



Review

Recent Development in the Understanding of Molecular and Cellular Mechanisms Underlying the Etiopathogenesis of Alzheimer's Disease

Atefeh Afsar, Maria del Carmen Chacon Castro , Adedamola Saidi Soladogun and Li Zhang *

Department of Biological Sciences, The University of Texas at Dallas, Richardson, TX 75080, USA

* Correspondence: li.zhang@utdallas.edu; Tel.: +1-972-883-5757

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to dementia and patient death. AD is characterized by intracellular neurofibrillary tangles, extracellular amyloid beta ($A\beta$) plaque deposition, and neurodegeneration. Diverse alterations have been associated with AD progression, including genetic mutations, neuroinflammation, blood–brain barrier (BBB) impairment, mitochondrial dysfunction, oxidative stress, and metal ion imbalance. Additionally, recent studies have shown an association between altered heme metabolism and AD. Unfortunately, decades of research and drug development have not produced any effective treatments for AD. Therefore, understanding the cellular and molecular mechanisms underlying AD pathology and identifying potential therapeutic targets are crucial for AD drug development. This review discusses the most common alterations associated with AD and promising therapeutic targets for AD drug discovery. Furthermore, it highlights the role of heme in AD development and summarizes mathematical models of AD, including a stochastic mathematical model of AD and mathematical models of the effect of $A\beta$ on AD. We also summarize the potential treatment strategies that these models can offer in clinical trials.

Keywords: Alzheimer's disease; amyloid β -protein; tau proteins; heme; heme oxygenase



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1. Introduction

In older people, Alzheimer's disease (AD) is now the most frequent type of dementia. Unfortunately, existing treatments are not highly effective. Therefore, it is crucial to increase our understanding of the mechanisms behind the emergence and progression of AD [1]. With 35.6 million cases globally, AD is considered one of the most common forms of aging-related dementia, and the number of cases is expected to triple or quadruple by 2050. AD impairs memory, cognition, and behavior, and ultimately results in death [2]. The accumulation of the extracellular $A\beta$ protein both inside and outside neurons and the existence of hyperphosphorylated tau tangles are all associated with neuronal impairment in AD [3]. It has been noted that the structure and operation of oligomeric forms of $A\beta$ and tau are among the most persuasive for comprehending pathogenesis, defining treatments, and providing a speculative synthesis for how their actions both start and fuel pathogenesis [4].

Numerous factors have been linked to the development of AD such as an abnormal blood–brain barrier (BBB), mitochondrial dysfunction, oxidative stress, metal ion imbalance, genetic risk factors, and more, as shown in Figure 1 [5–9]. The BBB serves a dual purpose, which involves the transportation of critical nutrients, hormones, and drugs to the brain while exporting metabolic end products from the CNS (as a carrier function). Additionally, it prevents circulating toxic substances and proteins with osmotic activity from entering the CNS (as a barrier function). As individuals age, the BBB stability decreases, causing its leakage. AD worsens this failure of BBB integrity, allowing peripheral immune cells to enter the brain, and potentially exacerbates the pathology by promoting

harmful neuroinflammation. According to most evidence, A β buildup is what causes BBB damage to spread. Nevertheless, BBB damage is also seen in tauopathies without A β pathology, pointing to a potential function for tau in BBB damage [5,10,11]. Traditionally, the BBB was thought to block the entry of both cellular and humoral components of the immune system from the blood in the brain's immunological privilege model. However, it is now increasingly clear that T cells frequently visit the brain. Although most T cells in the AD brain are not fully developed effectors, the cytokines they release may influence the pathogenic developments in AD [9,12]. Although T cell proliferation in the AD brain is low, once within the brain, T cells interact with microglia or astrocytes functioning as antigen-presenting cells (APC) to perform their effector tasks [13,14]. It is clear that microglia play a significant role in AD development. Early A β and tau deposition results in microglial activation, NLRP3 inflammasome assembly, and cytokine and protein release. However, because the original triggers, such as A β and tau, are not eliminated, continuous microglial activation exacerbates AD pathogenesis and results in greater protein buildup and neuroinflammation [14–16].

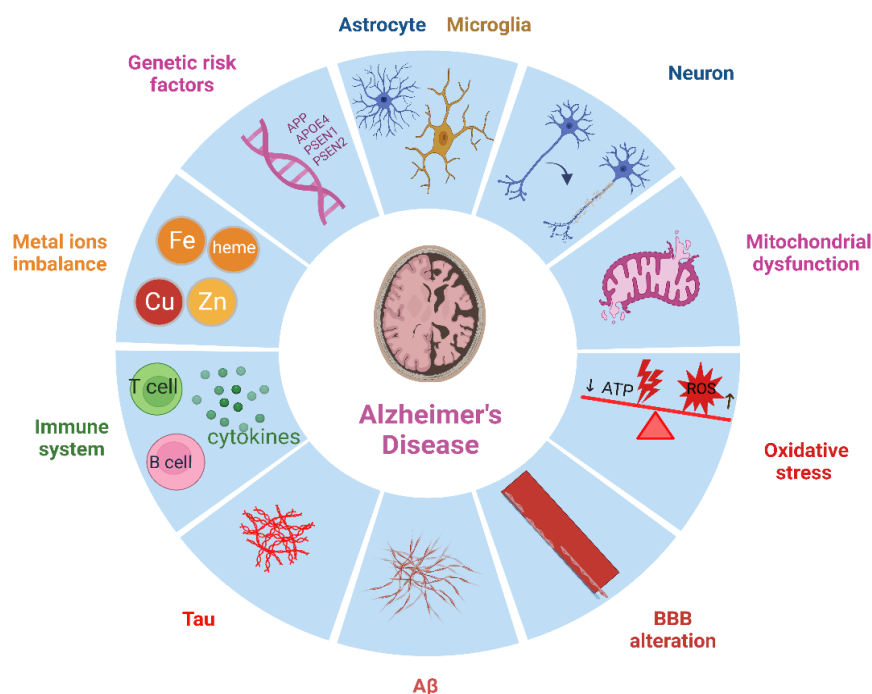


Figure 1. Multiple factors are associated with AD, including defective BBB, mitochondrial dysfunction, oxidative stress, metal ion imbalance, genetic risk factors, and the immune system. Additionally, AD pathogenesis involves T cells, A β , tau, microglia, and astrocytes. A comprehensive understanding of these factors and their interplay is crucial for advancing our understanding of AD and developing effective treatments. Created with BioRender (BioRender.com).

According to various studies, oxidative stress may increase the generation and aggregation of A β and facilitate the polymerization and phosphorylation of tau, thus creating a vicious cycle that favors the onset and progression of AD [17–20]. During the onset and development of AD, mitochondrial dysfunction is likely responsible for the initiation and/or amplification of oxidative stress. Oxidative stress can harm the integrity and function of the mitochondria. Defects in mitochondrial dynamics can result from metabolic or environmental changes, as well as responses to genetic deficiencies. This can limit the mitochondria's ability to adapt to changing cellular needs, which may have notably detrimental effects on neurons [21].

It has recently been demonstrated that the strongest genetic risk factor for AD, the apolipoprotein E (*APOE*) $\epsilon 4$ allele, is associated with a greater inflammatory response, although the exact mechanism is still unclear [22]. In the human population, there are three

prevalent *APOE* alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$), with $\epsilon 4$ being a risk factor and $\epsilon 2$ seen as protective compared to $\epsilon 3$ [23]. For the brain to continue to function normally, metal ions including iron, copper, zinc, and calcium must remain in a state of homeostasis. The imbalance of these metal ions in the brain plays a key role in the development of AD. Incorrect deposition of iron, copper, zinc, or calcium in various brain locations can encourage tau hyperphosphorylation, excessive $A\beta$ formation, and their accumulation [24].

This review covers the most prevalent changes related to AD. The purpose of this review is to provide an in-depth analysis of the mechanisms underpinning the onset and progression of AD. This paper presents the latest discoveries and updates on the various factors associated with AD, such as the role of T cells and microglia, genetic risk factors, and metal ion imbalance. Additionally, this review article highlights the role of heme in the development of AD and summarizes some mathematical models that demonstrate the effect of $A\beta$ on AD. By consolidating these findings, this review seeks to expand our knowledge of AD and inform further research in this field, with the ultimate goal of identifying new therapeutic targets and developing effective treatments for AD. Section 2 discusses the neuropathological hallmarks of AD. One specific alteration that can play a pivotal role in the development of AD is the alteration of the BBB, which results in an increased occurrence of T cells in the brain. Section 3 reviews the role of the immune system in AD, while genetic risk factors associated with AD are presented in Section 4. The imbalances of metal ions such as heme, Fe, Cu, and Zn are discussed in Section 5. Section 6 focuses on mitochondrial dysfunction and oxidative stress, followed by altered signaling pathways in Section 7. Section 8 summarizes mathematical models of AD, including the stochastic and discrete deterministic models. The review is concluded in Section 9.

2. Neuropathological Hallmarks of AD

2.1. The Role of $A\beta$ and Neurofibrillary tau Tangle in AD

The proteins $A\beta$ and tau have been identified as key contributors to the pathophysiology of AD, largely due to their deposition in the histopathological brain lesions, the senile plaques for $A\beta$ and the neurofibrillary tangles (NFTs) for tau. The soluble forms of $A\beta$ and tau are also found to be increased in the brains of AD patients [25]. In healthy individuals, $A\beta$ is naturally produced and eliminated from the brain at rates of 7.6% and 8.3% of total $A\beta$ every hour, respectively. However, in late-onset AD (LOAD) this percentage is reduced by around 30% [26–28]. As a result of $A\beta$ buildup, microglia and astrocytes are activated as part of the inflammatory response in an attempt to remove the plaque [3,29], but this also harms the nearby neurons and neurites. Additionally, NFTs, which are normally involved in intracellular activity, obstruct typical axonal transport, and eventually lead to neuronal death [3].

2.1.1. The Effects of $A\beta$ in AD

Mitochondria are the main energy source for brain cells to function properly. $A\beta$ and amyloid precursor protein (APP) have been found in the membranes of mitochondria, where they interact with mitochondrial proteins, increase the formation of reactive oxygen species (ROS), and damage the structure and function of mitochondria. This can lead to disruption in normal neural function. $A\beta$ oligomers can also harm mitochondria by causing an increase in intracellular Ca^{2+} levels and promoting the entry of Ca^{2+} into mitochondria, which can further damage their structure and function [30–34]. Cognitive impairments correlate with synaptic damage in AD [35]. It has been suggested that mitochondrial dysfunction and $A\beta$ buildup at synapses can cause synaptic injury, impaired neurotransmission, and cognitive decline in aging and AD patients [36]. Malfunctioning mitochondria have been shown to increase $A\beta$ generation from APP, and $A\beta$ causes mitochondrial dysfunction [37]. P-glycoprotein (P-gp) is essential for the regular clearance of $A\beta$ across the BBB and plays a crucial gatekeeping role. Endogenous $A\beta$ peptide release from the brain is part of this process. Emerging evidence supports the hypothesis that defective P-gp activity promotes $A\beta$ accumulation and contributes to the pathophysiology

of AD [26,38]. A β oligomers are known to promote inflammation and oxidative stress. Moreover, there is evidence suggesting that inflammation and oxidative stress can also contribute to the formation of A β oligomers [20,26,39]. It has been proposed that the combination of anti-inflammatory and anti-oxidant drugs may be a useful strategy for treating AD [40]. Heme, a key functional form of iron in cells that is synthesized in mitochondria, binds to A β to form the A β -heme complex [41], which inhibits A β accumulation and results in heme deficiency. Heme shortage reduces mitochondrial complex IV's activity and protein content, causing oxidative stress and disrupting Ca²⁺ homeostasis. Heme deficiency also affects zinc and iron homeostasis, APP, mitochondrial complex IV, and NO synthase (NOS) [42–44]. The aging brain exhibits many of the same phenotypic changes as heme-deficient cells, and these changes are more pronounced in neurodegenerative diseases such as AD. Heme-deficient brain cells cannot differentiate or conduct a complete cell cycle, suggesting that heme has a unique function beyond its traditional role in cell biology [44]. Table 1 summarizes the effects of A β .

Table 1. A summary of the effects of tau and A β , two main players that are associated with the development of AD.

Biomarkers	Effects	References
A β	results in heme deficiency, which changes: <ul style="list-style-type: none"> •Homeostasis of zinc, iron, and Ca²⁺; •APP; •NOS. 	Atamna et al. 2002, [43]
	causes oxidative stress and inflammation and vice versa produces hyperphosphorylated tau develops mitochondrial dysfunction and vice versa results in neurodegeneration	Chai et al. 2020, [26] Gotz et al. 2004, [45]; Ittner et al. 2011, [46] Morley et al. 2014, [37] Wang et al. 2020, [47]
Tau	NFTs build up instability of microtubule causes oxidative stress and vice versa results in neurodegeneration buildup of tau tangle results in:	Miao et al. 2019, [48] Brion 1998, [49] Rawat et al. 2022, [50] Eckert et al. 2011, [51] Rawat et al. 2022, [50]
	<ul style="list-style-type: none"> •Neuroinflammation; •impaired synaptic function; •dysfunctional autophagy; •dysfunctional mitochondria. 	

2.1.2. The Effects of tau in AD

The biological activities of the phosphoprotein tau are controlled by the amount of its phosphorylation. In the AD brain, tau is hyperphosphorylated [52]. NFTs, built up from hyperphosphorylated tau, are associated with tauopathies. Hyperphosphorylation causes tau to lose its common physiological role, become more toxic, and aggregate to form NFTs [48]. In previous studies, *in situ* hybridization was used to examine the distribution of α -tubulin mRNA in the human hippocampus of normal subjects and those with AD. The hybridization signal was significantly lower in NFT-rich regions, and NFT-containing neurons had a weaker hybridization signal than NFT-free neighboring neurons [53,54]. NFT-bearing neurons showed lower tubulin transcription, which might have a role in the reduced number of microtubules in these cells [54]. Microtubules are arranged in paraxial rows on the axons and dendrites. The structural backbone provided by the microtubule arrays allows axons and dendrites to develop and maintain their specific morphologies [55]. The development of NFTs is believed to be associated with neuronal dysfunction in AD. Microtubules are essential for maintaining the neuron's shape. The abnormal phosphorylation of tau likely causes microtubule disruption by reducing the levels of functional tau. Acetylated α -tubulin immunoreactivity decreased in most NFT-bearing neurons, even in the neuronal population with a relatively lower tau immunoreactivity, indicating early

microtubule instability [49,56,57]. It has been demonstrated that cells with tau overexpression are more susceptible to oxidative stress, and evidence suggests that oxidative stress may contribute to tau pathology [58]. Tau tangles, which are formed due to microtubule instability, consist of tau oligomers and monomers. The accumulation of tau tangles is linked to neuroinflammation, impaired synaptic function, dysfunctional autophagy, and dysfunctional mitochondria, all of which can cause neuronal injury. Additionally, tau oligomers can spread from one neuron to another [50,59–61]. Calafate et al. [62] used a mouse model to study the propagation of tau pathology, and found that the presence of synaptic contacts can facilitate tau pathology propagation between neurons and the amount of total accumulated tau significantly decreased when synaptic connectivity was reduced. Similarly, Wu et al. [63] used a mouse model to investigate how tau pathology spreads through the brain, finding that neuronal activity in one area of the brain can enhance the propagation of tau pathology to connected regions through a trans-synaptic mechanism. Overall, both studies provide evidence that tau oligomers can pass from neuron to neuron through a process of trans-synaptic spread. It has been demonstrated that the hyperphosphorylated tau that makes up the NFTs can hinder transport of mitochondria. This leads to an energy shortage and oxidative stress at the synapses, which can eventually lead to neurodegeneration [51]. A summary of the effects of tau can be seen in Table 1.

2.1.3. A β and tau Interplay

While A β and tau cause toxicity via different pathways, *in vitro* and *in vivo* research suggests that they can interact in three different ways [45,46,64,65]. The first mode of interaction is that A β drives tau pathology. In APP transgenic mice, A β deposition leads to hyperphosphorylated tau, whereas tau transgenic mice do not have observable A β plaque pathology [45,46]. It has been reported that mitochondrial malfunction and a lack of energy are early signs of AD [66,67]. In the second mode of interaction, both A β and tau contribute to interactive toxicity, damaging mitochondrial respiration in triple transgenic mice (triple AD mice), which show combined A β and tau pathologies. This results in an amplification of mitochondrial dysfunction when both pathologies are present together in mice compared to mice overexpressing tau or APP alone [46,64]. In previous studies [64,68], there was a considerable disturbance in the regulation of 24 proteins, out of which about a third were found to be mitochondrial proteins that are mainly associated with complexes I and IV of the oxidative phosphorylation system (OXPHOS). At both the protein and activity levels, the deregulation of complex IV was dependent on A β , whereas the deregulation of complex I was dependent on tau. According to Vossel et al. [65], in the third mode of interaction, A β disrupts axonal transport, which is essential for neuronal activity. A β -induced axonal transport impairments are prevented by a decrease in tau.

2.2. Neuroinflammation

Another underlying mechanism of AD pathology is neuroinflammation [69–72]. Inflammation is essential for repair processes in the brain, but prolonged inflammation can impair brain function [73–75]. The molecular mechanisms underlying the progression from chronic, low-grade systemic inflammation to neurodegeneration are still not fully understood [76]. Neuroinflammation is most likely the result of AD pathologies and risk factors, and it exacerbates the disease severity [77]. AD brains show elevated levels of proinflammatory cytokines and inflammatory markers, possibly as a response to the A β plaques and NFT deposition, which induce neuronal damage or death [76,78]. A β deposition activates the complement system, microglia, and astrocytes, and induces the secretion of inflammatory mediators such as IL-1 α , IL-1 β , IL-6, and TNF- α , and reactive oxygen and nitrogen species, which lower phagocytosis and prolong neuroinflammation [77,78]. Proinflammatory mediators activate microglia during the AD pre-symptomatic stage, leading to synaptic dysfunction and neuronal death [77]. This implies that neuroinflammation is an early event in the development of AD pathology [73,79]. Moreover, in a previous study, activated microglia surrounding amyloid plaques and elevated proinflammatory cytokine

levels were found in both the periphery and central nervous system (CNS), supporting the role of inflammation in AD [73,77]. Therefore, the inhibition of neuroinflammation could be a promising strategy to treat AD.

The role of cytokines in neuroinflammation in AD is diverse. TNF- α and IL-1 elevate the synthesis of A β from APP by β - and γ -secretase [80,81]. IL-1 also elevates tau phosphorylation by the p38-MAPK pathway [81,82]. IL-1 β suppresses astrocytic sonic hedgehog production, downregulates tight junction proteins, and elevates astrocytic activation with subsequent pro-inflammatory cytokine production, BBB disruption, and neuroinflammation. IL-6 increases APP expression and tau phosphorylation by the cdk5/p35 pathway [78,83]. Furthermore, elevated levels of chemokines and cytokines in AD brains may attract circulating immune cells in the periphery to cross the BBB to the CNS, exacerbating the inflammation [84]. Chemokines can also attract microglia to the periphery of A β plaques. Elevated expression levels of chemokine receptors on activated microglia were found in the brains of AD patients. Additionally, increased levels of MCP-1/CCL2 and CCL11 chemokines may reflect pathological changes and memory function alterations found in patients with early AD [85]. On the other hand, SDF-1/CXCR4 chemokine can activate microglia and reduce A β deposition. SDF-1 levels are low in early AD patients and negatively correlate with tau protein levels in the cerebrospinal fluid (CSF), consistent with its neuroprotective function [79,86]. Some other chemokines found to be elevated in the blood of AD patients are IP-10, IL-13, IL-8, MIP-1 α , and fractalkine; however, RANTES levels were found to be decreased in a previous study [79]. Nevertheless, controversy in the literature about these chemokines indicates that further studies are required to comprehend their role in AD progression.

A potential biomarker, the translocator protein (TSPO), an outer membrane mitochondrial protein, has been associated with neuroinflammation in AD [87–89]. TSPO expression is elevated in the brain periphery and is directly proportional to microglia, and potentially astrocyte, activation. TSPO radiotracers have been used for neuroinflammation imaging in vivo [73,90]. Other proteins that have been found to be dysregulated in AD are CSF1R, COX-1, COX-2, CB₂R, P2X7, and P2Y12 receptors [91–101]. Radiotracers for these proteins have been developed; however, further studies are required to determine their utilization as potential imaging biomarkers to detect neuroinflammation [90]. Another inflammatory biomarker explored is the complement system. Lower levels of plasma C3, the central component of the complement system activation, are associated with a higher risk of AD. C3 and C4 levels were to be found increased in AD patients in previous studies [79,102,103]. Moreover, the acute-phase inflammatory protein C-reactive protein (CRP) may promote A β ₄₂ synthesis and the activation of the complement system in the AD brain. While some studies found elevated levels of serum CRP in AD brains, others found decreased levels [104–106]. This controversy is likely due to the changes in its levels as the disease progresses [79]. Targeting inflammation biomarkers can be exploited to image neuroinflammation and monitor AD progression in vivo, and may be a promising strategy for early diagnosis and therapeutic intervention.

There is evidence of an association between diet and AD development. The Western diet (WD), which is based on ultra-processed foods and is rich in carbohydrates, salt, fat, and cholesterol [107], can enhance brain amyloid accumulation, tau protein phosphorylation, systemic inflammation, and the impairment of memory, learning, and cognitive functions [76,108–112]. WD has also been linked to neuroinflammation. Chronic WD-fed AD mouse models showed elevated levels of activated macroglia and astroglial cells in the hippocampus and entorhinal cortex. Moreover, neuroinflammation was indicated by increased levels of proinflammatory genes (*Trem2*, *Trem12*, *Tyrobp*, *CX3CR1*, *Ccl3*) and markers of phagocytic microglial cells (*Iba1*, *CD68*, *TREM2*) around the A β plaques [113–115]. WD-induced neuroinflammation seems to occur earlier, before A β plaque formation and brain deposition. Neuroinflammation can occur as a result of impaired amyloid clearance due to a loss of microglial phagocytic function and astrocyte-dependent disruption of

the glymphatic system. Additionally, a higher impact of WD on AD development was observed in APOE4 carriers in a previous study [76].

