. Chem. 287 (38) (2012) 32040–32053.
[62] Y. Feng, Y. Xia, G. Yu, X. Shu, H. Ge, K. Zeng, et al., Cleavage of GSK-3beta by calpain counteracts the inhibitory effect of Ser9 phosphorylation on GSK-3beta activity induced by H(2)O(2), J. Neurochem. 126 (2) (2013) 234–242.
[63] W.H. Zheng, S. Bastianetto, F. Mennicken, W. Ma, S. Kar, Amyloid beta peptide induces tau phosphorylation and loss of cholinergic neurons in rat primary septal cultures, Neuroscience 115 (1) (2002) 201–211.
[64] A. Takashima, T. Honda, K. Yasutake, G. Michel, O. Murayama, M. Murayama, et al., Activation of tau protein kinase I/glycogen synthase kinase-3beta by amyloid beta peptide (25-35) enhances phosphorylation of tau in hippocampal neurons, Neurosci. Res. 31 (4) (1998) 317–323.
[65] M. Jin, N. Shepardson, T. Yang, G. Chen, D. Walsh, D.J. Selkoe, Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration, Proc. Natl. Acad. Sci. U. S. A. 108 (14) (2011) 5819–5824.
[66] D. Chiabrando, F. Vinchi, V. Fiorito, S. Mercurio, E. Tolosano, Heme in pathophysiology: a matter of scavenging, metabolism and trafficking across cell membranes, Front. Pharmacol. 5 (2014) 61.
[67] Y. Zhu, T. Hon, L. Zhang, Heme initiates changes in the expression of a wide array of genes during the early erythroid differentiation stage, Biochem. Biophys. Res. Commun. 258 (1) (1999) 87–93.
[68] S.M. Mense, L. Zhang, Heme: a versatile signaling molecule controlling the activities of diverse regulators ranging from transcription factors to MAP kinases, Cell Res. 16 (8) (2006) 681–692.
[69] V. Jeney, J. Balla, A. Yachie, Z. Varga, G.M. Vercellotti, J.W. Eaton, et al., Pro-oxidant and cytotoxic effects of circulating heme, Blood 100 (3) (2002) 879–887.
[70] H. Atamna, Heme binding to Amyloid-beta peptide: mechanistic role in Alzheimer's disease, J Alzheimers Dis 10 (2–3) (2006) 255–266.
[71] H.M. Schipper, S. Cisse, E.G. Stopa, Expression of heme oxygenase-1 in the senescent and Alzheimer-diseased brain, Ann. Neurol. 37 (6) (1995) 758–768.
[72] T. Kimpara, A. Takeda, T. Yamaguchi, H. Arai, N. Okita, S. Takase, et al., Increased bilirubins and their derivatives in cerebrospinal fluid in Alzheimer's disease, Neurobiol. Aging 21 (4) (2000) 551–554.
[73] E. Chiziane, H. Telemann, M. Krueger, J. Adler, J. Arnhold, A. Alia, et al., Free heme and amyloid-beta: a fatal liaison in Alzheimer's disease, J Alzheimers Dis 61 (3) (2018) 963–984.
[74] H. Atamna, W.H. Frey 2nd, A role for heme in Alzheimer's disease: heme binds amyloid beta and has altered metabolism, Proc. Natl. Acad. Sci. U. S. A. 101 (30) (2004) 11153–11158.
[75] M.A. Smith, P.L. Harris, L.M. Sayre, G. Perry, Iron accumulation in Alzheimer disease is a source of redox-generated free radicals, Proc. Natl. Acad. Sci. U. S. A. 94 (18) (1997) 9866–9868.
[76] H. Atamna, K. Boyle, Amyloid-beta peptide binds with heme to form a peroxidase: relationship to the cytopathologies of Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 103 (9) (2006) 3381–3386.
[77] I. Pal, A.K. Nath, M. Roy, M. Seal, C. Ghosh, A. Dey, et al., Formation of compound I in heme bound Abeta-peptides relevant to Alzheimer's disease, Chem. Sci. 10 (36) (2019) 8405–8410.