Several studies demonstrated a link between diet, obesity, and AD [76,116–122]. Obesity increases the risk of cognitive decline and AD development six-fold in adulthood and midlife [76,123]. Obese individuals have an increased brain atrophy rate, decreased cortical and hippocampal volume, low performance in memory tasks, and deficits in executive functioning [124–128]. Diet-induced obesity has been associated with increased APP, p-tau levels, and hippocampal A β , decreased hippocampal neurogenesis, and cognitive tasks deficit in AD animal models [129–131]. Diet-induced hypercholesterolemia experiments in mice showed the exacerbated neuroinflammatory response, increased p-tau levels, and the generation and deposition of toxic A β in neurons and astrocytes, leading to impaired cognition [132–134]. Other studies have demonstrated that diet-related dysbiosis and alteration of the gut microbiome composition in humans might disturb neurotransmitter production, disrupt synaptogenesis, contribute to systemic inflammation, impair the BBB, and contribute to cognitive impairment and AD development [76,135,136]. Furthermore, diverse studies have suggested that type 2 diabetes mellitus (T2DM) is a major vascular risk factor, and contributes to AD development [117,137–140]. Patients with T2DM have a two-fold higher risk of developing AD than healthy individuals [116,141–143]. Future studies should address the influence and interaction of environmental and genetic risk factors in AD development and progression.

2.3. BBB Alteration

The BBB is a complex structure composed of endothelial cells, pericytes, glial cells, and neurons, which form microvascular networks within the CNS [76]. In addition to protecting the brain, the BBB can regulate the blood-to-brain transport of nutrients, respond to soluble factors and plasma proteins, communicate with peripheral immune system cells, impede the entry of circulating cells and harmful molecules such as pro-inflammatory factors and toxins, and remove neurotoxic molecules and metabolic waste from the brain [76,79].

The loss of BBB integrity combined with the migration of immune cells into brain vessels may exacerbate inflammation and neurodegeneration in patients with AD [116]. Some pathological features of BBB breakdown in AD brains include the extravasation of blood-derived proteins (fibrinogen, thrombin, plasminogen, immunoglobulin C, albumin) in the hippocampus and cortex, an increase in the CSF levels of a pericyte injury marker, an increase in the CSF-to-plasma-albumin ratio, iron accumulation, and brain microbleeds [76,117].

Diverse studies demonstrated that increased A β production and deposition induce BBB disruption [144–147]. Dysfunction of the BBB impairs A β clearance, and can promote or escalate A β production [144]. Thus, a vicious cycle between BBB damage and A β accumulation can be established, resulting in neuronal damage and a loss of neuronal networks [144,148]. BBB dysfunction can also induce tau hyperphosphorylation, and tau pathology can trigger BBB damage [5,144,149,150]. Moreover, BBB permeability was found to be increased in APOE4 carriers [151–154], which show accelerated pericyte degeneration and BBB breakdown [155]. The loss of pericytes in AD is associated with fibrinogen leakage, reduced oxygenation, and fibrillar A β accumulation [156]. Additionally, astrocytic dysfunction and reactive astrocytes may induce increased generation of A β [144,157]. Another common event in AD is the loss of tight junctions, which is associated with insoluble A β ₄₀ and synaptic dysfunction. Cortical tight junction proteins such as claudin-5 and occludin have been found to be decreased in AD brains [158]. Targeting the BBB and its components can result in a promising strategy to treat AD.

2.4. Cholinergic Neurons in AD

Cholinergic neurons are nerve cells that secrete the major brain neurotransmitter acetylcholine [159]. Early studies in rodent models and humans delineated the importance of acetylcholine and cholinergic neurons in memory function [160,161]. Although these

neurons are localized in specific regions of the brain, they project into almost all brain regions and have been implicated in diverse behavioral, cognitive, and systemic functions [162–165]. Acetylcholine released by the cholinergic system modulates behavioral flexibility [166–168], attention [169,170], and arousal [171–173]. Of particular interest are the basal forebrain cholinergic neurons, which are essential for cognitive and memory function [174]. These basal forebrain cholinergic neurons form the major projection into the cerebral cortex and hippocampus [175–178]. These central cholinergic neurons display age-related dysfunction, leading to mild cognitive impairment [179–181].

The selective reduction in pre-synaptic cholinergic enzyme activity in specific brain regions of AD patients was first reported in the 1970s [182]. This finding pointed to a possible role for the loss of cholinergic neurons in the onset of AD. It was then shown that this cholinergic system failure is due to the degeneration of cholinergic neurons in the basal forebrain region responsible for the innervation of the cerebral cortex [183–185]. This gave rise to the concept of the “cholinergic hypothesis”, which posited the loss of cholinergic neuronal function and acetylcholine activity as the primary event in the onset of AD [186,187]. This hypothesis was further strengthened after it was shown that treatment with an acetylcholinesterase inhibitor, tetrahydroaminoacridine (THA, Tacrine), produced clinical improvements in AD patients [188]. Although tacrine was the first acetylcholinesterase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of AD and provided modest improvement in cognitive and memory symptoms in mild AD patients, it was withdrawn due to its severe hepatotoxicity [189,190].

Acetylcholine impairment is the most widespread and important neurotransmitter alteration in AD [191]. Acetylcholinesterase hydrolyses acetylcholine to choline and acetate, and is an essential enzyme of the neuronal cholinergic system [192,193]. Decreased acetylcholine availability resulting from cholinergic deficiency can be corrected by targeting acetylcholinesterase via inhibition. The goal of this approach is to increase the neuronal availability of acetylcholine and cholinergic neurotransmission, and make up for the shortfall in secretion and synaptic availability of acetylcholine resulting from central cholinergic neurons’ dysfunction and degeneration in AD. Thus, following in the footsteps of Tacrine, several reversible inhibitors have been developed for the treatment of AD. Donepezil, galantamine, and rivastigmine are acetylcholinesterase inhibitors that have been approved by both the Food and Drug Administration and the European Medicines Agency for the treatment of AD [194,195]. In addition to these three, only two other treatments (Memantine and Aducanumab) have been approved for AD [196]. These drugs elicit improvement in certain cognitive and behavioral symptoms in mild to moderate AD, but do not treat the underlying problem of cholinergic neuronal degeneration or prevent disease progression [197,198]. In addition, they have several drawbacks such as (1) low efficacy, which wanes further as the disease progresses, and (2) severe adverse side effects such as cardiac arrhythmia, nausea, diarrhea, vomiting, and muscle cramps [199–201].

There is ongoing research to develop more effective and less toxic cholinergic inhibitors, as well as to incorporate molecular features of acetylcholinesterase inhibitors in multitarget drugs [202,203]. Drugs that improve cholinergic function are among the few FDA-approved therapeutics to treat AD, and will remain indispensable tools in the multifaceted approach to the treatment and management of AD patients. Therapeutics aimed at improving the cholinergic system have not been widely researched in recent years as attention has shifted to other promising mechanisms underpinning AD. Developing new therapeutics that can improve cholinergic function can provide further ammunition in the continued search for effective AD treatments.

Basal forebrain cholinergic neurons (BFCN) depend on nerve growth factor (NGF) for the maintenance of their biochemical phenotype. NGF released by cortical and hippocampal neurons also regulates the BFCN synaptic integrity and number [204]. The dependence of BFCN on NGF informed the hypothesis that BFCN atrophy is caused by NGF deficiency. Interestingly, the biosynthesis of NGF in the cerebral cortex is not altered in AD [205], while there is an increase in the levels of its precursor, proNGF [206,207]. However, evidence has

implicated an altered NGF signaling system and interaction with BFCN in AD [208,209]. Dysfunction in the NGF pathway seemed to be due to impaired retrograde transport and maturation of NGF [210]. Genetic delivery of NGF to the brain of AD patients has been used to activate the neuronal trophic response [211]. NGF-based therapy seeking to boost NGF trophic activity should be explored to halt BFCN atrophy, especially in early stages of AD.

2.5. Glial Cells

The nervous system is composed of two major cell types: neurons and glial cells, which include astrocytes, microglia, oligodendrocytes, polydendrocytes (NG2 glia), and Schwann cells. Astrocytes play a vital role in regulating neurogenesis and synaptogenesis, shaping the micro-architecture, providing structural support for neurons, and protecting the brain from injuries [212–216]. Microglia cells are the major immune cells of the central nervous system and serve as resident macrophages of brain parenchyma, providing the first line of defense against external insults [217–220]. Microglia are also involved in synaptic formation and remodeling [221–223]. As part of the complement cascade of the CNS innate immune system, macroglia engulf and prune synapses [224–226]. Oligodendrocytes are the CNS cells responsible for myelin formation. They wrap myelin sheaths around the neuronal axon and ensure the proper propagation of the electrical action potential through the axon [227,228]. NG2 glia (also called oligodendrocyte precursor cells) are used to produce oligodendrocytes during development and adulthood, and they are also involved in the maintenance of microglia homeostasis and the regulation of brain innate immunity [229–233]. The essential functions of glial cells in normal brain development, function, immune response, and homeostasis mean that disruption of normal glial function can cause neuro-glial metabolic dysfunction, which can lead to and accelerate neurodegeneration. Evidence has linked impaired glial cell function and homeostasis to the pathogenesis of AD, as discussed below.

2.5.1. Astrocytes

Astrocytes are the most prevalent glial cells, and constitute about a third of cells in the human central nervous system [214,215]. Many mechanisms link astrocytes to the development and progression of AD. *APOE*, the major genetic risk factor for LOAD, is expressed in the astrocytes of the normal brain. Astrocytes exhibit reactive astrogliosis in response to a CNS infection or injury. Reactive astrogliosis is the functional, molecular, cellular, morphological, and population alterations in astrocytes that serve as a protective mechanism against insults [234–237]. Reactive astrogliosis has been reported in the brains of mouse models of AD and AD patients. Astrocytes become more reactive and associate with A β plaques in the AD brain [236,238,239]. The reactive astrocytes display morphological hypertrophy and increase the expression of glial fibrillary acidic protein (GFAP). GFAP is being explored as an early marker of AD with promising results [240–242]. A β can activate astrocyte reactivity, upregulate the release of pro-inflammatory cytokines [243–246], and alter astrocyte-Ca²⁺ homeostasis [247–249]. Impaired calcium signaling mediated by astrocytes, especially increased Ca²⁺ activity leading to the hyperactivation of Ca²⁺-dependent proteins, can promote the release of transmitters such as GABA, which alters neuron-glial communication, disrupt synaptic plasticity and transmission, and accelerate cognitive deficits [247,250,251].

Atrophic astrocytes have been documented in both mouse models of AD and the post-mortem brains of AD patients [252–254]. It has been suggested that atrophy of astrocytes might be an early event in AD, leading to the loss of astrocyte homeostasis and function. Recent evidence indicates that astrocyte dysfunction and disease-associated astrocytes are present in the early stages of AD, providing support for this claim [253,255]. Astrocyte dysfunction can lead to synaptic impairment, which produces cognitive deficits that are hallmarks of the early stages of AD. Astrocytes are involved in the phagocytosis and clearance of A β [256,257]. A defective astrocyte might not be able to effectively clear A β . In

the later stages of neurodegeneration, as A β deposition increases, senile plaques promote the formation of reactive astrocytes, which, in turn, activate microglia. Activated microglia release neurotoxic and neuroinflammatory factors, which induce synaptic impairment, neuronal loss, and severe neurodegeneration in a feedforward vicious cycle.

2.5.2. Microglia

Microglia are innate immune cells of the CNS, and are vital for normal brain development and function both in the healthy and pathological state. They control the immune response in the brain by interacting with other immune cells [258–260]. Microglia are transformed into reactive states in response to infections and injuries in a process known as microglia activation. Depending on the type of stress or pathological change, reactive microglia undergo specific changes in phenotype, morphology, proliferation patterns, and activity. They release various neurochemicals including growth factors, cytokines, chemokines, and other inflammatory mediators [258,261,262]. Reactive microglia are a neuropathological hallmark of AD brain response to amyloid deposition, neurofibrillary tau tangles, and neuronal death [263–265]. Reactive microglia are widely considered to be a manifestation of AD pathology, but recent evidence points to active roles for microglia in the pathogenesis of AD and their potential as a therapeutic target.

2.5.3. AD Risk Loci Are Expressed by Microglia

Several genetic loci, including *APOE*, *TREM2*, *SPI1*, and *CD33*, which are highly associated with the risk of AD, are predominantly or exclusively expressed by microglia [266]. The *APOE4* allele is a major genetic risk factor for LOAD [267]. *APOE* is involved in amyloid clearance and plaque formation. The *APOE4* allele seems to reduce amyloid removal and elevate amyloid deposition in plaques [268–270]. *APOE4* has been reported to alter lipid homeostasis in glia cells [271] and promote dysfunctional microglia phenotypes in neurodegeneration [272]. *TREM2* is a surface receptor expressed on myeloid cells including microglia. *TREM2* is involved in the clearance of A β , the removal of cell debris, and microglial survival [273–276]. Dysfunctional *TREM* due to mutations in the *TREM* gene is likely to contribute to an increased risk of AD, although the exact mechanisms are not fully understood.

2.5.4. Microglia in the Complement System and Inflammatory Signaling

The microglia-mediated innate immune complement system is essential for engulfing and shaping synapses during development [277]. Some genes, such as *CR1*, involved in the complement system, are genetic risk factors for AD development [278,279]. Hyperactivation of the complement system is possibly involved in synaptic loss and neuronal degeneration in AD. This hypothesis is supported by experiments that show that inhibition of the complement system protects against synaptic loss and neurodegeneration [224,278].

2.6. Synaptic and Neuronal Loss in AD

A progressive decline in cognitive function is a major symptom and hallmark of AD [280,281]. Cognitive deficit has been reported to be present at early stages of the disease and decades before amyloid deposition [282,283]. Multiple lines of evidence point to synapse loss as the major cause of cognitive impairment in AD. Examination of the postmortem brains of AD patients shows that synapse loss is the best correlate to cognitive deficits in AD [284–289]. Synaptic dysfunction and loss have been extensively reported in animal models of AD [290–294]. The correlation between synapse loss and cognitive defects has been demonstrated using various methods and models [295–298].

Neuronal loss is a canonical neuropathological feature of AD [299–301]. The loss of neurons starts at early stages and accelerates as the disease progresses [302–304]. There is a pronounced loss of neurons in the entorhinal cortex and hippocampus compared to other brain regions [303–305]. Neuronal loss in these regions closely correlates with cognitive

impairments [306,307]. Various AD transgenic mouse models replicate the neuronal loss seen in AD [308–312].

Mechanisms of Synaptic Loss and Neuronal Loss

A β is connected to synaptic dysfunction in AD. However, it is the soluble oligomeric A β species, and not the total amyloid plaque deposition, that constitutes the most toxic forms of amyloid, contributing to synaptic damage and neuronal loss in the disease. [313–317]. The mechanism of A β -induced damage possibly involves the binding of A β to synaptic-associated proteins [318,319]. Advanced imaging techniques have been used to show the presence of soluble amyloid species in synapses [318,320]. The AD generic risk gene *APOE4* promotes the transport of these amyloid species to the synapse, where they exert toxic effects and mediate neuronal loss [321].

The accumulation of tau proteins correlates with cognitive decline and clinical symptoms in AD [322]. Although tau is found in healthy and AD synapses, there are higher levels of hyperphosphorylated tau in the synapses of the AD brain [323–327]. Tau toxicity to synapses and neurons seems to be mediated by soluble, hyperphosphorylated, oligomer forms [328–331]. Normal tau protein is involved in the axonal transport of mitochondria and other important molecules to synapses [332]. Impaired axonal transport resulting from tau pathology can contribute to synaptic dysfunction and neuronal atrophy. Indeed, reduced mitochondrial numbers have been observed in AD brains [65,326,333,334].

Inflammation, both local and systemic, possibly contributes to synaptic loss and neuronal death. Glia cells are highly involved in the innate immune system-mediated inflammatory response through the release of various factors and the expression of proteins that can affect synaptic function [29,335]. Microglia functions such as the pruning of synapses via the complement system, release of pro-inflammatory cytokines, and phagocytic activities have direct effects on synaptic integrity [336,337].

Neuronal cell death in AD has been reported to be mediated by cellular processes involving apoptosis, necrosis, autophagy, parthanatosis, ferroptosis, pyroptosis, and the mitochondrial permeability transition pore [338].

3. The Role of Immune System in AD

The BBB plays a critical role in maintaining a stable and favorable environment for neurons to function properly. It does this not only by physically separating the blood from the brain, but also by expressing particular transporters and ion channels that maintain the proper ion balance required for appropriate synaptic function [3,339]. The BBB is essential for maintaining the homeostasis of the CNS. BBB dysfunction is associated with a number of CNS disorders, including AD. The BBB impairment in AD can be both a source and a result of A β buildup in the CNS [340–342]. The BBB is highly durable, preserving its integrity in the face of significant brain atrophy, neuroinflammation, and toxic tau buildup. However, it has been shown that tau itself can trigger disruption of the BBB. Additionally, when tau levels drop, the BBB might regain its integrity. Moreover, A β buildup, especially along the vasculature, is responsible for this rise in BBB impairment [5,343].

3.1. The Role of the Innate Immune System in AD

In AD, activated microglia are found in the direct vicinity of A β plaques. The innate immune system in the brain is made from microglia. The microglial innate immune system is activated by A β and tau proteins contained in the AD brain, but because they accumulate over time rather than being eliminated from the microglia environment, this leads to chronic microglial activation [14,344]. Triggering receptor expressed on myeloid cells 2 (TREM2), as a microglial A β receptor, binds to A β oligomers and mediates A β degradation and activation in microglia [345]. Regulating the brain's levels of A β is one of the most significant roles played by glial cells in AD. Microglia and astrocytes have been associated with this process as key moderators of A β elimination and degradation. In numerous circumstances, astrocytes and microglia have a crucial function in the phagocytosis of

A β through a variety of receptors. Toll-like receptors (TLR) are engaged in monomeric, oligomeric, and fibrillar A β elimination in the microglia [346,347]. It has been revealed that pCD14, TLR4, and TLR2 are necessary at the cell surface for the recognition of fibrillar-amyloid β (fA) and the initiation of a phagocytic response [348].

3.2. Role of B Cells in AD

T and B cells constitute a substantial portion of the adaptive immune system [14]. Although B lymphocytes are not thought to penetrate the AD brain, evidence connects their existence in the brain parenchyma to the development of the illness. Immunoglobulin deposits around A β plaques are the consequence of the entry of B lymphocytes into the brain parenchyma. While it is believed that immunoglobulin promotes and facilitates the uptake of A β plaques by microglia, the A β -IgG complex in CSF is believed to adversely influence the cognitive condition of AD sufferers. Additionally, therapeutic B cell reduction, and thus IgG, slows the development of AD in mice, indicating that AD patients may also benefit from B cell targeting to control the disease's progression [349–351]. A β or phosphorylated tau are the targets of immunoglobulins (Igs) generated by B cells, according to Dujardin et al. [22]. One technique to eliminate self-antigens such as A β is to use immunoglobulin M (IgM) antibodies. B1 cells, a subgroup of B cells, generate IgM antibodies. B1 cells are essential for the elimination of self-antigens without overt inflammation, and they spontaneously produce IgM during homeostasis [1,352]. While the role of B cells is typically thought to be advantageous, recent research on AD animal models has shown that a genetic loss of B cells alone or their depletion at the onset of AD may be beneficial. This highlights that B cells may have a notable detrimental impact on AD progression [353].

3.3. Role of T Cells in AD

T cells, one component of the adaptive immune system, develop in the thymus and become activated in the presence of pathogens [354]. When faced with an infectious exposure, T cells that are specific for the antigen proliferate and supply essential aid in the generation of cytokines or even in the direct destruction of infected host cells to clear the body of the bacteria or virus [14]. T cells have been demonstrated to cross the BBB and penetrate the CNS, and both the elderly human hippocampus and the AD brain contain them [355]. A study comparing the majority of AD cases to the control group showed that the number of T cells is higher in AD. T cells have been activated and are in the process of becoming effector T cells. Clonal expansion that is initiated by an antigen does not appear to occur. T cell emigration or survival, which leads to an aggregation of T cells in the brain parenchyma, may be influenced by the local inflammatory environment, even if the mechanisms that attract T cells to the AD brain are still not understood [9,356]. T cell extravasation is triggered by tau-related neurodegenerative alterations in the late stages of AD, according to Merlini et al. [357]. In a mouse model of tauopathy, hippocampal T cell infiltration induces neuroinflammation and cognitive loss, while T cell removal prevents cognitive deficits [358]. Elderly people and those with AD have higher levels of T cell reactivity to the A β . However, T cells are more common in the brains of AD patients than in those of people with other degenerative dementias or age-matched controls [359].

In AD, the number of regulatory T cells (Tregs), which limit immunological activity, decreases. In a previous study, Tregs from AD patients lacked their inhibitory ability and were not able to restrict the growth of CD4⁺ T cells. Treg cell depletion worsened cognitive impairment in APP/PS1 mice, while raising the Treg population restored cognitive function [14,360,361]. Tregs either secrete immunosuppressive anti-inflammatory cytokines, including TGF- β , IL-10, and IL-35, or they directly cause cytotoxicity and apoptosis by expressing granzyme B and perforin 1 to inhibit T helper cells' activities [362].

Th1, Th2, and Th17 cells are produced as a result of the differentiation and proliferation of CD4⁺ helper T cells [363,364]. T cells have the ability to regulate the activity of their APC and surrounding cells through interaction and cytokine release. The production of pro-inflammatory cytokines by Th1 and Th17 cell types may have a negative bystander effect on

nearby neurons or glial cells, exacerbating the inflammatory environment in AD. However, in a mouse model, the induction of A β -specific Th2 cells reduces cognitive issues and amyloid accumulation in blood vessels [354,365]. In the mouse brain parenchyma, CD8⁺ T cells have been found to be closely linked to both microglial and neuronal structures, and these cells may directly influence neuronal dysfunction in regulating synaptic plasticity. The phenotype of microglia may be influenced by CNS-specific CD8⁺ T cells, which may then cause neuroinflammation and, consequently, synaptic plasticity [366].

3.4. Role of Cytokines in AD

Inflammatory cytokines such as IL-1 and IL-6 play a role in the buildup of A β . It has been demonstrated that in response to the buildup of A β peptide, both microglia and astrocytes secrete IL-1, which, in turn, increases the production of A β , speeding up A β deposition. Additionally, it has been demonstrated that A β peptide raises IL-6 generation by astrocytes either directly or indirectly through an IL-1 β -dependent pathway. Therefore, it appears that IL-6 acts as a secondary mechanism, enhancing the inflammatory reaction triggered by IL-1 [367–370]. Proinflammatory cytokines such as IL-1 and IL-6 are prevented from being produced in vitro by IL-10 cytokines [371]. Increased IL-10 levels also enhanced spatial learning in a previous study [372]. According to some research, IL-10 may be used therapeutically to treat neuroinflammation, cognitive decline, and neurodegeneration. In addition, limiting transforming growth factor- β signaling or administering Protollin as a nasal vaccine caused elevated IL-10 transcript levels together with decreased β -amyloidosis [372,373]. In a mouse model, IL-4 can lower levels of monomeric A β and several A β oligomeric forms. Decreased A β levels significantly support an advantageous impact of IL-4 on cognitive performance. It has been proven that IL-4 prevents mice from having defective spatial learning [374]. When compared with controls, AD patients were shown to have significantly higher IL-21 levels in a previous study [375]. The inflammatory cytokine IL-21 significantly correlated with IgG levels in AD, and it is possible that IL-21 contributed to the elevated IgG response [1]. The change in IgG in the mouse brain may be a crucial factor in promoting the buildup of A β and the progression of AD [376].

It has been claimed that Th17 cells, which have been found to enter the brain parenchyma of AD patients, contribute to the neuroinflammation and neurodegeneration of AD by secreting proinflammatory cytokines and by directly acting on neurons via the Fas/FasL apoptotic pathway. Th17 cells are very proinflammatory and create proinflammatory cytokines such as interleukin (IL)-17, IL-21, and IL-22. In individuals with AD, levels of the transcriptional factor (ROR γ) involved in the development of Th17 cells as well as the cytokines produced by Th17 cells are much higher. More information about the function and procedure of Th17 cells in the creation and progression of AD is still needed [375,377–379]. It has been established that interferon- γ (IFN- γ) and interleukin-4 (IL-4) are the two main cytokines secreted by Th1 and Th2 cells, respectively [380,381]. It has been proposed that an unmanaged increase in IL-4 or IFN- γ , as well as other pro- and anti-inflammatory cytokines, may enhance the negative effects of CNS damage or long-term neurodegeneration. It has been suggested that the duration of the reaction is most likely significant and that replacing an initial proinflammatory response, such as IFN- γ , with an anti-inflammatory response, such as IL-4, may remove a crucial beneficial impact of immune cells on astrocytes, namely keeping their glutamate clearance function [381]. In reaction to A β ₁₋₄₂ (use the same designation as before?), IFN- γ causes an increase in neuronal death [382]. IL-4 and IL-10 are examples of anti-inflammatory cytokines that Th2 cells produce in contrast [383]. A summary of the effects of T cells and cytokines is shown in Figure 2.

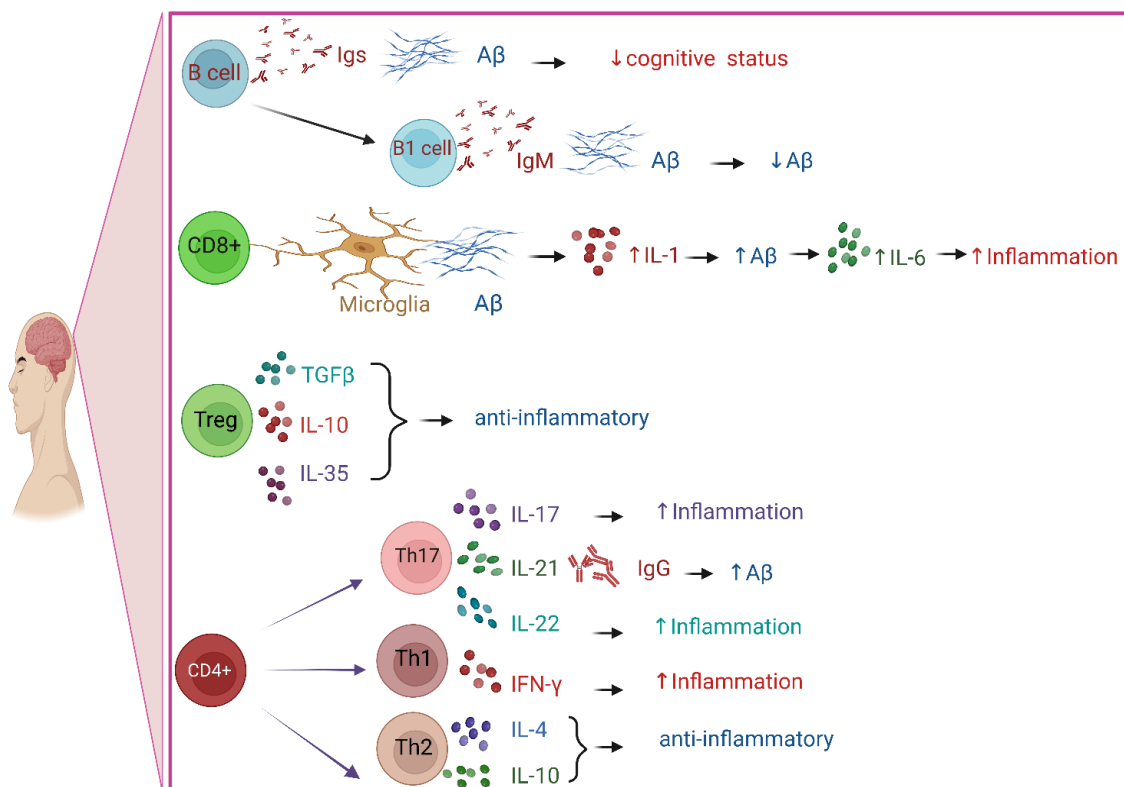


Figure 2. CD4⁺ T cells differentiate and proliferate into Th1, Th2, and Th17 cells. Th17 and Th1 cells secrete proinflammatory cytokines, but Th2 secrete anti-inflammatory cytokines. Depletion of Tregs worsens mice's cognitive impairment. Immunosuppressive anti-inflammatory cytokines are released by Tregs. While it is thought that immunoglobulin encourages and accelerates the uptake of A β plaques by microglia, it is also thought that the A β –IgG complex in the CSF has a negative impact on the cognitive health of AD patients. Created with BioRender (BioRender.com).

4. Genetic Risk Factors Associated with AD

Early-onset or familial AD is linked to mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes involved in the amyloidogenic pathway [76,117]. APP is cleaved by β - and γ -secretase to produce A β [384,385]. Initially, the β -APP-site cleaving enzyme (BACE), a membrane-bound aspartyl protease, cleaves APP, generating a secreted APP derivative, sAPP, and the membrane-bound protein β -secretase-derived C-terminal fragment (CTF β). Later, CTF β is cleaved by γ -secretase, producing different lengths of A β , which are released into the extracellular space, and an APP intracellular domain (AICD) released to the cytoplasm [386,387]. A β_{40} is the most abundant form of A β produced into the cells. However, A β_{42} is the one that mostly mediates neurotoxicity. A β_{42} is more insoluble than A β_{40} and more likely to form aggregates [388]. Moreover, an elevated A β_{42} /A β_{40} ratio is considered a pathogenic hallmark of AD [386]. Mutations in the *APP* gene usually affect the BACE and γ -secretase cleavage sites and the mid-domain A β region [386,389]. In total, 24 mutations were identified in *APP* and have been associated with increased A β_{42} :A β_{40} in AD brains [117].

PSEN1 and *PSEN2* are involved in the γ -secretase cleavage of APP to produce A β . Several *PSEN* mutations (185 mutations in *PSEN1* and 13 mutations in *PSEN2*) have been discovered in AD and have been implicated in the elevated levels of A β_{42} :A β_{40} in the brain. *PSEN1* mutations have been also linked to disruption of cerebral blood vessels, degeneration of pericytes and mural cells, breakdown of the BBB, and A β deposits in small cerebral blood vessels [117]. A recent study re-evaluated genetic variations of the genes involved in FAD. A total of 288 *PSEN1* variants were classified as pathogenic/likely pathogenic variants, followed by 31 *APP* variants classified as pathogenic/likely pathogenic.

The least pathogenic/likely pathogenic variants were from the *PSEN2* gene, with only 13 variants [390]. APOE is a protein that transports cholesterol and other lipids (apolipoprotein lipid) between cells in the CNS [389,391]. The main genetic risk factor for late-onset or sporadic AD is the $\epsilon 4$ allele of *APOE*, one of the three possible alleles ($\epsilon 2$, $\epsilon 3$, or $\epsilon 4$) [76,117]. The APOE isoforms differ in two amino acid residues at positions 112 and 158, which can be either Arg or Cys. These polymorphisms cause differences in the lipid binding properties of the APOE isoforms and receptor affinities; APOE4 is hypolipidated compared to APOE3 and APOE2 [269,389,392] (Figure 3). Carrying the $\epsilon 2$ allele reduces the risk for AD about 0.6-fold, while having the $\epsilon 3$ form is believed to have a neutral effect on AD risk. Individuals who carry a copy of $\epsilon 4$ allele have a risk of developing AD about three times higher than those with two copies of the $\epsilon 3$ allele, while those with two copies of the $\epsilon 4$ allele have an 8- to 12-fold higher risk. Additionally, those individuals who carry the $\epsilon 4$ allele are more likely to develop A β accumulation and AD dementia at a younger age than those carrying $\epsilon 2$ or $\epsilon 3$ alleles [76,389,391,393]. APOE4 increases pericyte degeneration, BBB breakdown, cerebral amyloid angiopathy, and fibrinogen deposits in the brain [117]. APOE binding and A β clearance capacity differ among isoforms. APOE2–A β , followed by the APOE3–A β complex, has a higher binding capacity to a major A β clearance receptor LRP1 at the abluminal side of the BBB, and is rapidly cleared across the BBB into circulation, whereas APOE4–A β complexes have a lower interaction with LRP1 and are cleared from the brain by a slower and less efficient mechanism that involves VLDLR. Additionally, APOE4 is associated with elevated vascular stiffness and increased vascular A β deposition; combined with a low CSF flow and low A β clearance, A β accumulation may escalate in the brain [76,117].

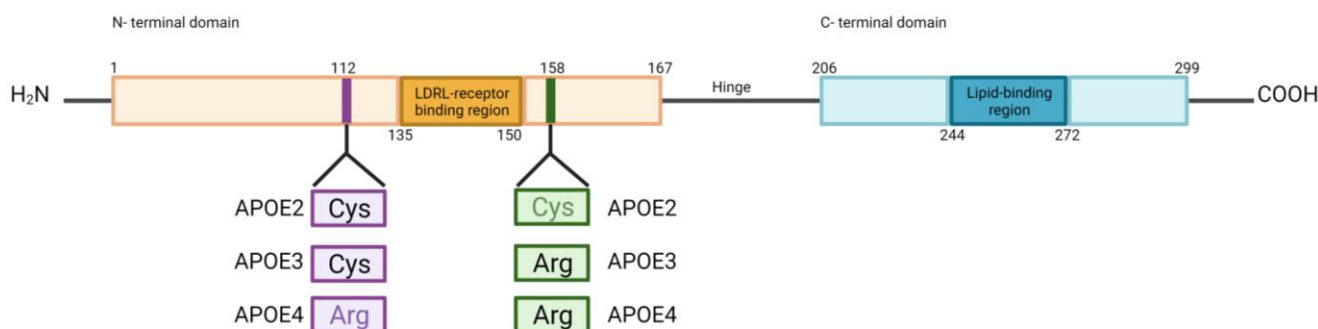


Figure 3. Amino acid residue substitutions of APOE isoforms. APOE consists of an N-terminal domain that contains an LDLR receptor-binding region connected by a hinge region with a C-terminal domain that contains a lipid-binding region. Positions 112 and 158 show amino acid substitutions among APOE isoforms. Cysteine (Cys). Arginine (Arg). Created with BioRender (BioRender.com).

Another protein downregulated in the AD brain endothelium is PICALM [117]. Genome-wide association studies (GWAS) found an association between AD and SNPs present in the non-coding region of *PICALM*. *PICALM* is a protein involved in endocytosis, cell receptor internalization, and endocytic protein intracellular trafficking [394–398]. *PICALM* regulates cleaved APP C-terminal fragment degradation via autophagosomes and clathrin-mediated endocytosis of gamma-secretase [399]. *PICALM* is recruited as a result of the A β binding to LRP1 at the abluminal side of the BBB, and starts an immediate *PICALM*/clathrin-dependent endocytosis of A β -LRP1 complexes. Subsequently, *PICALM* continues to guide the trafficking of the endocytic vesicles across the brain endothelium. Later, it fuses with Rab5 and leads to A β intracellular transport. Finally, the binding of *PICALM* with Rab11 induces A β exocytosis at the luminal side of the BBB [117,400]. Low or deficient expression of *PICALM* is correlated with A β accumulation and low clearance across the BBB [400]. Another protein involved in A β clearance is clusterin (*CLU*). *CLU* binds to A β , prevents its aggregation, and induces its clearance across the BBB via the LRP2 pathway. GWAS found an association between *CLU* and sporadic AD, where the C allele is

considered an AD risk factor. Rare coding variations in *CLU* in the β -chain were found to be enriched in AD patients [117,399,401,402].

A GWAS study also found an association between AD and the mesenchyme homeobox gene 2 (*MEOX2*), a transcription factor expressed in the brain vasculature and regulator of cell differentiation and remodeling [403]. AD brain endothelial cells express low levels of *MEOX2*, leading to vessel regression, LRP1 proteosomal degradation, and low $A\beta$ clearance across the BBB [117,404]. Other mutations that influence AD risk are those on *ABCA7*, *BIN*, *CD2AP*, *PLD3*, *UNC5C*, and *AKAP9*. *ABCA7* deficiency accelerates $A\beta$ deposition in AD mouse models. In a previous study, *SORL1* was also found to be associated with AD. Mutations in the *SORL1* gene induced decreased binding and $A\beta$ turnover. Furthermore, *MEF2C* and *PTK2B* have been associated with AD pathology. Additionally, mutations in genes involved in the immune system pathways have been associated with AD [399]. A GWAS revealed a connection between immune related mutations in the genes *TREM2*, *CD33*, *CR1*, *IL-8*, *ABI3*, and *PLCG2* with AD [73,79,399]. *TREM2* is a receptor that binds phospholipids and APOE- and clusterin-containing lipoprotein particles, and promotes phagocytosis of lipoprotein particle- $A\beta$ complexes [275,405,406]. Its expression is elevated in response to brain injury in resident microglia and infiltrating monocytes and macrophages in AD. The *TREM2* missense variant (R47H) can increase AD risk by about two-fold [407–409]. *CD33* is a receptor found on myeloid and microglia cells, and is involved in the anti-inflammatory immune response. Changes in *CD33* expression affect $A\beta$ levels. Monocytes expressing mutant *CD33* showed elevated *CD33* expression and reduced $A\beta$ phagocytic capacity, which correlated with elevated levels of $A\beta$ in the brain in a previous study [399,410]. The complement receptor 1 (*CR1*) is another high AD risk factor. *CR1* inhibits complement activation through C3b and C4b in blood cells and microglia. The complement system is activated in AD, and research on mice treated with $A\beta$ has reported elevated synapse elimination by phagocytic microglia. The association of AD risk with mutations in *CR1* can be explained by the overproduction of a longer *CR1* isoform, which increases the number of C3b/C4b sites [278,398,399,411].

5. Metal Ion Imbalance in AD (heme, Fe, Cu, Zn)

Biometals play essential roles in normal physiology, and the association between their dysregulation and AD pathology has attracted growing research interest. An imbalance of metal ions may cause neurotoxicity and neurological damage. Elements including iron, calcium, copper, zinc, and selenium have been found to be involved in AD pathology [6].

5.1. Iron Imbalance

Iron is the most abundant metal in the brain, and participates in neurotransmitter synthesis, myelination, and mitochondrial function [6]. MRI and mass spectrometry studies have shown iron accumulation in the bilateral hippocampus, frontal and parietal cortex, frontal white matter, putamen, caudate nucleus, and dentate nucleus in AD patients [6,117]. *APOE4*, the main genetic risk factor for AD, has been reported to elevate iron levels [412–414]. Brain iron accumulation has been implicated in $A\beta$ and hyperphosphorylated tau deposition, cognitive impairment, and brain atrophy, accelerating AD progression. Thus, iron may be considered a potential biomarker for AD progression. Increasing evidence shows that iron binds with $A\beta$ and tau and accumulates with senile plaques and NFTs in neurons in AD brains [6,412,415,416].

Iron levels increase with aging and accumulate considerably in the brains of AD patients. Abnormal levels of iron transport (transferrin), iron storage (ferritin), and iron export (ferroportin) regulator molecules are associated with ferroptosis and AD [412,417–422]. Excess free iron escalates $A\beta$ plaque formation, increases ferritin expression, promotes neuronal toxicity, and impairs spatial memory in AD mouse models [6,412]. An in vitro and in vivo study involving IFN- γ -induced microglia and AD mouse models revealed elevated iron accumulation, ferritin expression, and glycolysis, and decreased $A\beta$ phagocytosis [423]. Transferrin variant C2 may be associated with an elevated risk of AD [412,424,425].

Another study reported a disturbance of the peripheral iron metabolism, where low levels of plasma iron, possibly due to deficient transferrin processing, may compromise hemoglobin production and lead to a reduction in hemoglobin levels in AD [6,426]. Other research found ferroportin and ceruloplasmin (a cellular iron transport mediator) proteins to be downregulated in AD [427–429]. Additionally, iron dyshomeostasis is associated with the main proteins involved in AD pathology. Iron modulates APOE regulation in neurons and astrocytes and increases its secretion [430]. Iron has also been involved in APP processing [431,432]. Moreover, iron binds to tau and facilitates its aggregation and phosphorylation. Tau protein mediates APP trafficking to the cell surface, where APP stabilizes ferroportin and promotes iron export [6]. It has been revealed that CSF ferritin and serum non-heme iron levels may be utilized as biomarkers to predict the progression of mild cognitive impairment (MCI) to AD [412,433–435]. Iron-related protein levels, such as ferritin, an iron-sequestering protein, and ferroportin1, an iron exporter, are reduced in AD pathology. Free Fe^{3+} induces aggregation of hyperphosphorylated tau. On the other hand, Fe^{2+} can reverse the aggregation [436]. Discrepancies in expression levels of iron transport-related proteins such as ferritin [412,436] may be due to the differences in samples utilized in the studies. Therefore, further studies involving populations from different races, sexes, genders, ages, and ethnic groups are required to elucidate iron's role in AD pathology.

Heme Dysregulation

Heme (iron protoporphyrin IX) is a crucial co-factor for hemoglobin, cytochrome c, and cytochromes in complexes II, III, and IV of the mitochondrial electron transport chain (ETC). It is involved in diverse biological mechanisms such as oxygen and electron storage and transfer, including neuronal survival and differentiation. Heme excess promotes ROS production, leading to oxidative stress, lipid peroxidation, and cell death [437,438]. Studies in the brains of patients with AD showed that iron overload in the inferior temporal cortex may be involved in accelerated cognitive decline [436]. Dysregulation of heme metabolism and elevated heme/iron levels are associated with a poor prognosis in AD. Moreover, a heme molecule can bind an $\text{A}\beta$ peptide at the N-terminus (H13) to generate $\text{A}\beta$ -heme complexes. A second $\text{A}\beta$ peptide may provide R5 and Y10 for the peroxidase activity of the complex, which is observed in presence of H_2O_2 . However, the C-terminus of $\text{A}\beta$ may also considerably contribute to the peroxidase activity of the complex [438,439]. Despite the growing evidence that highlights the importance of heme- $\text{A}\beta$ interaction in AD pathology, the exact stoichiometry, structure, and biochemical mechanisms responsible for the peroxidase activity of these complexes are unknown and require further studies. Furthermore, disturbed heme metabolism and mitochondrial dysfunction of neuronal cells may contribute to $\text{A}\beta$ -heme complex formation [41,439]. $\text{A}\beta$ -heme complex-dependent peroxidase activity contributes to AD pathology, exacerbating oxidative stress and neurotoxicity, leading to neurotransmitter oxidation and $\text{A}\beta$ aggregation. The peroxidase activity of the complex may result from the activation of cerebral immune cells that induce an increase H_2O_2 production and heme peroxidase activity [438,439].

The exact mechanisms involved in heme accumulation in the brain are still unclear. However, analysis of brain tissue from AD patients suggests that blood-derived hemoglobin may be the source of heme. Blood vessel destruction due to $\text{A}\beta$ aggregation around brain vasculature may lead to localized brain hemorrhage and heme leakage [438–441].

Heme-related proteins/enzymes have been found to be altered in AD. Diverse studies have discovered the upregulation of hemopexin and heme oxygenases in AD [439]. Moreover, HO-1 upregulation and post-transcriptional modifications were detected in the brains of patients with AD in a previous study. Mouse studies demonstrated that HO-1 overexpression induces tau phosphorylation and facilitates aggregation [436,442,443]. HO-1 upregulation can induce Fe^{2+} excess in the cytoplasm, promote oxidative stress, and promote ferroptosis. Interestingly, APP was reported to bind and inhibit HO-1 and HO-2, where APP carrying mutations linked to FAD had a higher binding affinity and pro-

vided higher heme oxygenase inhibition [6]. Elevated HEBP1, a mitochondrial-associated heme-binding protein 1, is associated with AGE/RAGE-related neuronal damage, leading to neuronal loss in early AD. HEBP1-mediated apoptosis contributes to neuronal loss and dysfunction. Additionally, its cleavage product F2L regulates inflammation [438]. Moreover, the expression of BVR-A, an enzyme involved in the reduction of biliverdin to the antioxidant bilirubin during heme degradation, and its oxidative and nitrosative modifications, were elevated in samples from the hippocampus of patients with AD in a previous study. On the other hand, levels of phosphorylated BVR-A were decreased and associated with reduced cellular antioxidant activity in the cerebellum in AD [436]. Reduced BVR-A levels or impaired BVR-A activation contribute to the development of brain insulin resistance and metabolic alterations in AD. During AD progression, BVR-A Tyr phosphorylation is reduced, and BVR-A nitration is increased due to the elevated oxidative stress, a process that impairs the activation of the insulin signaling pathway and promotes CK1-mediated BACE1 recycling at the plasma membrane, where BACE1 cleaves APP and leads to elevated A β production. On the other hand, increased A β peptides trigger increased oxidative and nitrosative stress, leading to BVR-A impairment and resulting in a vicious cycle [444]. Moreover, studies have demonstrated that expression levels of the rate-limiting heme synthetic enzyme ALAS1 and the heme degradation enzyme HO-2 were selectively decreased in the hippocampi of AD brains. HO-2 and heme degradation were elevated in fully differentiated neuronal cells to support neuronal functions, but they were reduced after A β exposure. Furthermore, decreased heme metabolism, especially heme degradation, seems to be an early event in AD [445]. Therefore, targeting the HO-1 metabolites such as CO, bilirubin, and iron-mediated ferritin expression may suppress oxidative stress and ferroptosis, and mitigate AD progress [436].