[78] O. Yagensky, M. Kohansal-Nodehi, S. Gunaseelan, T. Rabe, S. Zafar, I. Zerr, et al., Increased expression of heme-binding protein 1 early in Alzheimer's disease is linked to neurotoxicity, Elife 8 (2019).
[79] J. Everett, J. Brooks, F. Lermyte, P.B. O'Connor, P.J. Sadler, J. Dobson, et al., Iron stored in ferritin is chemically reduced in the presence of aggregating Abeta(1-42), Sci. Rep. 10 (1) (2020) 10332.
[80] N.D. Telling, J. Everett, J.F. Collingwood, J. Dobson, G. van der Laan, J. J. Gallagher, et al., Iron biochemistry is correlated with amyloid plaque morphology in an established mouse model of Alzheimer's disease, Cell Chem. Biol. 24 (10) (2017) 1205–12015, e3.
[81] J. Everett, J.F. Collingwood, V. Tjendana-Tjhin, J. Brooks, F. Lermyte, G. Plascencia-Villa, et al., Nanoscale synchrotron X-ray speciation of iron and calcium compounds in amyloid plaque cores from Alzheimer's disease subjects, Nanoscale 10 (25) (2018) 11782–11796.
[82] J.F. Collingwood, A. Mikhaylova, M. Davidson, C. Batich, W.J. Streit, J. Terry, et al., In situ characterization and mapping of iron compounds in Alzheimer's disease tissue, J Alzheimers Dis 7 (4) (2005) 267–272.
[83] S. Masaldan, A.I. Bush, D. Devos, A.S. Rolland, C. Moreau, Striking while the iron is hot: iron metabolism and ferroptosis in neurodegeneration, Free Radic. Biol. Med. 133 (2019) 221–233.
[84] W.D. Bao, P. Pang, X.T. Zhou, F. Hu, W. Xiong, K. Chen, et al., Loss of ferroportin induces memory impairment by promoting ferroptosis in Alzheimer's disease, Cell Death Differ. 28 (5) (2021) 1548–1562.
[85] C. Ghadery, L. Pirpamer, E. Hofer, C. Langkammer, K. Petrovic, M. Loitfelder, et al., R2* mapping for brain iron: associations with cognition in normal aging, Neurobiol. Aging 36 (2) (2015) 925–932.
[86] A. Ashraf, J. Jeandriens, H.G. Parkes, P.W. So, Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Alzheimer's disease: evidence of ferroptosis, Redox Biol. 32 (2020) 101494.
[87] C.J. Matheou, N.D. Younan, J.H. Viles, Cu(2)(+) accentuates distinct misfolding of Abeta(1)(-)(4)(0) and Abeta(1)(-)(4)(2) peptides, and potentiates membrane disruption, Biochem. J. 466 (2) (2015) 233–242.
[88] Y. Miller, B. Ma, R. Nussinov, Zinc ions promote Alzheimer Abeta aggregation via population shift of polymorphic states, Proc. Natl. Acad. Sci. U. S. A. 107 (21) (2010) 9490–9495.
[89] Y. Tong, H. Yang, X. Tian, H. Wang, T. Zhou, S. Zhang, et al., High manganese, a risk for Alzheimer's disease: high manganese induces amyloid-beta related cognitive impairment, J Alzheimers Dis 42 (3) (2014) 865–878.
[90] K.V. Kuchibhotla, S.T. Goldman, C.R. Lattarulo, H.Y. Wu, B.T. Hyman, B. J. Bacskai, Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks, Neuron 59 (2) (2008) 214–225.
[91] S.A. James, Q.I. Churches, M.D. de Jonge, I.E. Birchall, V. Streltsov, G. McColl, et al., Iron, copper, and zinc concentration in abeta plaques in the APP/PS1 mouse model of Alzheimer's disease correlates with metal levels in the surrounding neuropil, ACS Chem. Neurosci. 8 (3) (2017) 629–637.
[92] L. Wang, Y.L. Yin, X.Z. Liu, P. Shen, Y.G. Zheng, X.R. Lan, et al., Current understanding of metal ions in the pathogenesis of Alzheimer's disease, Transl. Neurodegener. 9 (2020) 10.