Ferroptosis, an iron-dependent nonapoptotic form of regulated cell death, is potentially associated with AD [6,412]. The exact mechanism for iron-dependent ferroptosis is controversial, but it is believed that cytoplasmic Fe²⁺ reacts with membrane lipids and triggers a lethal lipid chain reaction and pore formation [6]. Iron imbalance may elevate hydroxyl free radicals and trigger neuroinflammation, leading to lipid peroxidation and redox dyshomeostasis, which are linked to the ferroptotic pathway [412]. Therefore, controlling iron levels and suppressing ferroptosis can be explored as a potential therapeutic approach for AD. Studies have demonstrated that ferroptosis can be suppressed by Nrf2-dependent induction of antioxidant enzymes such as GPx4, SOD2, and HO-1 [436]. Thus, exploring their therapeutic benefits may provide new insights into the treatment of AD pathology. Additionally, diverse studies have reported that using different iron chelators can rescue memory deficits, A β and tau pathologies, and neurodegeneration in AD patients [6]. Thus, targeting iron and heme might be a therapeutic strategy to overcome AD.

5.2. Calcium and Copper Imbalance

Dyshomeostasis of other minerals has been implicated in AD development. An analysis of the plasma of AD patients reported an increased phosphorus percentage but decreased levels of calcium, iron, copper, zinc, and selenium. Elevated serum phosphate is associated with increased pro-inflammatory cytokines and may contribute to escalating inflammation in AD [426].

Serum calcium levels are regulated by APOE, and the increase in neuronal calcium influx seems to correlate with the elevation of A β [446,447]. Dysregulation of calcium homeostasis may be the basis for APOE4 neurotoxicity in AD [426]. Mitochondrial Ca²⁺ overload in AD seems to depend on amyloid plaque deposition [133,448]. On the other hand, RNA-seq and microarray analyses showed an alteration of many genes involved in mitochondrial Ca²⁺ transport in AD brains. Several genes involved in mitochondrial Ca²⁺ influx were downregulated, while many of those involved in Ca²⁺ efflux were upregulated [448]. Even though this may result in decreased mitochondrial Ca²⁺ levels, it is believed to be a compensatory mechanism to avoid mitochondrial Ca²⁺ overload in the AD brain [449].

Copper (Cu) is a redox-active metal implicated in diverse brain metabolic activities [450–452]. Mutation of the Cu transporter *ATP7B* (K832R) increases the risk of AD and causes loss of its function [6,453,454]. Reduced plasma copper and ceruloplasmin, a cuproenzyme, levels correspond with impaired cognitive performance in AD patients [426]. Other studies also found low levels of SOD1, another cuproenzyme [6,455]. Similarly, APP overexpression in an AD mouse model induced copper deficiency, which is associated with impaired superoxide dismutase and ceruloplasmin preceding amyloid neuropathology appearance [426]. Other studies demonstrated that Cu concentrates with other metals in amyloid plaques. Ionic copper and iron facilitate A β aggregation and are involved in ROS generation [456–459]. Cu distribution in the AD brain is diverse; extracellular Cu²⁺ pooling can promote A β precipitation under acidic conditions and it can become trapped in the extracellular plaques, whereas intracellular copper deficiency may promote A β production [6]. Copper also upregulates APP expression [460,461]. Cell culture studies involving copper depletion reported increased A β generation [462,463], whereas dietary supplementation or upregulation of intraneuronal copper in APP transgenic mice suppressed A β production [455,464]. Copper–A β interaction can recruit substrates such as cholesterol to produce hydrogen peroxidase and promote oxidative stress, causing neurotoxicity [465–469]. Presenilin was reported to influence cellular copper turnover [470]. Moreover, *in vitro* and *in vivo* studies showed copper can also bind to tau protein, promote its aggregation, and induce the generation of hydrogen peroxidase, as observed in the copper ion–neurofibrillary tangle complexes within the neurons in AD brains [471–473]. Furthermore, copper modulates cyclin-dependent kinase 5 tau phosphorylation [6].

5.3. Zinc Imbalance

Zinc (Zn) is an essential element for brain function, concentrated in the gray matter and involved in neurotransmission [463,474,475]. Ionic zinc has been shown to induce histological amyloid structures. Zn²⁺ binds to A β , inducing its aggregation and deposition. The A β -zinc complex is resistant to proteolysis and promotes the stability of A β aggregates [476–478]. The slow turnover of synaptic Zn²⁺ released during glutamatergic synaptic transmission may induce amyloid deposition [6]. Furthermore, decreased levels of the zinc transporter ZnT3 in cortical tissues, combined with the Zn²⁺ trapped by extracellular A β aggregates, may cause a deficiency of intracellular Zn²⁺ and impair neuronal function [479,480]. Moreover, zinc may inhibit β -secretase cleavage activity of APP, and increased zinc may limit A β production, but it may also promote A β ₄₃ production through a different mechanism [6,463,481]. Zinc may also increase PSEN1 expression and affect APOE stability, particularly APOE4 [6,482]. Moreover, Zn²⁺ promotes tau phosphorylation and aggregation [483–485]. Despite the growing evidence that zinc dyshomeostasis inhibits neuronal function, its connection to neurodegeneration in AD is still unclear and requires extensive research [6].

5.4. Selenium Imbalance

In a previous study, selenium (Se) treatment of neuronal cells showed decreased A β production by reducing the BACE1 activity, protected cells against A β toxicity, and reduced 4-hydroxynonenal, a marker of ferroptosis [486]. Furthermore, Se plays an important role in ferroptosis and has been implicated in AD pathology [6]. Se is part of selenocysteine, which forms part of the active site of glutathione peroxidase 4 (GPx4), which is involved in ferroptosis [487,488]. Low Se levels have been reported in the serum and temporal cortex of AD brains [6,489–492]. Low Se levels in plasma were associated with an elevated risk of cognitive decline [493]. Additionally, selenium levels in the brain were found to be lower in APOE4 carriers [491]. Nutritional and environmental factors may modulate mineral levels in the serum and disease stage. Therefore, further research is required to understand the relationship between metal plasma levels and AD pathology.

6. Mitochondrial Dysfunction and Oxidative Stress in AD

An imbalance between the production of ROS and antioxidant defenses is known as oxidative stress [494]. There is evidence of significant levels of oxidative stress in AD [495,496]. A rise in oxidative stress is also reported as part of the aging process, but in the AD brain, oxidative stress is considerably higher compared to elderly controls of the same age. Mitochondria are the main source of oxidative stress. It has been proposed that defective mitochondria are less capable of generating adenosine triphosphate (ATP) but more capable of producing ROS, which may be a significant contributor to the oxidative imbalance observed in AD [21,497,498]. Increased ROS levels promote the transcription of proinflammatory genes and the production of cytokines such as IL-1, IL-6, and TNF- α , as well as chemokines, which result in neuroinflammation. On the other hand, inflammatory responses activate microglia and astrocytes to produce high levels of ROS. Therefore, neuroinflammation can be seen as both a cause and a result of persistent oxidative stress. The accumulation of A β peptide in the brain leads to the development of NFTs, inflammatory responses, increased oxidative stress, and mitochondrial dysfunction, which are the root causes of cell death and dementia [17,499]. Mitochondrial dysfunction is among the most noticeable and earliest indications of AD. It has been found that almost every component of mitochondrial activity is altered in AD [7]. Consistent aspects of mitochondrial dysfunction in AD include damaged mitochondrial bioenergetics, increased oxidative stress, and a disturbed mitochondrial genome. The significance of these defects in initiating mitochondrial dysfunction may vary depending on the specific biological, environmental, and genetic features of each patient with AD. However, any one of these abnormalities can lead to the other two, exacerbating neuronal dysfunction and neurodegeneration [47].

ATP, which is produced predominantly by mitochondria, is the cell's primary source of biological energy production [500,501]. Decreased ATP generation and the formation of ROS are all consequences of mitochondrial energy metabolism dysfunction [502,503]. Three mitochondrial enzyme complexes have been found to have low activity in AD: cytochrome oxidase (COX), the pyruvate dehydrogenase complex (PDHC), and α -ketoglutarate dehydrogenase complex (KGDHC) [498,504–506]. Genetic abnormalities may cause mitochondrial enzyme abnormalities in the AD brain, and other AD-related processes, including oxidative stress, may affect mitochondrial enzymes. COX, PDHC, and KGDHC may be crucial steps in the chain of events that results in AD, regardless of whether or not there are primary genetic problems or subsequent events induced by oxidative stress [498].

6.1. Protein Oxidation, Lipid Oxidation, DNA Oxidation, and Glycoxidation

During the progression of AD, brain tissue in patients is subject to oxidative stress, including protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation [507–510]. Protein carbonyl production is a significant marker of protein oxidation, which can be brought on by direct free radical attack on certain amino acid side chains, from the products of glycation and glycoxidation, or from products of lipid peroxidation interacting with proteins. The elevated levels of protein carbonyl and 3-NT in the AD brain, along with studies demonstrating that antioxidants can inhibit A β (1-42)-induced protein oxidation in neurons, are consistent with the idea that A β -induced protein oxidation may contribute to some of the neurodegeneration in the AD brain [511–516]. There is strong evidence that lipid peroxidation plays a key role in the neurodegeneration of AD. Lipid peroxidation caused by free radicals is common in AD. Free radical antioxidants prohibit lipid peroxidation in the membranes of brain cells, which is caused by A β . Taken together, lipid peroxidation caused by A β may contribute to the neurodegeneration of the AD brain [517–519]. In a previous study, nuclear DNA (nDNA) contained levels of oxidized bases about 10-fold lower than those found in mitochondrial DNA (mtDNA) [520]. The neurodegeneration found in AD may be influenced by the considerable oxidative damage to nDNA and mtDNA in the disease [521]. According to research on DNA oxidation, 8-Hydroxy-2-deoxyguanosine (8-OHdG) plasma levels are elevated in AD patients, indicating that this oxidized product could be employed as an AD diagnosis marker [522,523]. Accelerated oxidation of glycated

proteins (glycooxidation) results in the buildup of extracellular advanced glycation end products (AGEs) in AD [507,524]. In AD brains, AGE levels are increased, and AGEs can promote the production of A β . AGEs may cause tau hyperphosphorylation at a number of AD-related locations as well as problems in spatial memory [525,526].

6.2. A β , tau, OXPHOS, and Mitochondrial Dysfunction

APP, through the creation of A β , alters the balance of mitochondrial fission and fusion, leading mitochondria to fragment and distribute in an abnormal way, which effects mitochondrial and neural dysfunction [51,527,528]. Neurons serve as the most fundamental units in the nervous system to carry out the exchange of information. They have the capacity to receive, integrate, transmit, and export information. In order to maintain appropriate neuronal activity, mitochondria, the organelles responsible for giving energy to neurons, are carried to the dendrites and axons that require the most energy through the microtubule structure [529]. The balance of mitochondrial fission and fusion is indeed altered in AD neurons, which is thought to contribute to mitochondrial dysfunction and neurodegeneration in vivo [530]. Mitochondrial dysfunction caused by the formation of ROS increases A β production, creating a vicious cycle between mitochondrial dysfunction and ROS, as well as the harmful effects of A β [531,532]. The A β peptide needs functioning mitochondria to cause cell toxicity, as mitochondria are both the source and the target of ROS-induced neuronal damage, according to Cardoso et al. [533]. Mitochondrial dysfunction is the primary contributor to A β deposition, synaptic degeneration, and NFT generation in sporadic late-onset AD. The main distinction between sporadic and familial AD is that in the latter, A β appears to be the primary pathogenic event that results in subsequent mitochondrial malfunction [534,535].

A potential therapeutic target for mitochondria has been investigated [536,537]. Insulin has been found to stop the reduction in mitochondrial oxidative phosphorylation efficiency and prevent a rise in oxidative stress in the presence of the A β peptide, enhancing or maintaining the function of neurons in AD [536]. Additionally, treatment with coenzyme Q10 (CoQ10) can prevent brain mitochondrial dysfunction caused by A β_{1-40} , hence preventing the severe energy deficit underlying AD pathogenesis [537]. Moreover, evidence indicates that insulin regulates the metabolism of A β and tau proteins [538,539]. Research has established that hyperphosphorylated tau impairs mitochondrial transport, resulting in an energy deficit and oxidative stress at the synapses, resulting in neurodegeneration [51]. Tau accumulation and phosphorylation are consequences of mitochondrial malfunction. In the meantime, pathogenic tau disrupts mitochondrial dynamics and function as well as axonal transport. This creates a vicious cycle of increasing mitochondrial malfunction and tau pathology, influencing neuronal and synaptic function, and resulting in memory loss and cognitive issues in AD. Defective mitochondrial function markers include reduced ATP synthesis, enhanced ROS generation, defective OXPHOS complexes, and antioxidant enzymes [51,540–542]. While simultaneously monitoring cellular health to make a prompt choice (if required) to begin cell death, mitochondria are crucial for producing the energy that powers regular cellular function. Mitochondria are crucial for neuronal function since neuronal cells have a limited scope for glycolysis and rely heavily on aerobic OXPHOS for their energy needs. However, OXPHOS is the primary source of harmful free radicals, which are byproducts of regular cellular respiration [497,543,544]. Oxidative stress may facilitate tau polymerization and phosphorylation while increasing the construction and accumulation of A β . This sets up a vicious loop that encourages the development and spread of AD [17]. Figure 4 provides a summary of the effects of mitochondrial dysfunction, oxidative stress, tau, and A β in AD.

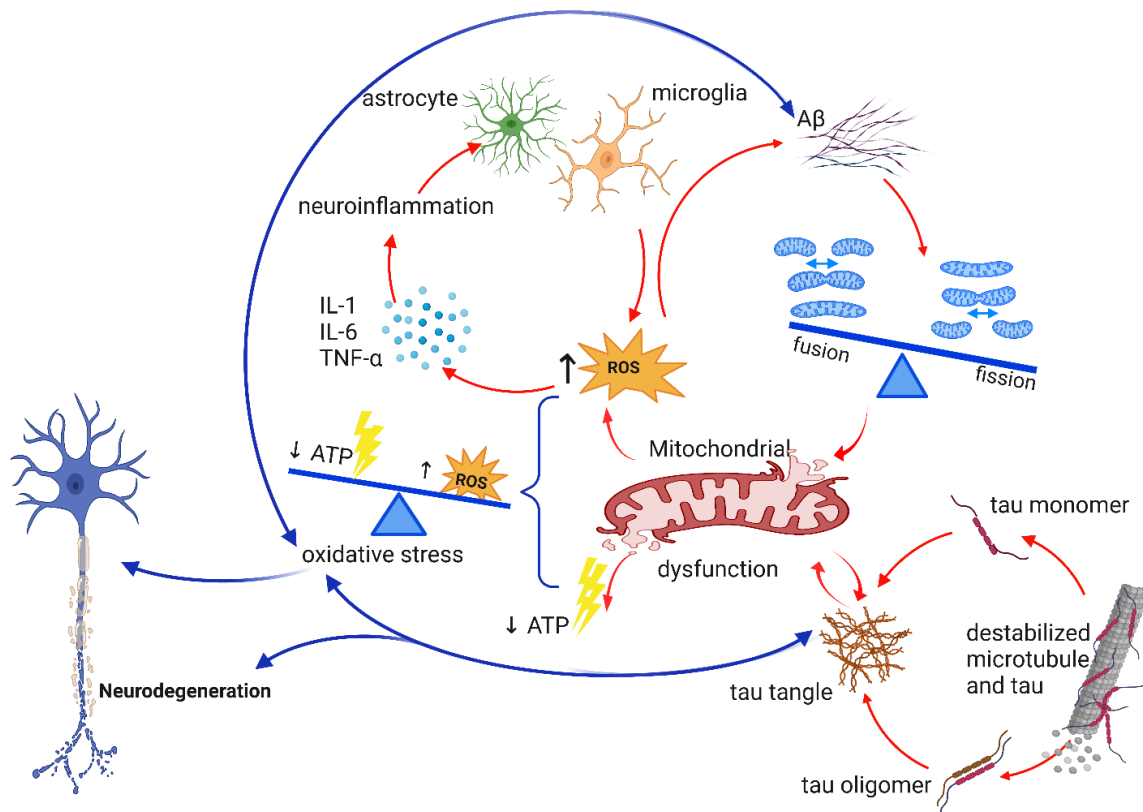


Figure 4. Production of A β alters the equilibrium between mitochondrial fusion and fission, leading to mitochondrial malfunction. Through the generation of ROS, mitochondrial malfunction causes an increase in A β production, starting a vicious cycle. Increased ROS levels increase the production of cytokines, including TNF- α , IL-1, and IL-6, which leads to neuroinflammation. On the other hand, inflammatory responses cause microglia and astrocytes to become highly active and generate high levels of ROS. Tau pathology and growing mitochondrial dysfunction are a vicious loop that affects synaptic and neuronal function. Created with BioRender (BioRender.com).

7. Altered Signaling Pathways in the AD Brain

A pathway found to be altered in AD is the cyclophilin A (CypA)-NF- κ B-matrix-metalloproteinase-9 (MMP-9) pathway. Activation of the CypA-NF κ B-MMP-9 pathway in pericytes of APOE4 mouse models may cause BBB tight junction and basement membrane protein degradation, inducing BBB disruption [117,545–547]. Additionally, diverse studies indicate that dysfunctional brain insulin signaling, and subsequent glucose metabolism disruption, are associated with sporadic AD [116,548]. Glucose uptake and utilization are reduced in the hippocampus, parietotemporal cortex, and/or posterior cingulate cortex in AD subjects [116,117,549]. Decreased levels of glucose transporter 1 (GLUT1) in cerebral microvessels have been found in AD brains. Glut1 transports glucose across the BBB from the blood to the brain and maintains brain capillary networks, cerebral blood flow (CBF), and BBB integrity [117].

Brain glucose dyshomeostasis may occur several years before the beginning of symptoms. Increased plasma fasting glucose is associated with elevated concentrations of brain tissue glucose, which is linked with severe A β plaque deposition and neurofibrillary pathology in brain areas susceptible to AD pathology [550]. However, rate-controlling glycolysis enzymes (hexokinase, phosphofructokinase, and pyruvate kinase) activity was found to be reduced in the inferior temporal gyrus and the middle frontal gyrus of AD patients, and was associated with acute neurofibrillary and amyloid pathology. All these observations suggest that regionally specific abnormalities in glycolytic flux may result in brain glucose accumulation and AD development [116,550]. Alterations in brain glucose concentration in

AD may be explained by the low protein levels of GLUT3, a neuronal glucose transporter, which are associated with increased neuritic plaque and neurofibrillary tangle pathology, possibly during the early stages of AD development [550–552].

Insulin resistance plays an important role in promoting cognitive dysfunction, and affects AD pathogenesis [553–556]. Postmortem brains show increased serine phosphorylation of IRS-1 and JNK expression with A β colocalization. A β oligomers and a high-fat diet stimulate the JNK phosphorylation in the hippocampal neurons, leading to insulin signaling downregulation [557,558]. Despite the risk factor of insulin resistance for AD development, it may also aggravate AD pathology. Insulin affects A β metabolism, and A β interferes with insulin binding to its receptor. Additionally, peripheral insulin resistance was found to be associated with low hippocampal glucose metabolism and low gray matter volume. Moreover, insulin resistance may be aggravated in AD due to chronic inflammation [116,559–561].

Studies have associated NLRP3 inflammasome activation with NFT formation and A β deposits in AD pathology [15,562]. NLRP3 activation induces IL-1 β production, promotes microglial synthesis, and releases proinflammatory cytokines and neurotoxic factors. However, an enhanced NLRP3 signaling pathway may induce elevated tau hyperphosphorylation, neurofibrillary tangle formation, synaptic dysfunction, and neuroinflammation [16,116,562]. Animal studies showed that the administration of an NLRP3 inhibitor improved cognitive impairment and hyperactive behavior by reducing A β deposition via increasing the microglia's ability to clear A β deposits [16,563]. Therefore, the association of NLRP3 and AD pathology can be explained as an endless loop [116].

Another pathway compromised in AD pathology is the glutathione (GSH) pathway, which promotes lipid peroxidation, which induces ferroptosis. GSH and glutathione peroxidase (GPx) expression are downregulated in the frontal cortex and hippocampus and correlate with the impairment's severity [6,564–566].

Another pathway found to be altered in AD is the ceramide pathway. Ceramides act as bioactive lipids, important regulators of synaptic function, and can affect the production of A β and tau phosphorylation. Elevated levels of ceramides were discovered in AD brains, suggesting the early implication of lipid metabolism in AD. Increased ceramide levels stimulate ROS generation, leading to neuronal death [567–569]. Enhanced levels of ceramides increase the levels of A β by stabilizing β -secretase, while A β induces an increase in ceramide levels by activating sphingomyelinases, which catabolize sphingomyelin into ceramide [567]. Moreover, studies found increased sphingomyelin levels in the CSF of prodromal AD patients [570–573]. An increased sphingomyelin/ceramides ratio can be a potential blood-based marker of AD progression. Elevated levels of ceramide are linked to JNK activation, which mediates cell death in AD. Ceramides decrease the phosphorylation of ERKs and MEKs, trigger JNK and p38 MAPK cascades, and induce neuronal death through the activation of caspase-3 and upregulation of c-jun, c-fos, and p53 [567,574–576].

Another pathway altered in AD is the Akt pathway. PI3k-Akt activation can protect against neuronal death in AD [577,578]. In a previous study, increased levels of active phosphorylated Akt were discovered in particulate fractions, with decreased Akt levels in cytosolic fractions of AD temporal cortex neurons, leading to increased activation of Akt in AD progression. Moreover, decreased levels of the Akt target p27^{kip1} and elevated phosphorylation levels of Akt substrates (GSK3 β ^{Ser9}, tau^{Ser214}, mTOR^{Ser244B}) were detected. Furthermore, a loss and altered distribution of the major Akt- negative regulator PTEN were observed in AD neurons [579]. S-nitrosylation may inactivate PTEN in AD and explain the loss of PTEN. PTEN regulates neuronal development and survival, axonal regeneration, and synaptic plasticity in the CNS [580–583]. Neurons containing phosphorylated Akt and PTEN were depleted in hippocampal CA1 at the end stages of AD [579]. Moreover, PTEN accumulates in intracellular fibrillary tangles and co-localizes with tau and senile plaques [583].

8. Mathematical Models of AD Progression

Many mathematical models of the pathophysiology of AD have been developed during the past few decades. The majority of studies concentrate on the aggregation of the A β . Numerous models have been presented to investigate the spread of prion proteins [2,584–587]. For proper operation, a protein must appropriately fold into a suitable three-dimensional (3D) shape. Aggregates generated by misfolded proteins can occasionally form, and are extremely toxic to normal healthy cells. A clump of particular proteins has been associated with a variety of illnesses, including AD. The two proteins that combine to create protein aggregates in the brains of AD patients are A β and tau. According to Heller, these A β and tau aggregates hinder common brain activities [588]. Synthetic A β oligomers attach to cellular prion protein (PrPC). The spatial learning and memory of AD transgenic mice with intact PrPC expression are impaired. It has been claimed that PrPC-deficient AD transgenic mice accumulate A β but, nevertheless, exhibit normal survival and no decline in spatial learning and memory [589].