[93] A. de Almeida, J. de Oliveira, L.V. da Silva Pontes, J.F. de Souza Junior, T.A. F. Goncalves, S.H. Dantas, et al., ROS: basic concepts, sources, cellular signaling, and its implications in aging pathways, Oxid. Med. Cell. Longev. 2022 (2022) 1225578.
[94] C. Giorgi, S. Marchi, I.C.M. Simoes, Z. Ren, G. Morciano, M. Perrone, et al., Mitochondria and reactive oxygen species in aging and age-related diseases, Int Rev Cell Mol Biol 340 (2018) 209–344.
[95] J.F. Passos, G. Saretzki, S. Ahmed, G. Nelson, T. Richter, H. Peters, et al., Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence, PLoS Biol. 5 (5) (2007) e110.
[96] J.F. Passos, G. Nelson, C. Wang, T. Richter, C. Simillion, C.J. Proctor, et al., Feedback between p21 and reactive oxygen production is necessary for cell senescence, Mol. Syst. Biol. 6 (2010) 347.
[97] S. Miwa, S. Kashyap, E. Chini, T. von Zglinicki, Mitochondrial dysfunction in cell senescence and aging, J. Clin. Invest. 132 (13) (2022).
[98] W. Dong, S. Cheng, F. Huang, W. Fan, Y. Chen, H. Shi, et al., Mitochondrial dysfunction in long-term neuronal cultures mimics changes with aging, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 17 (4) (2011) BR91–B96.
[99] M.J. Calkins, M. Manczak, P. Mao, U. Shirendeb, P.H. Reddy, Impaired mitochondrial biogenesis, defective axonal transport of mitochondria, abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer's disease, Hum. Mol. Genet. 20 (23) (2011) 4515–4529.
[100] P. Mecocci, M.F. Beal, R. Cecchetti, M.C. Polidori, A. Cherubini, F. Chionne, et al., Mitochondrial membrane fluidity and oxidative damage to mitochondrial DNA in aged and AD human brain, Mol. Chem. Neuropathol. 31 (1) (1997) 53–64.
[101] J. Wang, S. Xiong, C. Xie, W.R. Markesbery, M.A. Lovell, Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease, J. Neurochem. 93 (4) (2005) 953–962.
[102] S.S. Cao, R.J. Kaufman, Endoplasmic reticulum stress and oxidative stress in cell fate decision and human disease, Antioxidants Redox Signal. 21 (3) (2014) 396–413.
[103] B. Bhandary, A. Marahatta, H.R. Kim, H.J. Chae, An involvement of oxidative stress in endoplasmic reticulum stress and its associated diseases, Int. J. Mol. Sci. 14 (1) (2012) 434–456.
[104] F. Chiti, C.M. Dobson, Protein misfolding, amyloid formation, and human disease: a summary of progress over the last decade, Annu. Rev. Biochem. 86 (2017) 27–68.
[105] A. Ajoolabady, D. Lindholm, J. Ren, D. Pratico, ER stress and UPR in Alzheimer's disease: mechanisms, pathogenesis, treatments, Cell Death Dis. 13 (8) (2022) 706.
[106] K. Ohta, A. Mizuno, S. Li, M. Itoh, M. Ueda, E. Ohta, et al., Endoplasmic reticulum stress enhances gamma-secretase activity, Biochem. Biophys. Res. Commun. 416 (3–4) (2011) 362–366.
[107] U. Unterberger, R. Hoftberger, E. Gelpi, H. Flicker, H. Budka, T. Voigtlander, Endoplasmic reticulum stress features are prominent in Alzheimer disease but not in prion diseases in vivo, J. Neuropathol. Exp. Neurol. 65 (4) (2006) 348–357.
[108] J.J. Hoozemans, E.S. van Haastert, D.A. Nijholt, A.J. Rozemuller, P. Eikelenboom, W. Scheper, The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus, Am. J. Pathol. 174 (4) (2009) 1241–1251.
[109] J.H. Lee, S.M. Won, J. Suh, S.J. Son, G.J. Moon, U.J. Park, et al., Induction of the unfolded protein response and cell death pathway in Alzheimer's disease, but not in aged Tg2576 mice, Exp. Mol. Med. 42 (5) (2010) 386–394.
[110] E.L. Wilson, E. Metzakopian, ER-mitochondria contact sites in neurodegeneration: genetic screening approaches to investigate novel disease mechanisms, Cell Death Differ. 28 (6) (2021) 1804–1821.
[111] D. Martinvalet, The role of the mitochondria and the endoplasmic reticulum contact sites in the development of the immune responses, Cell Death Dis. 9 (3) (2018) 336.
[112] E. Tubbs, J. Rieusset, Metabolic signaling functions of ER-mitochondria contact sites: role in metabolic diseases, J. Mol. Endocrinol. 58 (2) (2017) R87–R106.
[113] M. Krols, G. Bultynck, S. Janssens, ER-Mitochondria contact sites: a new regulator of cellular calcium flux comes into play, J. Cell Biol. 214 (4) (2016) 367–370.
[114] L. Xu, X. Wang, C. Tong, Endoplasmic reticulum-mitochondria contact sites and neurodegeneration, Front. Cell Dev. Biol. 8 (2020) 428.
[115] E. Area-Gomez, A.J. de Groof, I. Boldogh, T.D. Bird, G.E. Gibson, C.M. Koehler, et al., Presenilins are enriched in endoplasmic reticulum membranes associated with mitochondria, Am. J. Pathol. 175 (5) (2009) 1810–1816.
[116] B. Schreiner, L. Hedskog, B. Wiehager, M. Ankarcrona, Amyloid-beta peptides are generated in mitochondria-associated endoplasmic reticulum membranes, J Alzheimers Dis 43 (2) (2015) 369–374.

[117] L. Hedskog, C.M. Pinho, R. Filadi, A. Ronnback, L. Hertwig, B. Wiehager, et al., Modulation of the endoplasmic reticulum-mitochondria interface in Alzheimer's disease and related models, Proc. Natl. Acad. Sci. U. S. A. 110 (19) (2013) 7916–7921.
[118] N.S. Leal, G. Dentoni, B. Schreiner, L. Naia, A. Piras, C. Graff, et al., Amyloid beta-peptide increases mitochondria-endoplasmic reticulum contact altering mitochondrial function and autophagosome formation in Alzheimer's disease-related models, Cells 9 (12) (2020).
[119] A. Alzheimer's, FDA-approved Treatments for Alzheimer's, 2023.
[120] J.C. Duvigneau, H. Esterbauer, A.V. Kozlov, Role of heme oxygenase as a modulator of heme-mediated pathways, Antioxidants 8 (10) (2019) 475.
[121] C. Vidal, L. Zhang, An analysis of the neurological and molecular alterations underlying the pathogenesis of Alzheimer's disease, Cells 10 (3) (2021).
[122] M. Seal, S. Uppal, S. Kundu, S.G. Dey, Interaction of apoNeuroglobin with heme-Abeta complexes relevant to Alzheimer's disease, J. Biol. Inorg. Chem. 20 (3) (2015) 563–574.
[123] H. Atamna, A. Nguyen, C. Schultz, K. Boyle, J. Newberry, H. Kato, et al., Methylene blue delays cellular senescence and enhances key mitochondrial biochemical pathways, Faseb. J. 22 (3) (2008) 703–712.
[124] D. Pramanik, C. Ghosh, S. Mukherjee, S.G. Dey, Interaction of amyloid β peptides with redox active heme cofactor: relevance to Alzheimer's disease, Coord. Chem. Rev. 257 (1) (2013) 81–92.
[125] S.J. Martindale, J.C. Stedeford, Neurological sequelae following methylene blue injection for parathyroidectomy, Anaesthesia 58 (10) (2003) 1041–1042.
[126] C.M. Wischik, R.T. Staff, D.J. Wischik, P. Bentham, A.D. Murray, J.M.D. Storey, et al., Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease, J. Alzheim. Dis.: JAD. 44 (2) (2015) 705–720.
[127] D. McLachlan, Intramuscular desferrioxamine in patients with Alzheimer's disease, Lancet 337 (8753) (1991) 1304–1308.