8.1. Deterministic Mathematical Models

Mathematical models of A β aggregation have been previously developed. There are some deterministic mathematical approaches to studying AD [2,585–587]. An elaborate kinetic model has been created that quantitatively explains the kinetics of A β self-association from the unfolded state. Nonlinear regression was used to fit the model to the experimental data and identify the parameters. The model incorporated data on changes in both the distribution of mass and the length of the protein aggregates. It took into account the co-existence of different species of the protein, including monomers, dimers, and larger aggregates. The model also provided mechanisms for the generation and elongation of the fibrils, while explicitly accounting for the filaments and fibrils themselves. As a result, the model was able to accurately represent the key features of the experimental data and provide a detailed and comprehensive quantitative description of the kinetics of the protein aggregates [586]. A compartmental mathematical model has been created to track the accumulation of A β protein in the brain, CSF, and plasma during AD. The analysis showed that the total A β burden in the brain is influenced by a dimensionless quantity known as the polymerization ratio, which is equal to the product of production and elongation rates divided by the product of fragmentation and loss rates. The finding suggests that the A β levels in all three compartments are likely going to decrease when production inhibitors are used. The presentation of straightforward formulae and numerical findings offers some insights into system behavior, which may be utilized to determine important transport, production, and clearance parameters as new clinical data become available [587]. Helal et al. [2] presented a mathematical model for the development of AD that utilizes differential equations to explain the dynamic production of A β plaques depending on concentrations of A β oligomers, PrPC proteins, and the A β -x-PrPC complex that is believed to create synaptic toxicity. The model of AD evolution is based on the idea that A β oligomers can exist bound and unbound to PrPC proteins. Dayeh et al. [585] presented a model that described a strategy to lessen the formation of oligomers, and created a discrete mathematical model for the accumulation of monomers into oligomers. This hypothesis is based on the idea that soluble oligomers are what cause AD. Following that, a stability analysis establishes the aggregation condition. For the purpose of creating oligomers, a formula for the necessary number of monomers is given.

8.2. Stochastic Mathematical Models and Potential Development of the Models for T Cells in AD

The deterministic models did not take into account the involvement of random factors. The neurobiological environment and the transfer of its signals are more random than deterministic, incorporating a variety of random elements. For instance, in the same environment, various cells and infectious virus reactions can produce various outcomes. Hu et al. [590–592] studied a stochastic AD model that took the effects of prions into account for the first time. They investigated the peculiar ergodic stationary distribution of

the model to understand how AD progresses, and discovered that the system has a unique ergodic stationary distribution under weak conditions. This suggests that AD will likely continue after a person develops it. Later on, Li et al. [584] presented an AD model that takes into account two forms of A β , the interaction of oligomers with Prpc, and the use of anti-A β medications. The existence, singularity, and non-negativity of the solutions were examined. Additionally, it has been demonstrated that the model has a single globally asymptotically stable equilibrium, indicating that the medicine cannot totally cure AD. Finally, some numerical simulations have been provided, and the relative contributions to AD of the two forms of A β , A β_{40} and A β_{42} , have been explored.

None of the earlier mathematical models took the development of AD in connection to the role of T cells into consideration. However, there are certain mathematical models that could be constructed for AD as an autoimmune illness. These studies used a set of ordinary differential equations (ODE) to describe CD4⁺ helper T cells' immune responses in the existence of Tregs. In addition to formulas for the concentration of T cells, the concentration of Tregs, and antigenic stimulation of T cells, the equilibria of the corresponding ODE systems were also determined. This model, which uses two T cell clonotypes, was used to investigate how bystander T cell proliferation contributes to the development of autoimmune responses and the prevention of autoimmune disease. Hysteresis, which was apparent for the parameter values, also suggests that severe immune suppression may be needed for the therapy of autoimmunity. If this is the case, the system may not enter the managed steady state's basin of attraction as a result of this treatment [354,593–595].

9. Conclusions

Millions of people worldwide suffer from AD, a neurological condition for which there are no effective treatments available. While estimates vary, experts believe that over 6 million Americans, the majority of whom are aged 65 or older, may have dementia brought on by AD. Researchers are still working to understand the complex brain alterations that occur in AD, which can begin years or even decades before symptoms appear. While there is no cure for AD at present, a deeper understanding of these changes may lead to the development of effective treatments. Common modifications observed in AD include A β aggregation, NFTs, BBB alteration, neuroinflammation, impaired metal ion homeostasis, mitochondrial dysfunction, oxidative stress, disruption of normal glial function, synaptic and neuronal loss, metal ion imbalance, genetic risk factors, cholinergic neuronal degeneration, and the immune system. These modifications, along with mathematical models of AD, shed important light on diverse strategies that can be used to combat AD pathology.

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Abbreviations

Alzheimer's disease, AD; amyloid beta, A β ; blood–brain barrier, BBB; antigen-presenting cells, APC; apolipoprotein-E, ApoE; neurofibrillary tangles, NFTs; late-onset AD, LOAD; amyloid precursor protein, APP; P-glycoprotein, P-gp; NO synthase, NOS; central nervous system, CNS; cerebrospinal fluid, CSF; the translocator protein, TSPO; C-reactive protein, CRP; Western diet, WD; type 2 diabetes mellitus, T2DM; tetrahydroaminoacridine, THA; Food and Drug Administration, FDA; basal forebrain cholinergic neurons, BFCN; nerve growth factor, NGF; glial fibrillary acidic protein, GFAP; Toll-like receptors, TLR; fibrillar-amyloid, fA; immunoglobulins, Igs; immunoglobulin M, IgM; regulatory T cells, Tregs; interleukin, IL; interferon- γ , IFN- γ ; Presenilin 1, PSEN1; Presenilin 2, PSEN2;

β -APP-site cleaving enzyme, BACE; β -secretase-derived C-terminal fragment, CTF β ; APP intracellular domain, AICD; cysteine, Cys; arginine, Arg; genome-wide association studies, GWAS; Clusterin, CLU; mesenchyme homeobox gene 2, *MEOX2*; mild cognitive impairment, MCI; electron transport chain, ETC; copper, Cu; zinc, Zn; selenium, Se; glutathione peroxidase 4, GPx4; adenosine triphosphate, ATP; cytochrome oxidase, COX; pyruvate dehydrogenase complex, PDHC; ketoglutarate dehydrogenase complex, KGDHC; nuclear DNA, nDNA; mitochondrial DNA, mtDNA; 8-Hydroxy-2-deoxyguanosine, 8-OHdG; advanced glycation end products, AGEs; coenzyme Q10, CoQ10; oxidative phosphorylation system, OXPHOS; glucose transporter 1, GLUT1; glutathione, GSH; glutathione peroxidase, GPx; cerebral blood flow, CBF; three-dimensional, 3D; ordinary differential equations, ODE.

References

- Baulch, J.E.; Acharya, M.M.; Agrawal, S.; Apodaca, L.A.; Monteiro, C.; Agrawal, A. Immune and Inflammatory Determinants Underlying Alzheimer's Disease Pathology. *J. Neuroimmune Pharmacol.* **2020**, *15*, 852–862. [[CrossRef](#)] [[PubMed](#)]
- Helal, M.; Hingant, E.; Pujol-Menjouet, L.; Webb, G.F. Alzheimer's disease: Analysis of a mathematical model incorporating the role of prions. *J. Math. Biol.* **2014**, *69*, 1207–1235. [[CrossRef](#)] [[PubMed](#)]
- Chakraborty, A.; de Wit, N.M.; van der Flier, W.M.; de Vries, H.E. The blood brain barrier in Alzheimer's disease. *Vascul. Pharmacol.* **2017**, *89*, 12–18. [[CrossRef](#)]
- Chen, X.Q.; Mobley, W.C. Alzheimer Disease Pathogenesis: Insights From Molecular and Cellular Biology Studies of Oligomeric Abeta and Tau Species. *Front. Neurosci.* **2019**, *13*, 659. [[CrossRef](#)] [[PubMed](#)]
- Blair, L.J.; Frauen, H.D.; Zhang, B.; Nordhues, B.A.; Bijan, S.; Lin, Y.C.; Zamudio, F.; Hernandez, L.D.; Sabbagh, J.J.; Selenica, M.L.; et al. Tau depletion prevents progressive blood-brain barrier damage in a mouse model of tauopathy. *Acta Neuropathol. Commun.* **2015**, *3*, 8. [[CrossRef](#)] [[PubMed](#)]
- Lei, P.; Ayton, S.; Bush, A.I. The essential elements of Alzheimer's disease. *J. Biol. Chem.* **2021**, *296*, 100105. [[CrossRef](#)]
- Wang, X.; Su, B.; Zheng, L.; Perry, G.; Smith, M.A.; Zhu, X. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. *J. Neurochem.* **2009**, *109* (Suppl. 1), 153–159. [[CrossRef](#)]
- Guo, T.; Zhang, D.; Zeng, Y.; Huang, T.Y.; Xu, H.; Zhao, Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Mol. Neurodegener.* **2020**, *15*, 40. [[CrossRef](#)]
- Togo, T.; Akiyama, H.; Iseki, E.; Kondo, H.; Ikeda, K.; Kato, M.; Oda, T.; Tsuchiya, K.; Kosaka, K. Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. *J. Neuroimmunol.* **2002**, *124*, 83–92. [[CrossRef](#)]
- Kovac, A.; Zilkova, M.; Deli, M.A.; Zilka, N.; Novak, M. Human truncated tau is using a different mechanism from amyloid-beta to damage the blood-brain barrier. *J. Alzheimers Dis.* **2009**, *18*, 897–906. [[CrossRef](#)]
- Mooradian, A.D. Effect of aging on the blood-brain barrier. *Neurobiol. Aging* **1988**, *9*, 31–39. [[CrossRef](#)] [[PubMed](#)]
- Owens, T.; Renno, T.; Taupin, V.; Krakowski, M. Inflammatory cytokines in the brain: Does the CNS shape immune responses? *Immunol. Today* **1994**, *15*, 566–571. [[CrossRef](#)] [[PubMed](#)]
- McManus, R.M.; Mills, K.H.; Lynch, M.A. T Cells—Protective or Pathogenic in Alzheimer's Disease? *J. Neuroimmune Pharmacol.* **2015**, *10*, 547–560. [[CrossRef](#)]
- McManus, R.M. The Role of Immunity in Alzheimer's Disease. *Adv. Biol.* **2022**, *6*, e2101166. [[CrossRef](#)] [[PubMed](#)]
- Ising, C.; Venegas, C.; Zhang, S.; Scheiblich, H.; Schmidt, S.V.; Vieira-Saecker, A.; Schwartz, S.; Albasset, S.; McManus, R.M.; Tejera, D.; et al. NLRP3 inflammasome activation drives tau pathology. *Nature* **2019**, *575*, 669–673. [[CrossRef](#)] [[PubMed](#)]
- Heneka, M.T.; Kummer, M.P.; Stutz, A.; Delekate, A.; Schwartz, S.; Vieira-Saecker, A.; Griep, A.; Axt, D.; Remus, A.; Tzeng, T.C.; et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* **2013**, *493*, 674–678. [[CrossRef](#)]
- Bhat, A.H.; Dar, K.B.; Anees, S.; Zargar, M.A.; Masood, A.; Sofi, M.A.; Ganie, S.A. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. *Biomed. Pharmacother.* **2015**, *74*, 101–110. [[CrossRef](#)]
- Cheignon, C.; Tomas, M.; Bonnefont-Rousselot, D.; Faller, P.; Hureau, C.; Collin, F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol.* **2018**, *14*, 450–464. [[CrossRef](#)]
- Tong, Y.; Zhou, W.; Fung, V.; Christensen, M.A.; Qing, H.; Sun, X.; Song, W. Oxidative stress potentiates BACE1 gene expression and Abeta generation. *J. Neural Transm.* **2005**, *112*, 455–469. [[CrossRef](#)]
- Zhao, Y.; Zhao, B. Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxidative Med. Cell. Longev.* **2013**, *2013*, 316523. [[CrossRef](#)]
- Wang, X.; Wang, W.; Li, L.; Perry, G.; Lee, H.G.; Zhu, X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim. Biophys. Acta* **2014**, *1842*, 1240–1247. [[CrossRef](#)] [[PubMed](#)]
- Dujardin, P.; Vandenbroucke, R.E.; Van Hoecke, L. Fighting fire with fire: The immune system might be key in our fight against Alzheimer's disease. *Drug Discov. Today* **2022**, *27*, 1261–1283. [[CrossRef](#)] [[PubMed](#)]
- Shi, Y.; Holtzman, D.M. Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight. *Nat. Rev. Immunol.* **2018**, *18*, 759–772. [[CrossRef](#)] [[PubMed](#)]

24. Wang, L.; Yin, Y.L.; Liu, X.Z.; Shen, P.; Zheng, Y.G.; Lan, X.R.; Lu, C.B.; Wang, J.Z. Current understanding of metal ions in the pathogenesis of Alzheimer's disease. *Transl. Neurodegener.* **2020**, *9*, 10. [[CrossRef](#)] [[PubMed](#)]
25. Gulisano, W.; Maugeri, D.; Baltrons, M.A.; Fa, M.; Amato, A.; Palmeri, A.; D'Adamio, L.; Grassi, C.; Devanand, D.P.; Honig, L.S.; et al. Role of Amyloid-beta and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. *J. Alzheimers Dis.* **2018**, *64*, S611–S631. [[CrossRef](#)]
26. Chai, A.B.; Leung, G.K.F.; Callaghan, R.; Gelissen, I.C. P-glycoprotein: A role in the export of amyloid-beta in Alzheimer's disease? *FEBS J.* **2020**, *287*, 612–625. [[CrossRef](#)]
27. Bateman, R.J.; Munsell, L.Y.; Morris, J.C.; Swarm, R.; Yarasheski, K.E.; Holtzman, D.M. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nat. Med.* **2006**, *12*, 856–861. [[CrossRef](#)]
28. Mawuenyega, K.G.; Sigurdson, W.; Ovod, V.; Munsell, L.; Kasten, T.; Morris, J.C.; Yarasheski, K.E.; Bateman, R.J. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* **2010**, *330*, 1774. [[CrossRef](#)]
29. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune attack: The role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **2015**, *16*, 358–372. [[CrossRef](#)]
30. Reddy, P.H. Amyloid beta, mitochondrial structural and functional dynamics in Alzheimer's disease. *Exp. Neurol.* **2009**, *218*, 286–292. [[CrossRef](#)]
31. Manczak, M.; Anekonda, T.S.; Henson, E.; Park, B.S.; Quinn, J.; Reddy, P.H. Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression. *Hum. Mol. Genet.* **2006**, *15*, 1437–1449. [[CrossRef](#)] [[PubMed](#)]
32. Devi, L.; Prabhu, B.M.; Galati, D.F.; Avadhani, N.G.; Anandatheerthavarada, H.K. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. *J. Neurosci.* **2006**, *26*, 9057–9068. [[CrossRef](#)]
33. Sanz-Blasco, S.; Valero, R.A.; Rodriguez-Crespo, I.; Villalobos, C.; Nunez, L. Mitochondrial Ca²⁺ overload underlies Abeta oligomers neurotoxicity providing an unexpected mechanism of neuroprotection by NSAIDs. *PLoS ONE* **2008**, *3*, e2718. [[CrossRef](#)] [[PubMed](#)]
34. Nunez, L.; Senovilla, L.; Sanz-Blasco, S.; Chamero, P.; Alonso, M.T.; Villalobos, C.; Garcia-Sancho, J. Bioluminescence imaging of mitochondrial Ca²⁺ dynamics in soma and neurites of individual adult mouse sympathetic neurons. *J. Physiol.* **2007**, *580*, 385–395. [[CrossRef](#)]
35. John, A.; Reddy, P.H. Synaptic basis of Alzheimer's disease: Focus on synaptic amyloid beta, P-tau and mitochondria. *Ageing Res. Rev.* **2021**, *65*, 101208. [[CrossRef](#)]
36. Reddy, P.H.; Beal, M.F. Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol. Med.* **2008**, *14*, 45–53. [[CrossRef](#)] [[PubMed](#)]
37. Morley, J.E.; Farr, S.A. The role of amyloid-beta in the regulation of memory. *Biochem. Pharmacol.* **2014**, *88*, 479–485. [[CrossRef](#)] [[PubMed](#)]
38. Vogelgesang, S.; Cascorbi, I.; Schroeder, E.; Pahnke, J.; Kroemer, H.K.; Siegmund, W.; Kunert-Keil, C.; Walker, L.C.; Warzok, R.W. Deposition of Alzheimer's beta-amyloid is inversely correlated with P-glycoprotein expression in the brains of elderly non-demented humans. *Pharmacogenetics* **2002**, *12*, 535–541. [[CrossRef](#)]
39. Cai, Z.; Zhao, B.; Ratka, A. Oxidative stress and beta-amyloid protein in Alzheimer's disease. *Neuromolecular Med.* **2011**, *13*, 223–250. [[CrossRef](#)]
40. Yao, Y.; Chinnici, C.; Tang, H.; Trojanowski, J.Q.; Lee, V.M.; Pratico, D. Brain inflammation and oxidative stress in a transgenic mouse model of Alzheimer-like brain amyloidosis. *J. Neuroinflammation* **2004**, *1*, 21. [[CrossRef](#)]
41. Atamna, H.; Frey, W.H., 2nd; Ko, N. Human and rodent amyloid-beta peptides differentially bind heme: Relevance to the human susceptibility to Alzheimer's disease. *Arch. Biochem. Biophys.* **2009**, *487*, 59–65. [[CrossRef](#)] [[PubMed](#)]
42. Atamna, H.; Boyle, K. Amyloid-beta peptide binds with heme to form a peroxidase: Relationship to the cytopathologies of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 3381–3386. [[CrossRef](#)] [[PubMed](#)]
43. Atamna, H.; Killilea, D.W.; Killilea, A.N.; Ames, B.N. Heme deficiency may be a factor in the mitochondrial and neuronal decay of aging. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 14807–14812. [[CrossRef](#)] [[PubMed](#)]
44. Atamna, H.; Liu, J.; Ames, B.N. Heme deficiency selectively interrupts assembly of mitochondrial complex IV in human fibroblasts: Relevance to aging. *J. Biol. Chem.* **2001**, *276*, 48410–48416. [[CrossRef](#)] [[PubMed](#)]
45. Gotz, J.; Streffer, J.R.; David, D.; Schild, A.; Hoernndli, F.; Pennanen, L.; Kurosinski, P.; Chen, F. Transgenic animal models of Alzheimer's disease and related disorders: Histopathology, behavior and therapy. *Mol. Psychiatry* **2004**, *9*, 664–683. [[CrossRef](#)]
46. Ittner, L.M.; Gotz, J. Amyloid-beta and tau—a toxic pas de deux in Alzheimer's disease. *Nat. Rev. Neurosci.* **2011**, *12*, 65–72. [[CrossRef](#)]
47. Wang, W.; Zhao, F.; Ma, X.; Perry, G.; Zhu, X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: Recent advances. *Mol. Neurodegener.* **2020**, *15*, 30. [[CrossRef](#)]
48. Miao, J.; Shi, R.; Li, L.; Chen, F.; Zhou, Y.; Tung, Y.C.; Hu, W.; Gong, C.X.; Iqbal, K.; Liu, F. Pathological Tau From Alzheimer's Brain Induces Site-Specific Hyperphosphorylation and SDS- and Reducing Agent-Resistant Aggregation of Tau in vivo. *Front. Aging Neurosci.* **2019**, *11*, 34. [[CrossRef](#)]
49. Brion, J.P. Neurofibrillary tangles and Alzheimer's disease. *Eur. Neurol.* **1998**, *40*, 130–140. [[CrossRef](#)]

50. Rawat, P.; Sehar, U.; Bisht, J.; Selman, A.; Culberson, J.; Reddy, P.H. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. *Int. J. Mol. Sci.* **2022**, *23*, 12841. [[CrossRef](#)]
51. Eckert, A.; Schmitt, K.; Gotz, J. Mitochondrial dysfunction—The beginning of the end in Alzheimer's disease? Separate and synergistic modes of tau and amyloid-beta toxicity. *Alzheimers Res. Ther.* **2011**, *3*, 15. [[CrossRef](#)] [[PubMed](#)]
52. Alonso, A.D.; Zaidi, T.; Novak, M.; Barra, H.S.; Grundke-Iqbal, I.; Iqbal, K. Interaction of tau isoforms with Alzheimer's disease abnormally hyperphosphorylated tau and in vitro phosphorylation into the disease-like protein. *J. Biol. Chem.* **2001**, *276*, 37967–37973. [[CrossRef](#)] [[PubMed](#)]
53. Brion, J.P.; Anderton, B.H.; Authélet, M.; Dayanandan, R.; Leroy, K.; Lovestone, S.; Octave, J.N.; Pradier, L.; Touchet, N.; Tremp, G. Neurofibrillary tangles and tau phosphorylation. *Biochem. Soc. Symp.* **2001**, *67*, 81–88. [[CrossRef](#)]
54. Brion, J.P.; Flament-Durand, J. Distribution and expression of the alpha-tubulin mRNA in the hippocampus and the temporal cortex in Alzheimer's disease. *Pathol. Res. Pract.* **1995**, *191*, 490–498. [[CrossRef](#)] [[PubMed](#)]
55. Baas, P.W.; Rao, A.N.; Matamoros, A.J.; Leo, L. Stability properties of neuronal microtubules. *Cytoskeleton* **2016**, *73*, 442–460. [[CrossRef](#)]
56. Hempen, B.; Brion, J.P. Reduction of acetylated alpha-tubulin immunoreactivity in neurofibrillary tangle-bearing neurons in Alzheimer's disease. *J. Neuropathol. Exp. Neurol.* **1996**, *55*, 964–972. [[CrossRef](#)]
57. Alonso, A.C.; Zaidi, T.; Grundke-Iqbal, I.; Iqbal, K. Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5562–5566. [[CrossRef](#)]
58. Stamer, K.; Vogel, R.; Thies, E.; Mandelkow, E.; Mandelkow, E.M. Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. *J. Cell Biol.* **2002**, *156*, 1051–1063. [[CrossRef](#)]
59. Yoshiyama, Y.; Higuchi, M.; Zhang, B.; Huang, S.M.; Iwata, N.; Saido, T.C.; Maeda, J.; Suhara, T.; Trojanowski, J.Q.; Lee, V.M. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* **2007**, *53*, 337–351. [[CrossRef](#)]
60. Reddy, P.H.; Oliver, D.M. Amyloid Beta and Phosphorylated Tau-Induced Defective Autophagy and Mitophagy in Alzheimer's Disease. *Cells* **2019**, *8*, 488. [[CrossRef](#)]
61. Kuang, H.; Tan, C.Y.; Tian, H.Z.; Liu, L.H.; Yang, M.W.; Hong, F.F.; Yang, S.L. Exploring the bi-directional relationship between autophagy and Alzheimer's disease. *CNS Neurosci. Ther.* **2020**, *26*, 155–166. [[CrossRef](#)] [[PubMed](#)]
62. Calafate, S.; Buist, A.; Miskiewicz, K.; Vijayan, V.; Daneels, G.; de Strooper, B.; de Wit, J.; Verstreken, P.; Moechars, D. Synaptic Contacts Enhance Cell-to-Cell Tau Pathology Propagation. *Cell Rep.* **2015**, *11*, 1176–1183. [[CrossRef](#)]
63. Wu, J.W.; Hussaini, S.A.; Bastille, I.M.; Rodriguez, G.A.; Mrejeru, A.; Rilett, K.; Sanders, D.W.; Cook, C.; Fu, H.; Boonen, R.A.; et al. Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat. Neurosci.* **2016**, *19*, 1085–1092. [[CrossRef](#)] [[PubMed](#)]
64. Rhein, V.; Song, X.; Wiesner, A.; Ittner, L.M.; Baysang, G.; Meier, F.; Ozmen, L.; Bluethmann, H.; Drose, S.; Brandt, U.; et al. Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 20057–20062. [[CrossRef](#)]
65. Vossel, K.A.; Zhang, K.; Brodbeck, J.; Daub, A.C.; Sharma, P.; Finkbeiner, S.; Cui, B.; Mucke, L. Tau reduction prevents Abeta-induced defects in axonal transport. *Science* **2010**, *330*, 198. [[CrossRef](#)]
66. Hauptmann, S.; Scherping, I.; Drose, S.; Brandt, U.; Schulz, K.L.; Jendrach, M.; Leuner, K.; Eckert, A.; Muller, W.E. Mitochondrial dysfunction: An early event in Alzheimer pathology accumulates with age in AD transgenic mice. *Neurobiol. Aging* **2009**, *30*, 1574–1586. [[CrossRef](#)] [[PubMed](#)]
67. Rhein, V.; Baysang, G.; Rao, S.; Meier, F.; Bonert, A.; Muller-Spahn, F.; Eckert, A. Amyloid-beta leads to impaired cellular respiration, energy production and mitochondrial electron chain complex activities in human neuroblastoma cells. *Cell. Mol. Neurobiol.* **2009**, *29*, 1063–1071. [[CrossRef](#)] [[PubMed](#)]
68. Eckert, A.; Schulz, K.L.; Rhein, V.; Gotz, J. Convergence of amyloid-beta and tau pathologies on mitochondria in vivo. *Mol. Neurobiol.* **2010**, *41*, 107–114. [[CrossRef](#)] [[PubMed](#)]
69. Akiyama, H.; Barger, S.; Barnum, S.; Bradt, B.; Bauer, J.; Cole, G.M.; Cooper, N.R.; Eikelenboom, P.; Emmerling, M.; Fiebich, B.L.; et al. Inflammation and Alzheimer's disease. *Neurobiol. Aging* **2000**, *21*, 383–421. [[CrossRef](#)]
70. Heneka, M.T.; Carson, M.J.; El Khoury, J.; Landreth, G.E.; Brosseron, F.; Feinstein, D.L.; Jacobs, A.H.; Wyss-Coray, T.; Vitorica, J.; Ransohoff, R.M.; et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* **2015**, *14*, 388–405. [[CrossRef](#)]
71. Fu, W.Y.; Wang, X.; Ip, N.Y. Targeting Neuroinflammation as a Therapeutic Strategy for Alzheimer's Disease: Mechanisms, Drug Candidates, and New Opportunities. *ACS Chem. Neurosci.* **2019**, *10*, 872–879. [[CrossRef](#)] [[PubMed](#)]
72. Calsolaro, V.; Edison, P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimers Dement.* **2016**, *12*, 719–732. [[CrossRef](#)] [[PubMed](#)]
73. Chaney, A.; Williams, S.R.; Boutin, H. In vivo molecular imaging of neuroinflammation in Alzheimer's disease. *J. Neurochem.* **2019**, *149*, 438–451. [[CrossRef](#)] [[PubMed](#)]
74. Kinney, J.W.; Bemiller, S.M.; Murtishaw, A.S.; Leisgang, A.M.; Salazar, A.M.; Lamb, B.T. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement.* **2018**, *4*, 575–590. [[CrossRef](#)] [[PubMed](#)]
75. Kim, Y.S.; Joh, T.H. Microglia, major player in the brain inflammation: Their roles in the pathogenesis of Parkinson's disease. *Exp. Mol. Med.* **2006**, *38*, 333–347. [[CrossRef](#)]
76. Wieckowska-Gacek, A.; Mietelska-Porowska, A.; Wydrych, M.; Wojda, U. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. *Ageing Res. Rev.* **2021**, *70*, 101397. [[CrossRef](#)]

77. Ozben, T.; Ozben, S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. *Clin. Biochem.* **2019**, *72*, 87–89. [[CrossRef](#)]
78. Sung, P.S.; Lin, P.Y.; Liu, C.H.; Su, H.C.; Tsai, K.J. Neuroinflammation and Neurogenesis in Alzheimer's Disease and Potential Therapeutic Approaches. *Int. J. Mol. Sci.* **2020**, *21*, 701. [[CrossRef](#)]
79. Hao, J.; Guo, Y.; Guo, K.; Yang, Q. Peripheral Inflammatory Biomarkers of Alzheimer's Disease. *J. Alzheimers Dis.* **2022**, *88*, 389–398. [[CrossRef](#)]
80. Blasko, I.; Marx, F.; Steiner, E.; Hartmann, T.; Grubeck-Loebenstien, B. TNFalpha plus IFNgamma induce the production of Alzheimer beta-amyloid peptides and decrease the secretion of APPs. *FASEB J.* **1999**, *13*, 63–68. [[CrossRef](#)]
81. Blasko, I.; Veerhuis, R.; Stampfer-Kountchev, M.; Saurwein-Teissl, M.; Eikelenboom, P.; Grubeck-Loebenstien, B. Costimulatory effects of interferon-gamma and interleukin-1beta or tumor necrosis factor alpha on the synthesis of Abeta1-40 and Abeta1-42 by human astrocytes. *Neurobiol. Dis.* **2000**, *7*, 682–689. [[CrossRef](#)] [[PubMed](#)]
82. Li, Y.; Liu, L.; Barger, S.W.; Griffin, W.S. Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. *J. Neurosci.* **2003**, *23*, 1605–1611. [[CrossRef](#)] [[PubMed](#)]
83. Parodi-Rullan, R.M.; Javadov, S.; Fossati, S. Dissecting the Crosstalk between Endothelial Mitochondrial Damage, Vascular Inflammation, and Neurodegeneration in Cerebral Amyloid Angiopathy and Alzheimer's Disease. *Cells* **2021**, *10*, 2903. [[CrossRef](#)] [[PubMed](#)]
84. Fiala, M.; Zhang, L.; Gan, X.; Sherry, B.; Taub, D.; Graves, M.C.; Hama, S.; Way, D.; Weinand, M.; Witte, M.; et al. Amyloid-beta induces chemokine secretion and monocyte migration across a human blood-brain barrier model. *Mol. Med.* **1998**, *4*, 480–489. [[CrossRef](#)]
85. Bettcher, B.M.; Fitch, R.; Wynn, M.J.; Lalli, M.A.; Elofson, J.; Jastrzab, L.; Mitic, L.; Miller, Z.A.; Rabinovici, G.D.; Miller, B.L.; et al. MCP-1 and eotaxin-1 selectively and negatively associate with memory in MCI and Alzheimer's disease dementia phenotypes. *Alzheimers Dement.* **2016**, *3*, 91–97. [[CrossRef](#)]
86. Laske, C.; Stellos, K.; Eschweiler, G.W.; Leyhe, T.; Gawaz, M. Decreased CXCL12 (SDF-1) plasma levels in early Alzheimer's disease: A contribution to a deficient hematopoietic brain support? *J. Alzheimers Dis.* **2008**, *15*, 83–95. [[CrossRef](#)]
87. Papadopoulos, V.; Lecanu, L.; Brown, R.C.; Han, Z.; Yao, Z.X. Peripheral-type benzodiazepine receptor in neurosteroid biosynthesis, neuropathology and neurological disorders. *Neuroscience* **2006**, *138*, 749–756. [[CrossRef](#)]
88. Diorio, D.; Welner, S.A.; Butterworth, R.F.; Meaney, M.J.; Suranyi-Cadotte, B.E. Peripheral benzodiazepine binding sites in Alzheimer's disease frontal and temporal cortex. *Neurobiol. Aging* **1991**, *12*, 255–258. [[CrossRef](#)]
89. McGeer, E.G.; Singh, E.A.; McGeer, P.L. Peripheral-type benzodiazepine binding in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **1988**, *2*, 331–336. [[CrossRef](#)]
90. Zhou, R.; Ji, B.; Kong, Y.; Qin, L.; Ren, W.; Guan, Y.; Ni, R. PET Imaging of Neuroinflammation in Alzheimer's Disease. *Front. Immunol.* **2021**, *12*, 739130. [[CrossRef](#)]
91. Chitu, V.; Biundo, F.; Shlager, G.G.L.; Park, E.S.; Wang, P.; Gulinello, M.E.; Gokhan, S.; Ketchum, H.C.; Saha, K.; DeTure, M.A.; et al. Microglial Homeostasis Requires Balanced CSF-1/CSF-2 Receptor Signaling. *Cell Rep.* **2020**, *30*, 3004–3019.e3005. [[CrossRef](#)] [[PubMed](#)]
92. Hu, B.; Duan, S.; Wang, Z.; Li, X.; Zhou, Y.; Zhang, X.; Zhang, Y.W.; Xu, H.; Zheng, H. Insights Into the Role of CSF1R in the Central Nervous System and Neurological Disorders. *Front. Aging Neurosci.* **2021**, *13*, 789834. [[CrossRef](#)]
93. Hoozemans, J.J.; O'Banion, M.K. The role of COX-1 and COX-2 in Alzheimer's disease pathology and the therapeutic potentials of non-steroidal anti-inflammatory drugs. *Curr. Drug Targets CNS Neurol. Disord.* **2005**, *4*, 307–315. [[CrossRef](#)]
94. Solas, M.; Francis, P.T.; Franco, R.; Ramirez, M.J. CB2 receptor and amyloid pathology in frontal cortex of Alzheimer's disease patients. *Neurobiol. Aging* **2013**, *34*, 805–808. [[CrossRef](#)]
95. Basavarajappa, B.S.; Shivakumar, M.; Joshi, V.; Subbanna, S. Endocannabinoid system in neurodegenerative disorders. *J. Neurochem.* **2017**, *142*, 624–648. [[CrossRef](#)]
96. Francistiova, L.; Bianchi, C.; Di Lauro, C.; Sebastian-Serrano, A.; de Diego-Garcia, L.; Kobolak, J.; Dinnyes, A.; Diaz-Hernandez, M. The Role of P2X7 Receptor in Alzheimer's Disease. *Front. Mol. Neurosci.* **2020**, *13*, 94. [[CrossRef](#)]
97. Parvathenani, L.K.; Tertyshnikova, S.; Greco, C.R.; Roberts, S.B.; Robertson, B.; Posmantur, R. P2X7 mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease. *J. Biol. Chem.* **2003**, *278*, 13309–13317. [[CrossRef](#)] [[PubMed](#)]
98. Martin, E.; Amar, M.; Dalle, C.; Youssef, I.; Boucher, C.; Le Duigou, C.; Bruckner, M.; Prigent, A.; Sazdovitch, V.; Halle, A.; et al. New role of P2X7 receptor in an Alzheimer's disease mouse model. *Mol. Psychiatry* **2019**, *24*, 108–125. [[CrossRef](#)] [[PubMed](#)]
99. Mildner, A.; Huang, H.; Radke, J.; Stenzel, W.; Priller, J. P2Y(12) receptor is expressed on human microglia under physiological conditions throughout development and is sensitive to neuroinflammatory diseases. *Glia* **2017**, *65*, 375–387. [[CrossRef](#)]
100. Kenkhuis, B.; Somarakis, A.; Kleindouwel, L.R.T.; van Roon-Mom, W.M.C.; Holtt, T.; van der Weerd, L. Co-expression patterns of microglia markers Iba1, TMEM119 and P2RY12 in Alzheimer's disease. *Neurobiol. Dis.* **2022**, *167*, 105684. [[CrossRef](#)]
101. Maeda, J.; Minamihisamatsu, T.; Shimojo, M.; Zhou, X.; Ono, M.; Matsuba, Y.; Ji, B.; Ishii, H.; Ogawa, M.; Akatsu, H.; et al. Distinct microglial response against Alzheimer's amyloid and tau pathologies characterized by P2Y12 receptor. *Brain Commun.* **2021**, *3*, fcab011. [[CrossRef](#)]
102. Zhou, J.; Fonseca, M.I.; Pisalyaput, K.; Tenner, A.J. Complement C3 and C4 expression in C1q sufficient and deficient mouse models of Alzheimer's disease. *J. Neurochem.* **2008**, *106*, 2080–2092. [[CrossRef](#)] [[PubMed](#)]

103. Daborg, J.; Andreasson, U.; Pekna, M.; Lautner, R.; Hanse, E.; Minthon, L.; Blennow, K.; Hansson, O.; Zetterberg, H. Cerebrospinal fluid levels of complement proteins C3, C4 and CR1 in Alzheimer's disease. *J. Neural Transm.* **2012**, *119*, 789–797. [[CrossRef](#)] [[PubMed](#)]
104. Bi, B.T.; Lin, H.B.; Cheng, Y.F.; Zhou, H.; Lin, T.; Zhang, M.Z.; Li, T.J.; Xu, J.P. Promotion of beta-amyloid production by C-reactive protein and its implications in the early pathogenesis of Alzheimer's disease. *Neurochem. Int.* **2012**, *60*, 257–266. [[CrossRef](#)]
105. Zaciragic, A.; Lepara, O.; Valjevac, A.; Arslanagic, S.; Fajkic, A.; Hadzovic-Dzuvo, A.; Avdagic, N.; Alajbegovic, A.; Mehmedika-Suljic, E.; Coric, G. Elevated serum C-reactive protein concentration in Bosnian patients with probable Alzheimer's disease. *J. Alzheimers Dis.* **2007**, *12*, 151–156. [[CrossRef](#)]
106. Gong, C.; Wei, D.; Wang, Y.; Ma, J.; Yuan, C.; Zhang, W.; Yu, G.; Zhao, Y. A Meta-Analysis of C-Reactive Protein in Patients With Alzheimer's Disease. *Am. J. Alzheimers Dis. Other Dement.* **2016**, *31*, 194–200. [[CrossRef](#)]
107. Hoscheidt, S.; Sanderlin, A.H.; Baker, L.D.; Jung, Y.; Lockhart, S.; Kellar, D.; Whitlow, C.T.; Hanson, A.J.; Friedman, S.; Register, T.; et al. Mediterranean and Western diet effects on Alzheimer's disease biomarkers, cerebral perfusion, and cognition in mid-life: A randomized trial. *Alzheimers Dement.* **2022**, *18*, 457–468. [[CrossRef](#)]
108. Lin, B.; Hasegawa, Y.; Takane, K.; Koibuchi, N.; Cao, C.; Kim-Mitsuyama, S. High-Fat-Diet Intake Enhances Cerebral Amyloid Angiopathy and Cognitive Impairment in a Mouse Model of Alzheimer's Disease, Independently of Metabolic Disorders. *J. Am. Heart Assoc.* **2016**, *5*, e003154. [[CrossRef](#)] [[PubMed](#)]
109. Zhou, M.M.; Ding, L.; Wen, M.; Che, H.X.; Huang, J.Q.; Zhang, T.T.; Xue, C.H.; Mao, X.Z.; Wang, Y.M. Mechanisms of DHA-enriched phospholipids in improving cognitive deficits in aged SAMP8 mice with high-fat diet. *J. Nutr. Biochem.* **2018**, *59*, 64–75. [[CrossRef](#)] [[PubMed](#)]
110. Walker, J.M.; Dixit, S.; Saulsberry, A.C.; May, J.M.; Harrison, F.E. Reversal of high fat diet-induced obesity improves glucose tolerance, inflammatory response, beta-amyloid accumulation and cognitive decline in the APP/PSEN1 mouse model of Alzheimer's disease. *Neurobiol. Dis.* **2017**, *100*, 87–98. [[CrossRef](#)]
111. Wen, J.; Wang, Y.; Wang, C.; Yuan, M.; Chen, F.; Zou, Q.; Cai, Z.; Zhao, B. Dietary High-Fat Promotes Cognitive Impairment by Suppressing Mitophagy. *Oxidative Med. Cell. Longev.* **2023**, *2023*, 4822767. [[CrossRef](#)]
112. Martin, S.A.; Jameson, C.H.; Allan, S.M.; Lawrence, C.B. Maternal high-fat diet worsens memory deficits in the triple-transgenic (3xTgAD) mouse model of Alzheimer's disease. *PLoS ONE* **2014**, *9*, e99226. [[CrossRef](#)] [[PubMed](#)]
113. Graham, L.C.; Harder, J.M.; Soto, I.; de Vries, W.N.; John, S.W.; Howell, G.R. Chronic consumption of a western diet induces robust glial activation in aging mice and in a mouse model of Alzheimer's disease. *Sci. Rep.* **2016**, *6*, 21568. [[CrossRef](#)]
114. Nam, K.N.; Mounier, A.; Wolfe, C.M.; Fitz, N.F.; Carter, A.Y.; Castranio, E.L.; Kambh, H.L.; Reeves, V.L.; Wang, J.; Han, X.; et al. Effect of high fat diet on phenotype, brain transcriptome and lipidome in Alzheimer's model mice. *Sci. Rep.* **2017**, *7*, 4307. [[CrossRef](#)]
115. Wieckowska-Gacek, A.; Mietelska-Porowska, A.; Chutoranski, D.; Wydrych, M.; Dlugosz, J.; Wojda, U. Western Diet Induces Impairment of Liver-Brain Axis Accelerating Neuroinflammation and Amyloid Pathology in Alzheimer's Disease. *Front. Aging Neurosci.* **2021**, *13*, 654509. [[CrossRef](#)] [[PubMed](#)]
116. Litwiniuk, A.; Bik, W.; Kalisz, M.; Baranowska-Bik, A. Inflammasome NLRP3 Potentially Links Obesity-Associated Low-Grade Systemic Inflammation and Insulin Resistance with Alzheimer's Disease. *Int. J. Mol. Sci.* **2021**, *22*, 5603. [[CrossRef](#)] [[PubMed](#)]
117. Nelson, A.R.; Sweeney, M.D.; Sagare, A.P.; Zlokovic, B.V. Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochim. Biophys. Acta* **2016**, *1862*, 887–900. [[CrossRef](#)]
118. Baranowski, B.J.; Marko, D.M.; Fenech, R.K.; Yang, A.J.T.; MacPherson, R.E.K. Healthy brain, healthy life: A review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. *Appl. Physiol. Nutr. Metab.* **2020**, *45*, 1055–1065. [[CrossRef](#)]
119. Tabassum, S.; Misrani, A.; Yang, L. Exploiting Common Aspects of Obesity and Alzheimer's Disease. *Front. Hum. Neurosci.* **2020**, *14*, 602360. [[CrossRef](#)]
120. Lee, E.B. Obesity, leptin, and Alzheimer's disease. *Ann. N. Y. Acad. Sci.* **2011**, *1243*, 15–29. [[CrossRef](#)]
121. Terzo, S.; Amato, A.; Mule, F. From obesity to Alzheimer's disease through insulin resistance. *J. Diabetes Complicat.* **2021**, *35*, 108026. [[CrossRef](#)]
122. Gannon, O.J.; Robison, L.S.; Salinero, A.E.; Abi-Ghanem, C.; Mansour, F.M.; Kelly, R.D.; Tyagi, A.; Brawley, R.R.; Ogg, J.D.; Zuloaga, K.L. High-fat diet exacerbates cognitive decline in mouse models of Alzheimer's disease and mixed dementia in a sex-dependent manner. *J. Neuroinflammation* **2022**, *19*, 110. [[CrossRef](#)]
123. Yang, H.; Graham, L.C.; Reagan, A.M.; Grabowska, W.A.; Schott, W.H.; Howell, G.R. Transcriptome profiling of brain myeloid cells revealed activation of Itgal, Trem1, and Spp1 in western diet-induced obesity. *J. Neuroinflammation* **2019**, *16*, 169. [[CrossRef](#)] [[PubMed](#)]
124. Coppin, G.; Nolan-Poupart, S.; Jones-Gotman, M.; Small, D.M. Working memory and reward association learning impairments in obesity. *Neuropsychologia* **2014**, *65*, 146–155. [[CrossRef](#)] [[PubMed](#)]
125. Isaac, V.; Sim, S.; Zheng, H.; Zagorodnov, V.; Tai, E.S.; Chee, M. Adverse Associations between Visceral Adiposity, Brain Structure, and Cognitive Performance in Healthy Elderly. *Front. Aging Neurosci.* **2011**, *3*, 12. [[CrossRef](#)] [[PubMed](#)]
126. Shefer, G.; Marcus, Y.; Stern, N. Is obesity a brain disease? *Neurosci. Biobehav. Rev.* **2013**, *37*, 2489–2503. [[CrossRef](#)]
127. Gomez-Apo, E.; Mondragon-Maya, A.; Ferrari-Diaz, M.; Silva-Pereyra, J. Structural Brain Changes Associated with Overweight and Obesity. *J. Obes.* **2021**, *2021*, 6613385. [[CrossRef](#)]