[128] C. Grossi, S. Francese, A. Casini, M.C. Rosi, I. Luccarini, A. Fiorentini, et al., Clioquinol decreases amyloid-β burden and reduces working memory impairment in a transgenic mouse model of Alzheimer's disease, JAD 17 (2) (2009) 423–440.
[129] L. Lannfelt, K. Blennow, H. Zetterberg, S. Batsman, D. Ames, J. Harrison, et al., Safety, efficacy, and biomarker findings of PBT2 in targeting Aβ as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial, Lancet Neurol. 7 (9) (2008) 779–786.
[130] S.J.S. Flora, V. Pachauri, Chelation in metal intoxication, Int. J. Environ. Res. Publ. Health 7 (7) (2010) 2745–2788.
[131] K.D. Fasae, A.O. Abolaji, T.R. Faloye, A.Y. Odunsi, B.O. Oyetayo, J.I. Enya, et al., Metallobiology and therapeutic chelation of biometals (copper, zinc and iron) in Alzheimer's disease: limitations, and current and future perspectives, J. Trace Elem. Med. Biol. 67 (2021) 126779.
[132] I. Pal, S.G. Dey, The role of heme and copper in Alzheimer's disease and type 2 diabetes mellitus, JACS Au 3 (3) (2023) 657–681.
[133] P.J. Whitehouse, A.M. Martino, K.A. Marcus, R.M. Zweig, H.S. Singer, D.L. Price, et al., Reductions in acetylcholine and nicotine binding in several degenerative diseases, Arch. Neurol. 45 (7) (1988) 722–724.
[134] P. Davies, A.J. Maloney, Selective loss of central cholinergic neurons in Alzheimer's disease, Lancet 2 (8000) (1976) 1403.
[135] F.J. Carvajal, N.C. Inestrosa, Interactions of AChE with Aβ aggregates in Alzheimer's brain: therapeutic relevance of IDN 5706, Front. Mol. Neurosci. 4 (2011) 19.
[136] I. Vecchio, L. Sorrentino, A. Paoletti, R. Marra, M. Arbitrio, The state of the art on acetylcholinesterase inhibitors in the treatment of Alzheimer's disease, J. Cent. Nerv. Syst. Dis. 13 (2021) 11795735211029113.
[137] G. Saxena, S.P. Singh, R. Agrawal, C. Nath, Effect of donepezil and tacrine on oxidative stress in intracerebral streptozotocin-induced model of dementia in mice, Eur. J. Pharmacol. 581 (3) (2008) 283–289.
[138] P. Atukeren, M. Cengiz, H. Yavuzer, R. Gelisgen, E. Altunoglu, S. Oner, et al., The efficacy of donepezil administration on acetylcholinesterase activity and altered redox homeostasis in Alzheimer's disease, Biomed. Pharmacother. 90 (2017) 786–795.
[139] M. Junaid, N. Islam, M.K. Hossain, M.O. Ullah, M.A. Halim, Metal based donepezil analogues designed to inhibit human acetylcholinesterase for Alzheimer's disease, PLoS One 14 (2) (2019) e0211935.
[140] M.-Y. Wu, G. Esteban, S. Brogi, M. Shionoya, L. Wang, G. Campiani, et al., Donepezil-like multifunctional agents: design, synthesis, molecular modeling and biological evaluation, Eur. J. Med. Chem. 121 (2016) 864–879.
[141] F. Li, Z.-M. Wang, J.-J. Wu, J. Wang, S.-S. Xie, J.-S. Lan, et al., Synthesis and pharmacological evaluation of donepezil-based agents as new cholinesterase/monoamine oxidase inhibitors for the potential application against Alzheimer's disease, J. Enzym. Inhib. Med. Chem. 31 (sup3) (2016) 41–53.
[142] P.P. Zandi, J.C. Anthony, A.S. Khachaturian, S.V. Stone, D. Gustafson, J. T. Tschanz, et al., Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study, Arch. Neurol. 61 (1) (2004) 82–88.