128. Tanaka, H.; Gourley, D.D.; Dekhtyar, M.; Haley, A.P. Cognition, Brain Structure, and Brain Function in Individuals with Obesity and Related Disorders. *Curr. Obes. Rep.* **2020**, *9*, 544–549. [[CrossRef](#)]
129. Koga, S.; Kojima, A.; Kuwabara, S.; Yoshiyama, Y. Immunohistochemical analysis of tau phosphorylation and astroglial activation with enhanced leptin receptor expression in diet-induced obesity mouse hippocampus. *Neurosci. Lett.* **2014**, *571*, 11–16. [[CrossRef](#)]
130. Puig, K.L.; Floden, A.M.; Adhikari, R.; Golovko, M.Y.; Combs, C.K. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PLoS ONE* **2012**, *7*, e30378. [[CrossRef](#)]
131. Thirumangalakudi, L.; Prakasam, A.; Zhang, R.; Bimonte-Nelson, H.; Sambamurti, K.; Kindy, M.S.; Bhat, N.R. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. *J. Neurochem.* **2008**, *106*, 475–485. [[CrossRef](#)]
132. Heverin, M.; Maioli, S.; Pham, T.; Mateos, L.; Camporesi, E.; Ali, Z.; Winblad, B.; Cedazo-Minguez, A.; Bjorkhem, I. 27-hydroxycholesterol mediates negative effects of dietary cholesterol on cognition in mice. *Behav. Brain Res.* **2015**, *278*, 356–359. [[CrossRef](#)] [[PubMed](#)]
133. Park, S.H.; Kim, J.H.; Choi, K.H.; Jang, Y.J.; Bae, S.S.; Choi, B.T.; Shin, H.K. Hypercholesterolemia accelerates amyloid beta-induced cognitive deficits. *Int. J. Mol. Med.* **2013**, *31*, 577–582. [[CrossRef](#)] [[PubMed](#)]
134. Rutkowski, J.M.; Lee, L.L.; Puchowicz, M.; Golub, M.S.; Befroy, D.E.; Wilson, D.W.; Anderson, S.; Cline, G.; Bini, J.; Borkowski, K.; et al. Reduced cognitive function, increased blood-brain-barrier transport and inflammatory responses, and altered brain metabolites in LDLr^{-/-} and C57BL/6 mice fed a western diet. *PLoS ONE* **2018**, *13*, e0191909. [[CrossRef](#)]
135. de J R De-Paula, V.; Forlenza, A.S.; Forlenza, O.V. Relevance of gutmicrobiota in cognition, behaviour and Alzheimer’s disease. *Pharmacol. Res.* **2018**, *136*, 29–34. [[CrossRef](#)]
136. Giau, V.V.; Wu, S.Y.; Jamerlan, A.; An, S.S.A.; Kim, S.Y.; Hulme, J. Gut Microbiota and Their Neuroinflammatory Implications in Alzheimer’s Disease. *Nutrients* **2018**, *10*, 1765. [[CrossRef](#)] [[PubMed](#)]
137. Tumminia, A.; Vinciguerra, F.; Parisi, M.; Frittitta, L. Type 2 Diabetes Mellitus and Alzheimer’s Disease: Role of Insulin Signalling and Therapeutic Implications. *Int. J. Mol. Sci.* **2018**, *19*, 3306. [[CrossRef](#)]
138. Arnold, S.E.; Arvanitakis, Z.; Macauley-Rambach, S.L.; Koenig, A.M.; Wang, H.Y.; Ahima, R.S.; Craft, S.; Gandy, S.; Buettner, C.; Stoeckel, L.E.; et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. *Nat. Rev. Neurol.* **2018**, *14*, 168–181. [[CrossRef](#)]
139. Hamze, R.; Delangre, E.; Tolu, S.; Moreau, M.; Janel, N.; Bailbe, D.; Movassat, J. Type 2 Diabetes Mellitus and Alzheimer’s Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets. *Int. J. Mol. Sci.* **2022**, *23*, 15287. [[CrossRef](#)]
140. Pakdin, M.; Toutounchian, S.; Namazi, S.; Arabpour, Z.; Pouladi, A.; Afsahi, S.; Poudineh, M.; Nasab, M.M.M.; Yaghoobpoor, S.; Deravi, N. Type 2 Diabetes Mellitus and Alzheimer’s Disease: A Review of the Potential Links. *Curr. Diabetes Rev.* **2022**, *18*, e051121197760. [[CrossRef](#)]
141. Zemva, J.; Schubert, M. Central insulin and insulin-like growth factor-1 signaling: Implications for diabetes associated dementia. *Curr. Diabetes Rev.* **2011**, *7*, 356–366. [[CrossRef](#)] [[PubMed](#)]
142. Marrano, N.; Biondi, G.; Borrelli, A.; Rella, M.; Zambetta, T.; Di Gioia, L.; Caporusso, M.; Logroscino, G.; Perrini, S.; Giorgino, F.; et al. Type 2 Diabetes and Alzheimer’s Disease: The Emerging Role of Cellular Lipotoxicity. *Biomolecules* **2023**, *13*, 183. [[CrossRef](#)]
143. Pruzin, J.J.; Nelson, P.T.; Abner, E.L.; Arvanitakis, Z. Review: Relationship of type 2 diabetes to human brain pathology. *Neuropathol. Appl. Neurobiol.* **2018**, *44*, 347–362. [[CrossRef](#)]
144. Cai, Z.; Qiao, P.F.; Wan, C.Q.; Cai, M.; Zhou, N.K.; Li, Q. Role of Blood-Brain Barrier in Alzheimer’s Disease. *J. Alzheimers Dis.* **2018**, *63*, 1223–1234. [[CrossRef](#)]
145. Li, J.; Li, M.; Ge, Y.; Chen, J.; Ma, J.; Wang, C.; Sun, M.; Wang, L.; Yao, S.; Yao, C. beta-amyloid protein induces mitophagy-dependent ferroptosis through the CD36/PINK/PARKIN pathway leading to blood-brain barrier destruction in Alzheimer’s disease. *Cell Biosci.* **2022**, *12*, 69. [[CrossRef](#)] [[PubMed](#)]
146. del Valle, J.; Duran-Vilaregut, J.; Manich, G.; Pallas, M.; Camins, A.; Vilaplana, J.; Pelegri, C. Cerebral amyloid angiopathy, blood-brain barrier disruption and amyloid accumulation in SAMP8 mice. *Neurodegener. Dis.* **2011**, *8*, 421–429. [[CrossRef](#)] [[PubMed](#)]
147. Cuevas, E.; Rosas-Hernandez, H.; Burks, S.M.; Ramirez-Lee, M.A.; Guzman, A.; Imam, S.Z.; Ali, S.F.; Sarkar, S. Amyloid Beta 25-35 induces blood-brain barrier disruption in vitro. *Metab. Brain Dis.* **2019**, *34*, 1365–1374. [[CrossRef](#)]
148. Yamazaki, Y.; Kanekiyo, T. Blood-Brain Barrier Dysfunction and the Pathogenesis of Alzheimer’s Disease. *Int. J. Mol. Sci.* **2017**, *18*, 1965. [[CrossRef](#)]
149. Ramos-Cejudo, J.; Wisniewski, T.; Marmar, C.; Zetterberg, H.; Blennow, K.; de Leon, M.J.; Fossati, S. Traumatic Brain Injury and Alzheimer’s Disease: The Cerebrovascular Link. *EBioMedicine* **2018**, *28*, 21–30. [[CrossRef](#)]
150. Nation, D.A.; Sweeney, M.D.; Montagne, A.; Sagare, A.P.; D’Orazio, L.M.; Pachicano, M.; Seppehrband, F.; Nelson, A.R.; Buennagel, D.P.; Harrington, M.G.; et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat. Med.* **2019**, *25*, 270–276. [[CrossRef](#)]
151. Kurz, C.; Walker, L.; Rauchmann, B.S.; Perneczky, R. Dysfunction of the blood-brain barrier in Alzheimer’s disease: Evidence from human studies. *Neuropathol. Appl. Neurobiol.* **2022**, *48*, e12782. [[CrossRef](#)] [[PubMed](#)]

152. Zipser, B.D.; Johanson, C.E.; Gonzalez, L.; Berzin, T.M.; Tavares, R.; Hulette, C.M.; Vitek, M.P.; Hovanesian, V.; Stopa, E.G. Microvascular injury and blood-brain barrier leakage in Alzheimer's disease. *Neurobiol. Aging* **2007**, *28*, 977–986. [[CrossRef](#)] [[PubMed](#)]
153. Montagne, A.; Nation, D.A.; Zlokovic, B.V. APOE4 Accelerates Development of Dementia After Stroke: Is There a Role for Cerebrovascular Dysfunction? *Stroke* **2020**, *51*, 699–700. [[CrossRef](#)]
154. Riphagen, J.M.; Ramakers, I.; Freeze, W.M.; Pagen, L.H.G.; Hanseeuw, B.J.; Verbeek, M.M.; Verhey, F.R.J.; Jacobs, H.I.L. Linking APOE-epsilon4, blood-brain barrier dysfunction, and inflammation to Alzheimer's pathology. *Neurobiol. Aging* **2020**, *85*, 96–103. [[CrossRef](#)]
155. Halliday, M.R.; Rege, S.V.; Ma, Q.; Zhao, Z.; Miller, C.A.; Winkler, E.A.; Zlokovic, B.V. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 216–227. [[CrossRef](#)] [[PubMed](#)]
156. Miners, J.S.; Schulz, I.; Love, S. Differing associations between Abeta accumulation, hypoperfusion, blood-brain barrier dysfunction and loss of PDGFRB pericyte marker in the precuneus and parietal white matter in Alzheimer's disease. *J. Cereb. Blood Flow Metab.* **2018**, *38*, 103–115. [[CrossRef](#)] [[PubMed](#)]
157. Cai, Z.; Wan, C.Q.; Liu, Z. Astrocyte and Alzheimer's disease. *J. Neurol.* **2017**, *264*, 2068–2074. [[CrossRef](#)]
158. Yamazaki, Y.; Shinohara, M.; Shinohara, M.; Yamazaki, A.; Murray, M.E.; Liesinger, A.M.; Heckman, M.G.; Lesser, E.R.; Parisi, J.E.; Petersen, R.C.; et al. Selective loss of cortical endothelial tight junction proteins during Alzheimer's disease progression. *Brain* **2019**, *142*, 1077–1092. [[CrossRef](#)] [[PubMed](#)]
159. Mesulam, M.M. Cholinergic circuitry of the human nucleus basalis and its fate in Alzheimer's disease. *J. Comp. Neurol.* **2013**, *521*, 4124–4144. [[CrossRef](#)]
160. Deutsch, J.A. The cholinergic synapse and the site of memory. *Science* **1971**, *174*, 788–794. [[CrossRef](#)]
161. Drachman, D.A.; Leavitt, J. Human memory and the cholinergic system. A relationship to aging? *Arch. Neurol.* **1974**, *30*, 113–121. [[CrossRef](#)]
162. Bonsi, P.; Cuomo, D.; Martella, G.; Madeo, G.; Schirinzi, T.; Puglisi, F.; Ponterio, G.; Pisani, A. Centrality of striatal cholinergic transmission in Basal Ganglia function. *Front. Neuroanat.* **2011**, *5*, 6. [[CrossRef](#)] [[PubMed](#)]
163. Dautan, D.; Hacioglu Bay, H.; Bolam, J.P.; Gerdjikov, T.V.; Mena-Segovia, J. Extrinsic Sources of Cholinergic Innervation of the Striatal Complex: A Whole-Brain Mapping Analysis. *Front. Neuroanat.* **2016**, *10*, 1. [[CrossRef](#)] [[PubMed](#)]
164. Everitt, B.J.; Robbins, T.W. Central cholinergic systems and cognition. *Annu. Rev. Psychol.* **1997**, *48*, 649–684. [[CrossRef](#)]
165. Sarter, M.; Bruno, J.P. Cognitive functions of cortical acetylcholine: Toward a unifying hypothesis. *Brain Res. Rev.* **1997**, *23*, 28–46. [[CrossRef](#)]
166. Aoki, S.; Liu, A.W.; Akamine, Y.; Zucca, A.; Zucca, S.; Wickens, J.R. Cholinergic interneurons in the rat striatum modulate substitution of habits. *Eur. J. Neurosci.* **2018**, *47*, 1194–1205. [[CrossRef](#)]
167. Beccaria, J.P.; Pretell Annan, C.A.; Keifman, E.; Murer, M.G.; Belforte, J.E. Striatal Cholinergic Interneurons Are Required for Contending Strategy Selection While Solving Spatial Navigation Problems. *J. Neurosci.* **2022**, *42*, 1303–1315. [[CrossRef](#)]
168. Okada, K.; Nishizawa, K.; Setogawa, S.; Hashimoto, K.; Kobayashi, K. Task-dependent function of striatal cholinergic interneurons in behavioural flexibility. *Eur. J. Neurosci.* **2018**, *47*, 1174–1183. [[CrossRef](#)] [[PubMed](#)]
169. Decker, A.L.; Duncan, K. Acetylcholine and the complex interdependence of memory and attention. *Curr. Opin. Behav. Sci.* **2020**, *32*, 21–28. [[CrossRef](#)]
170. Howe, W.M.; Gritton, H.J.; Lusk, N.A.; Roberts, E.A.; Hetrick, V.L.; Berke, J.D.; Sarter, M. Acetylcholine Release in Prefrontal Cortex Promotes Gamma Oscillations and Theta-Gamma Coupling during Cue Detection. *J. Neurosci.* **2017**, *37*, 3215–3230. [[CrossRef](#)]
171. Hangya, B.; Ranade, S.P.; Lorenc, M.; Kepecs, A. Central Cholinergic Neurons Are Rapidly Recruited by Reinforcement Feedback. *Cell* **2015**, *162*, 1155–1168. [[CrossRef](#)]
172. Kasanuki, K.; Ferman, T.J.; Murray, M.E.; Heckman, M.G.; Pedraza, O.; Hanna Al-Shaikh, F.S.; Mishima, T.; Diehl, N.N.; van Gerpen, J.A.; Uitti, R.J.; et al. Daytime sleepiness in dementia with Lewy bodies is associated with neuronal depletion of the nucleus basalis of Meynert. *Park. Relat. Disord.* **2018**, *50*, 99–103. [[CrossRef](#)] [[PubMed](#)]
173. Teles-Grilo Ruivo, L.M.; Baker, K.L.; Conway, M.W.; Kinsley, P.J.; Gilmour, G.; Phillips, K.G.; Isaac, J.T.R.; Lowry, J.P.; Mellor, J.R. Coordinated Acetylcholine Release in Prefrontal Cortex and Hippocampus Is Associated with Arousal and Reward on Distinct Timescales. *Cell Rep.* **2017**, *18*, 905–917. [[CrossRef](#)] [[PubMed](#)]
174. Ballinger, E.C.; Ananth, M.; Talmage, D.A.; Role, L.W. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. *Neuron* **2016**, *91*, 1199–1218. [[CrossRef](#)]
175. Bloem, B.; Schoppink, L.; Rotaru, D.C.; Faiz, A.; Hendriks, P.; Mansvelter, H.D.; van de Berg, W.D.; Wouterlood, F.G. Topographic mapping between basal forebrain cholinergic neurons and the medial prefrontal cortex in mice. *J. Neurosci.* **2014**, *34*, 16234–16246. [[CrossRef](#)] [[PubMed](#)]
176. Chandler, D.J.; Lamperski, C.S.; Waterhouse, B.D. Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. *Brain Res.* **2013**, *1522*, 38–58. [[CrossRef](#)]
177. Henny, P.; Jones, B.E. Projections from basal forebrain to prefrontal cortex comprise cholinergic, GABAergic and glutamatergic inputs to pyramidal cells or interneurons. *Eur. J. Neurosci.* **2008**, *27*, 654–670. [[CrossRef](#)]

178. Kondo, H.; Zaborszky, L. Topographic organization of the basal forebrain projections to the perirhinal, postrhinal, and entorhinal cortex in rats. *J. Comp. Neurol.* **2016**, *524*, 2503–2515. [[CrossRef](#)]
179. Mesulam, M.M.; Mufson, E.J.; Levey, A.I.; Wainer, B.H. Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J. Comp. Neurol.* **1983**, *214*, 170–197. [[CrossRef](#)]
180. Schliebs, R.; Arendt, T. The cholinergic system in aging and neuronal degeneration. *Behav. Brain Res.* **2011**, *221*, 555–563. [[CrossRef](#)]
181. Woolf, N.J. Cholinergic systems in mammalian brain and spinal cord. *Prog. Neurobiol.* **1991**, *37*, 475–524. [[CrossRef](#)] [[PubMed](#)]
182. Davies, P.; Maloney, A.J. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* **1976**, *2*, 1403. [[CrossRef](#)] [[PubMed](#)]
183. Coyle, J.T.; Price, D.L.; DeLong, M.R. Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science* **1983**, *219*, 1184–1190. [[CrossRef](#)] [[PubMed](#)]
184. Whitehouse, P.J.; Price, D.L.; Clark, A.W.; Coyle, J.T.; DeLong, M.R. Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann. Neurol.* **1981**, *10*, 122–126. [[CrossRef](#)]
185. Whitehouse, P.J.; Price, D.L.; Struble, R.G.; Clark, A.W.; Coyle, J.T.; Delon, M.R. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. *Science* **1982**, *215*, 1237–1239. [[CrossRef](#)] [[PubMed](#)]
186. Contestabile, A. The history of the cholinergic hypothesis. *Behav. Brain Res.* **2011**, *221*, 334–340. [[CrossRef](#)]
187. Craig, L.A.; Hong, N.S.; McDonald, R.J. Revisiting the cholinergic hypothesis in the development of Alzheimer's disease. *Neurosci. Biobehav. Rev.* **2011**, *35*, 1397–1409. [[CrossRef](#)]
188. Summers, W.K.; Majovski, L.V.; Marsh, G.M.; Tachiki, K.; Kling, A. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. *N. Engl. J. Med.* **1986**, *315*, 1241–1245. [[CrossRef](#)]
189. Bautista-Aguilera, O.M.; Ismaili, L.; Iriepa, I.; Diez-Iriepa, D.; Chabchoub, F.; Marco-Contelles, J.; Perez, M. Tacrines as Therapeutic Agents for Alzheimer's Disease. V. Recent Developments. *Chem. Rec.* **2021**, *21*, 162–174. [[CrossRef](#)]
190. Eckroat, T.J.; Manross, D.L.; Cowan, S.C. Merged Tacrine-Based, Multitarget-Directed Acetylcholinesterase Inhibitors 2015-Present: Synthesis and Biological Activity. *Int. J. Mol. Sci.* **2020**, *21*, 5965. [[CrossRef](#)]
191. Pena-Bautista, C.; Torres-Cuevas, I.; Baquero, M.; Ferrer, I.; Garcia, L.; Vento, M.; Chafer-Pericas, C. Early neurotransmission impairment in non-invasive Alzheimer Disease detection. *Sci. Rep.* **2020**, *10*, 16396. [[CrossRef](#)] [[PubMed](#)]
192. Sharma, K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). *Mol. Med. Rep.* **2019**, *20*, 1479–1487. [[CrossRef](#)] [[PubMed](#)]
193. Stanciu, G.D.; Luca, A.; Rusu, R.N.; Bild, V.; Beschea Chiriac, S.I.; Solcan, C.; Bild, W.; Ababei, D.C. Alzheimer's Disease Pharmacotherapy in Relation to Cholinergic System Involvement. *Biomolecules* **2019**, *10*, 40. [[CrossRef](#)]
194. Bond, M.; Rogers, G.; Peters, J.; Anderson, R.; Hoyle, M.; Miners, A.; Moxham, T.; Davis, S.; Thokala, P.; Wailoo, A.; et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): A systematic review and economic model. *Health Technol. Assess.* **2012**, *16*, 1–470. [[CrossRef](#)]
195. Tricco, A.C.; Ashoor, H.M.; Soobiah, C.; Rios, P.; Veroniki, A.A.; Hamid, J.S.; Ivory, J.D.; Khan, P.A.; Yazdi, F.; Ghassemi, M.; et al. Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis. *J. Am. Geriatr. Soc.* **2018**, *66*, 170–178. [[CrossRef](#)]
196. Tampi, R.R.; Forester, B.P.; Agronin, M. Aducanumab: Evidence from clinical trial data and controversies. *Drugs Context* **2021**, *10*, 2021-7-3. [[CrossRef](#)]
197. Dou, K.X.; Tan, M.S.; Tan, C.C.; Cao, X.P.; Hou, X.H.; Guo, Q.H.; Tan, L.; Mok, V.; Yu, J.T. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: A network meta-analysis of 41 randomized controlled trials. *Alzheimers Res. Ther.* **2018**, *10*, 126. [[CrossRef](#)]
198. Sharma, P.; Tripathi, M.K.; Shrivastava, S.K. Cholinesterase as a Target for Drug Development in Alzheimer's Disease. *Methods Mol. Biol.* **2020**, *2089*, 257–286. [[CrossRef](#)] [[PubMed](#)]
199. Corey-Bloom, J.; Anand, R.; Veach, J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int. J. Geriatr. Psychopharmacol.* **1998**, *1*, 55–65.
200. Kho, J.; Ioannou, A.; Mandal, A.K.J.; Missouriis, C.G. Donepezil induces ventricular arrhythmias by delayed repolarisation. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2021**, *394*, 559–560. [[CrossRef](#)]
201. Weinstock, M. Selectivity of Cholinesterase Inhibition. *CNS Drugs* **1999**, *12*, 307–323. [[CrossRef](#)]
202. Li, Q.; He, S.; Chen, Y.; Feng, F.; Qu, W.; Sun, H. Donepezil-based multi-functional cholinesterase inhibitors for treatment of Alzheimer's disease. *Eur. J. Med. Chem.* **2018**, *158*, 463–477. [[CrossRef](#)] [[PubMed](#)]
203. Reis, J.; Cagide, F.; Valencia, M.E.; Teixeira, J.; Bagetta, D.; Perez, C.; Uriarte, E.; Oliveira, P.J.; Ortuso, F.; Alcaro, S.; et al. Multi-target-directed ligands for Alzheimer's disease: Discovery of chromone-based monoamine oxidase/cholinesterase inhibitors. *Eur. J. Med. Chem.* **2018**, *158*, 781–800. [[CrossRef](#)]
204. Iulita, M.F.; Cuello, A.C. Nerve growth factor metabolic dysfunction in Alzheimer's disease and Down syndrome. *Trends Pharmacol. Sci.* **2014**, *35*, 338–348. [[CrossRef](#)]