[143] M.W. Dysken, M. Sano, S. Asthana, J.E. Vertrees, M. Pallaki, M. Llorente, et al., Effect of vitamin E and memantine on functional decline in alzheimer disease: the TEAM-AD VA cooperative randomized trial, JAMA 311 (1) (2014) 33.
[144] E.E. Devore, F. Grodstein, F.J.A. van Rooij, A. Hofman, M.J. Stampfer, J.C. M. Witteman, et al., Dietary antioxidants and long-term risk of dementia, Arch. Neurol. 67 (7) (2010) 819–825.
[145] S.L. Gray, M.L. Anderson, P.K. Crane, J.C.S. Breitner, W. McCormick, J.D. Bowen, et al., Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults, J. Am. Geriatr. Soc. 56 (2) (2008) 291–295.
[146] V.M. Labunskyy, D.L. Hatfield, V.N. Gladyshev, Selenoproteins: molecular pathways and physiological roles, Physiol. Rev. 94 (3) (2014) 739–777.
[147] R.H.L.H. Rueli, A.C. Parubrub, A.S.T. Dewing, A.C. Hashimoto, M.T. Bellinger, E. J. Weeber, et al., Increased selenoprotein P in choroid plexus and cerebrospinal fluid in Alzheimer's disease brain, JAD 44 (2) (2015) 379–383.
[148] M.E. Pereira, J.V. Souza, M.E.A. Galiciolli, F. Sare, G.S. Vieira, I.L. Kruk, et al., Effects of selenium supplementation in patients with mild cognitive impairment or Alzheimer's disease: a systematic review and meta-analysis, Nutrients 14 (15) (2022) 3205.
[149] J. Jia, X. Zeng, G. Xu, Z. Wang, The potential roles of redox enzymes in Alzheimer's disease: focus on thioredoxin, ASN Neuro 13 (2021) 1759091421994351.
[150] R. Bridi, F.P. Crossetti, V.M. Steffen, A.T. Henriques, The antioxidant activity of standardized extract of Ginkgo biloba (EGb 761) in rats, Phytother Res.: PT 15 (5) (2001) 449–451.
[151] C. Shi, J. Liu, F. Wu, D. Yew, Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice, Int. J. Mol. Sci. 11 (1) (2010) 107–123.
[152] S. Saleem, H. Zhuang, S. Biswal, Y. Christen, S. Doré, Ginkgo biloba extract neuroprotective action is dependent on heme oxygenase 1 in ischemic reperfusion brain injury, Stroke 39 (12) (2008) 3389–3396.
[153] M. Bakhtiari, Y. Panahi, J. Ameli, B. Darvishi, Protective effects of flavonoids against Alzheimer's disease-related neural dysfunctions, Biomed. Pharmacother. 93 (2017) 218–229.
[154] E.J. Novais, V.A. Tran, S.N. Johnston, K.R. Darris, A.J. Roupas, G.A. Sessions, et al., Long-term treatment with senolytic drugs Dasatinib and Quercetin ameliorates age-dependent intervertebral disc degeneration in mice, Nat. Commun. 12 (1) (2021) 5213.
[155] P. Zhang, Y. Kishimoto, I. Grammatikakis, K. Gottimukkala, R.G. Cutler, S. Zhang, et al., Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model, Nat. Neurosci. 22 (5) (2019) 719–728.
[156] S. Chaib, T. Tchkonia, J.L. Kirkland, Cellular senescence and senolytics: the path to the clinic, Nat. Med. 28 (8) (2022) 1556–1568.
[157] J.L. Kirkland, T. Tchkonia, Senolytic drugs: from discovery to translation, J. Intern. Med. 288 (5) (2020) 518–536.
[158] P. Banerjee, S. Kotla, L. Reddy Velatooru, R.J. Abe, E.A. Davis, J.P. Cooke, et al., Senescence-associated secretory phenotype as a hinge between cardiovascular diseases and cancer, Frontiers in Cardiovascular Medicine 8 (2021).
[159] M. Raffaele, M. Vinciguerra, The costs and benefits of senotherapeutics for human health, The Lancet Healthy Longevity 3 (1) (2022) e67–e77.