205. Fahnstock, M.; Scott, S.A.; Jette, N.; Weingartner, J.A.; Crutcher, K.A. Nerve growth factor mRNA and protein levels measured in the same tissue from normal and Alzheimer's disease parietal cortex. *Brain Res. Mol. Brain Res.* **1996**, *42*, 175–178. [[CrossRef](#)]
206. Bruno, M.A.; Leon, W.C.; Fragoso, G.; Mushynski, W.E.; Almazan, G.; Cuello, A.C. Amyloid beta-induced nerve growth factor dysmetabolism in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **2009**, *68*, 857–869. [[CrossRef](#)] [[PubMed](#)]
207. Cuello, A.C.; Bruno, M.A.; Bell, K.F. NGF-cholinergic dependency in brain aging, MCI and Alzheimer's disease. *Curr. Alzheimer Res.* **2007**, *4*, 351–358. [[CrossRef](#)] [[PubMed](#)]
208. Calissano, P.; Amadoro, G.; Matrone, C.; Ciafre, S.; Marolda, R.; Corsetti, V.; Ciotti, M.T.; Mercanti, D.; Di Luzio, A.; Severini, C.; et al. Does the term 'trophic' actually mean anti-amyloidogenic? The case of NGF. *Cell Death Differ.* **2010**, *17*, 1126–1133. [[CrossRef](#)]
209. Triaca, V.; Calissano, P. Impairment of the nerve growth factor pathway driving amyloid accumulation in cholinergic neurons: The incipit of the Alzheimer's disease story? *Neural Regen. Res.* **2016**, *11*, 1553–1556. [[CrossRef](#)] [[PubMed](#)]
210. Iulita, M.F.; Bistue Millon, M.B.; Pentz, R.; Aguilar, L.F.; Do Carmo, S.; Allard, S.; Michalski, B.; Wilson, E.N.; Ducatenzeiler, A.; Bruno, M.A.; et al. Differential deregulation of NGF and BDNF neurotrophins in a transgenic rat model of Alzheimer's disease. *Neurobiol. Dis.* **2017**, *108*, 307–323. [[CrossRef](#)]
211. Tuszynski, M.H.; Yang, J.H.; Barba, D.; Hoi-Sang, U.; Bakay, R.A.; Pay, M.M.; Masliah, E.; Conner, J.M.; Kobalka, P.; Roy, S.; et al. Nerve Growth Factor Gene Therapy: Activation of Neuronal Responses in Alzheimer Disease. *JAMA Neurol.* **2015**, *72*, 1139–1147. [[CrossRef](#)]
212. Barreto, G.E.; Gonzalez, J.; Torres, Y.; Morales, L. Astrocytic-neuronal crosstalk: Implications for neuroprotection from brain injury. *Neurosci. Res.* **2011**, *71*, 107–113. [[CrossRef](#)] [[PubMed](#)]
213. Casse, F.; Richetin, K.; Toni, N. Astrocytes' Contribution to Adult Neurogenesis in Physiology and Alzheimer's Disease. *Front. Cell. Neurosci.* **2018**, *12*, 432. [[CrossRef](#)]
214. Shan, L.; Zhang, T.; Fan, K.; Cai, W.; Liu, H. Astrocyte-Neuron Signaling in Synaptogenesis. *Front. Cell. Dev. Biol.* **2021**, *9*, 680301. [[CrossRef](#)] [[PubMed](#)]
215. Stogsdill, J.A.; Ramirez, J.; Liu, D.; Kim, Y.H.; Baldwin, K.T.; Enustun, E.; Ejikeme, T.; Ji, R.R.; Eroglu, C. Astrocytic neuroligins control astrocyte morphogenesis and synaptogenesis. *Nature* **2017**, *551*, 192–197. [[CrossRef](#)] [[PubMed](#)]
216. Zamboni, M.; Llorens-Bobadilla, E.; Magnusson, J.P.; Frisen, J. A Widespread Neurogenic Potential of Neocortical Astrocytes Is Induced by Injury. *Cell Stem Cell* **2020**, *27*, 605–617.e605. [[CrossRef](#)]
217. Borst, K.; Dumas, A.A.; Prinz, M. Microglia: Immune and non-immune functions. *Immunity* **2021**, *54*, 2194–2208. [[CrossRef](#)]
218. Schafer, D.P.; Stevens, B. Microglia Function in Central Nervous System Development and Plasticity. *Cold Spring Harb. Perspect. Biol.* **2015**, *7*, a020545. [[CrossRef](#)]
219. Song, W.M.; Colonna, M. The identity and function of microglia in neurodegeneration. *Nat. Immunol.* **2018**, *19*, 1048–1058. [[CrossRef](#)]
220. Xu, Y.; Jin, M.Z.; Yang, Z.Y.; Jin, W.L. Microglia in neurodegenerative diseases. *Neural Regen. Res.* **2021**, *16*, 270–280. [[CrossRef](#)]
221. Akiyoshi, R.; Wake, H.; Kato, D.; Horiuchi, H.; Ono, R.; Ikegami, A.; Haruwaka, K.; Omori, T.; Tachibana, Y.; Moorhouse, A.J.; et al. Microglia Enhance Synapse Activity to Promote Local Network Synchronization. *eNeuro* **2018**, *5*, 1–13. [[CrossRef](#)]
222. Parkhurst, C.N.; Yang, G.; Ninan, I.; Savas, J.N.; Yates, J.R., 3rd; Lafaille, J.J.; Hempstead, B.L.; Littman, D.R.; Gan, W.B. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* **2013**, *155*, 1596–1609. [[CrossRef](#)]
223. Weinhard, L.; di Bartolomei, G.; Bolasco, G.; Machado, P.; Schieber, N.L.; Neniskyte, U.; Exiga, M.; Vadisiute, A.; Raggioli, A.; Schertel, A.; et al. Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. *Nat. Commun.* **2018**, *9*, 1228. [[CrossRef](#)]
224. Hong, S.; Beja-Glasser, V.F.; Nfonoyim, B.M.; Frouin, A.; Li, S.; Ramakrishnan, S.; Merry, K.M.; Shi, Q.; Rosenthal, A.; Barres, B.A.; et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **2016**, *352*, 712–716. [[CrossRef](#)]
225. Paolicelli, R.C.; Bolasco, G.; Pagani, F.; Maggi, L.; Scianni, M.; Panzanelli, P.; Giustetto, M.; Ferreira, T.A.; Guiducci, E.; Dumas, L.; et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* **2011**, *333*, 1456–1458. [[CrossRef](#)] [[PubMed](#)]
226. Wang, C.; Yue, H.; Hu, Z.; Shen, Y.; Ma, J.; Li, J.; Wang, X.D.; Wang, L.; Sun, B.; Shi, P.; et al. Microglia mediate forgetting via complement-dependent synaptic elimination. *Science* **2020**, *367*, 688–694. [[CrossRef](#)] [[PubMed](#)]
227. Duncan, G.J.; Simkins, T.J.; Emery, B. Neuron-Oligodendrocyte Interactions in the Structure and Integrity of Axons. *Front. Cell. Dev. Biol.* **2021**, *9*, 653101. [[CrossRef](#)]
228. Kuhn, S.; Gritti, L.; Crooks, D.; Dombrowski, Y. Oligodendrocytes in Development, Myelin Generation and Beyond. *Cells* **2019**, *8*, 1424. [[CrossRef](#)]
229. Dimou, L.; Gallo, V. NG2-glia and their functions in the central nervous system. *Glia* **2015**, *63*, 1429–1451. [[CrossRef](#)] [[PubMed](#)]
230. Liu, Y.; Aguzzi, A. NG2 glia are required for maintaining microglia homeostatic state. *Glia* **2020**, *68*, 345–355. [[CrossRef](#)]
231. Parolisi, R.; Boda, E. NG2 Glia: Novel Roles beyond Re-/Myelination. *Neuroglia* **2018**, *1*, 151–175. [[CrossRef](#)]
232. Vigano, F.; Dimou, L. The heterogeneous nature of NG2-glia. *Brain Res.* **2016**, *1638*, 129–137. [[CrossRef](#)]
233. Zhang, S.Z.; Wang, Q.Q.; Yang, Q.Q.; Gu, H.Y.; Yin, Y.Q.; Li, Y.D.; Hou, J.C.; Chen, R.; Sun, Q.Q.; Sun, Y.F.; et al. NG2 glia regulate brain innate immunity via TGF-beta2/TGFBR2 axis. *BMC Med.* **2019**, *17*, 204. [[CrossRef](#)] [[PubMed](#)]

234. Kumar, A.; Fontana, I.C.; Nordberg, A. Reactive astrogliosis: A friend or foe in the pathogenesis of Alzheimer's disease. *J. Neurochem.* **2021**, *164*, 309–324. [[CrossRef](#)]
235. Pekny, M.; Pekna, M. Astrocyte reactivity and reactive astrogliosis: Costs and benefits. *Physiol. Rev.* **2014**, *94*, 1077–1098. [[CrossRef](#)] [[PubMed](#)]
236. Serrano-Pozo, A.; Muzikansky, A.; Gomez-Isla, T.; Growdon, J.H.; Betensky, R.A.; Frosch, M.P.; Hyman, B.T. Differential relationships of reactive astrocytes and microglia to fibrillar amyloid deposits in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **2013**, *72*, 462–471. [[CrossRef](#)]
237. Sofroniew, M.V.; Vinters, H.V. Astrocytes: Biology and pathology. *Acta Neuropathol.* **2010**, *119*, 7–35. [[CrossRef](#)] [[PubMed](#)]
238. Beach, T.G.; McGeer, E.G. Lamina-specific arrangement of astrocytic gliosis and senile plaques in Alzheimer's disease visual cortex. *Brain Res.* **1988**, *463*, 357–361. [[CrossRef](#)]
239. Nagele, R.G.; D'Andrea, M.R.; Lee, H.; Venkataraman, V.; Wang, H.Y. Astrocytes accumulate A beta 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res.* **2003**, *971*, 197–209. [[CrossRef](#)]
240. Chatterjee, P.; Pedrini, S.; Stoops, E.; Goozee, K.; Villemagne, V.L.; Asih, P.R.; Verberk, I.M.W.; Dave, P.; Taddei, K.; Sohrabi, H.R.; et al. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. *Transl. Psychiatry* **2021**, *11*, 27. [[CrossRef](#)]
241. Cicognola, C.; Janelidze, S.; Hertzog, J.; Zetterberg, H.; Blennow, K.; Mattsson-Carlsson, N.; Hansson, O. Plasma glial fibrillary acidic protein detects Alzheimer pathology and predicts future conversion to Alzheimer dementia in patients with mild cognitive impairment. *Alzheimers Res. Ther.* **2021**, *13*, 68. [[CrossRef](#)]
242. Viejo, L.; Noori, A.; Merrill, E.; Das, S.; Hyman, B.T.; Serrano-Pozo, A. Systematic review of human post-mortem immunohistochemical studies and bioinformatics analyses unveil the complexity of astrocyte reaction in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* **2022**, *48*, e12753. [[CrossRef](#)] [[PubMed](#)]
243. Choi, S.S.; Lee, H.J.; Lim, I.; Satoh, J.; Kim, S.U. Human astrocytes: Secretome profiles of cytokines and chemokines. *PLoS ONE* **2014**, *9*, e92325. [[CrossRef](#)]
244. Kashon, M.L.; Ross, G.W.; O'Callaghan, J.P.; Miller, D.B.; Petrovitch, H.; Burchfiel, C.M.; Sharp, D.S.; Markesbery, W.R.; Davis, D.G.; Hardman, J.; et al. Associations of cortical astrogliosis with cognitive performance and dementia status. *J. Alzheimers Dis.* **2004**, *6*, 595–604; discussion 673–581. [[CrossRef](#)]
245. Olabarria, M.; Noristani, H.N.; Verkhratsky, A.; Rodriguez, J.J. Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. *Glia* **2010**, *58*, 831–838. [[CrossRef](#)]
246. Sajja, V.S.; Hlavac, N.; VandeVord, P.J. Role of Glia in Memory Deficits Following Traumatic Brain Injury: Biomarkers of Glia Dysfunction. *Front. Integr. Neurosci.* **2016**, *10*, 7. [[CrossRef](#)]
247. Alberdi, E.; Wyssenbach, A.; Alberdi, M.; Sanchez-Gomez, M.V.; Cavaliere, F.; Rodriguez, J.J.; Verkhratsky, A.; Matute, C. Ca(2+)-dependent endoplasmic reticulum stress correlates with astrogliosis in oligomeric amyloid beta-treated astrocytes and in a model of Alzheimer's disease. *Aging Cell* **2013**, *12*, 292–302. [[CrossRef](#)]
248. Alves, V.S.; Alves-Silva, H.S.; Orts, D.J.B.; Ribeiro-Silva, L.; Arcisio-Miranda, M.; Oliveira, F.A. Calcium Signaling in Neurons and Glial Cells: Role of Cav1 channels. *Neuroscience* **2019**, *421*, 95–111. [[CrossRef](#)] [[PubMed](#)]
249. Lim, D.; Iyer, A.; Ronco, V.; Grolla, A.A.; Canonico, P.L.; Aronica, E.; Genazzani, A.A. Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-kB. *Glia* **2013**, *61*, 1134–1145. [[CrossRef](#)]
250. Pleiss, M.M.; Sompol, P.; Kraner, S.D.; Abdul, H.M.; Furman, J.L.; Guttman, R.P.; Wilcock, D.M.; Nelson, P.T.; Norris, C.M. Calcineurin proteolysis in astrocytes: Implications for impaired synaptic function. *Biochim. Biophys. Acta* **2016**, *1862*, 1521–1532. [[CrossRef](#)] [[PubMed](#)]
251. Sompol, P.; Norris, C.M. Ca(2+), Astrocyte Activation and Calcineurin/NFAT Signaling in Age-Related Neurodegenerative Diseases. *Front. Aging Neurosci.* **2018**, *10*, 199. [[CrossRef](#)] [[PubMed](#)]
252. Colombo, J.A.; Quinn, B.; Puissant, V. Disruption of astroglial interlaminar processes in Alzheimer's disease. *Brain Res. Bull.* **2002**, *58*, 235–242. [[CrossRef](#)] [[PubMed](#)]
253. Hsu, E.T.; Gangolli, M.; Su, S.; Holleran, L.; Stein, T.D.; Alvarez, V.E.; McKee, A.C.; Schmidt, R.E.; Brody, D.L. Astrocytic degeneration in chronic traumatic encephalopathy. *Acta Neuropathol.* **2018**, *136*, 955–972. [[CrossRef](#)]
254. Verkhratsky, A.; Zorec, R.; Rodriguez, J.J.; Parpura, V. Astroglia dynamics in ageing and Alzheimer's disease. *Curr. Opin. Pharmacol.* **2016**, *26*, 74–79. [[CrossRef](#)]
255. Galea, E.; Weinstock, L.D.; Larramona-Arcas, R.; Pybus, A.F.; Gimenez-Llort, L.; Escartin, C.; Wood, L.B. Multi-transcriptomic analysis points to early organelle dysfunction in human astrocytes in Alzheimer's disease. *Neurobiol. Dis.* **2022**, *166*, 105655. [[CrossRef](#)]
256. Fong, L.K.; Yang, M.M.; Dos Santos Chaves, R.; Reyna, S.M.; Langness, V.F.; Woodruff, G.; Roberts, E.A.; Young, J.E.; Goldstein, L.S.B. Full-length amyloid precursor protein regulates lipoprotein metabolism and amyloid-beta clearance in human astrocytes. *J. Biol. Chem.* **2018**, *293*, 11341–11357. [[CrossRef](#)]
257. Thal, D.R. The role of astrocytes in amyloid beta-protein toxicity and clearance. *Exp. Neurol.* **2012**, *236*, 1–5. [[CrossRef](#)]
258. Kierdorf, K.; Prinz, M. Microglia in steady state. *J. Clin. Investig.* **2017**, *127*, 3201–3209. [[CrossRef](#)]
259. Sarlus, H.; Heneka, M.T. Microglia in Alzheimer's disease. *J. Clin. Investig.* **2017**, *127*, 3240–3249. [[CrossRef](#)] [[PubMed](#)]
260. Wolf, S.A.; Boddeke, H.W.; Kettenmann, H. Microglia in Physiology and Disease. *Annu. Rev. Physiol.* **2017**, *79*, 619–643. [[CrossRef](#)]

261. Hanisch, U.K.; Kettenmann, H. Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.* **2007**, *10*, 1387–1394. [[CrossRef](#)]
262. Kreutzberg, G.W. Microglia: A sensor for pathological events in the CNS. *Trends Neurosci.* **1996**, *19*, 312–318. [[CrossRef](#)]
263. Itagaki, S.; McGeer, P.L.; Akiyama, H.; Zhu, S.; Selkoe, D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *J. Neuroimmunol.* **1989**, *24*, 173–182. [[CrossRef](#)]
264. Labzin, L.I.; Heneka, M.T.; Latz, E. Innate Immunity and Neurodegeneration. *Annu. Rev. Med.* **2018**, *69*, 437–449. [[CrossRef](#)] [[PubMed](#)]
265. Morales, I.; Guzman-Martinez, L.; Cerda-Troncoso, C.; Farias, G.A.; Maccioni, R.B. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Front. Cell. Neurosci.* **2014**, *8*, 112. [[CrossRef](#)]
266. Verheijen, J.; Sleegers, K. Understanding Alzheimer Disease at the Interface between Genetics and Transcriptomics. *Trend Genet.* **2018**, *34*, 434–447. [[CrossRef](#)]
267. Lanfranco, M.F.; Sepulveda, J.; Kopetsky, G.; Rebeck, G.W. Expression and secretion of apoE isoforms in astrocytes and microglia during inflammation. *Glia* **2021**, *69*, 1478–1493. [[CrossRef](#)]
268. Castellano, J.M.; Kim, J.; Stewart, F.R.; Jiang, H.; DeMattos, R.B.; Patterson, B.W.; Fagan, A.M.; Morris, J.C.; Mawuenyega, K.G.; Cruchaga, C.; et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci. Transl. Med.* **2011**, *3*, 89ra57. [[CrossRef](#)] [[PubMed](#)]
269. Serrano-Pozo, A.; Das, S.; Hyman, B.T. APOE and Alzheimer's disease: Advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol.* **2021**, *20*, 68–80. [[CrossRef](#)] [[PubMed](#)]
270. Verghese, P.B.; Castellano, J.M.; Garai, K.; Wang, Y.; Jiang, H.; Shah, A.; Bu, G.; Frieden, C.; Holtzman, D.M. ApoE influences amyloid-beta (Abeta) clearance despite minimal apoE/Abeta association in physiological conditions. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E1807–E1816. [[CrossRef](#)]
271. Sienski, G.; Narayan, P.; Bonner, J.M.; Kory, N.; Boland, S.; Arczewska, A.A.; Ralvenius, W.T.; Akay, L.; Lockshin, E.; He, L.; et al. APOE4 disrupts intracellular lipid homeostasis in human iPSC-derived glia. *Sci. Transl. Med.* **2021**, *13*, eaaz4564. [[CrossRef](#)]
272. Krasemann, S.; Madore, C.; Cialic, R.; Baufeld, C.; Calcagno, N.; El Fatimy, R.; Beckers, L.; O'Loughlin, E.; Xu, Y.; Fanek, Z.; et al. The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. *Immunity* **2017**, *47*, 566–581.e569. [[CrossRef](#)]
273. Poliani, P.L.; Wang, Y.; Fontana, E.; Robinette, M.L.; Yamanishi, Y.; Gilfillan, S.; Colonna, M. TREM2 sustains microglial expansion during aging and response to demyelination. *J. Clin. Investig.* **2015**, *125*, 2161–2170. [[CrossRef](#)]
274. Song, W.; Hooli, B.; Mullin, K.; Jin, S.C.; Cella, M.; Ulland, T.K.; Wang, Y.; Tanzi, R.E.; Colonna, M. Alzheimer's disease-associated TREM2 variants exhibit either decreased or increased ligand-dependent activation. *Alzheimer's Dement.* **2017**, *13*, 381–387. [[CrossRef](#)]
275. Yeh, F.L.; Wang, Y.; Tom, I.; Gonzalez, L.C.; Sheng, M. TREM2 Binds to Apolipoproteins, Including APOE and CLU/APOJ, and Thereby Facilitates Uptake of Amyloid-Beta by Microglia. *Neuron* **2016**, *91*, 328–340. [[CrossRef](#)]
276. Zheng, H.; Jia, L.; Liu, C.C.; Rong, Z.; Zhong, L.; Yang, L.; Chen, X.F.; Fryer, J.D.; Wang, X.; Zhang, Y.W.; et al. TREM2 Promotes Microglial Survival by Activating Wnt/beta-Catenin Pathway. *J. Neurosci.* **2017**, *37*, 1772–1784. [[CrossRef](#)]
277. Schafer, D.P.; Lehrman, E.K.; Kautzman, A.G.; Koyama, R.; Mardinly, A.R.; Yamasaki, R.; Ransohoff, R.M.; Greenberg, M.E.; Barres, B.A.; Stevens, B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* **2012**, *74*, 691–705. [[CrossRef](#)] [[PubMed](#)]
278. Brouwers, N.; Van Cauwenberghe, C.; Engelborghs, S.; Lambert, J.C.; Bettens, K.; Le Bastard, N.; Pasquier, F.; Montoya, A.G.; Peeters, K.; Mattheijssens, M.; et al. Alzheimer risk associated with a copy number variation in the complement receptor 1 increasing C3b/C4b binding sites. *Mol. Psychiatry* **2012**, *17*, 223–233. [[CrossRef](#)] [[PubMed](#)]
279. Jun, G.; Naj, A.C.; Beecham, G.W.; Wang, L.S.; Buross, J.; Gallins, P.J.; Buxbaum, J.D.; Ertekin-Taner, N.; Fallin, M.D.; Friedland, R.; et al. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch. Neurol.* **2010**, *67*, 1473–1484. [[CrossRef](#)] [[PubMed](#)]
280. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E.M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **1984**, *34*, 939–944. [[CrossRef](#)]
281. Wilson, R.S.; Leurgans, S.E.; Boyle, P.A.; Bennett, D.A. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch. Neurol.* **2011**, *68*, 351–356. [[CrossRef](#)]
282. Morris, J.C.; Storandt, M.; Miller, J.P.; McKeel, D.W.; Price, J.L.; Rubin, E.H.; Berg, L. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch. Neurol.* **2001**, *58*, 397–405. [[CrossRef](#)]
283. Petersen, R.C.; Roberts, R.O.; Knopman, D.S.; Boeve, B.F.; Geda, Y.E.; Ivnik, R.J.; Smith, G.E.; Jack, C.R., Jr. Mild cognitive impairment: Ten years later. *Arch. Neurol.* **2009**, *66*, 1447–1455. [[CrossRef](#)]
284. Blennow, K.; Bogdanovic, N.; Alafuzoff, I.; Ekman, R.; Davidsson, P. Synaptic pathology in Alzheimer's disease: Relation to severity of dementia, but not to senile plaques, neurofibrillary tangles, or the ApoE4 allele. *J Neural Transm.* **1996**, *103*, 603–618. [[CrossRef](#)]
285. DeKosky, S.T.; Scheff, S.W.; Styren, S.D. Structural correlates of cognition in dementia: Quantification and assessment of synapse change. *Neurodegeneration* **1996**, *5*, 417–421. [[CrossRef](#)]

286. Gomez-Isla, T.; Hollister, R.; West, H.; Mui, S.; Growdon, J.H.; Petersen, R.C.; Parisi, J.E.; Hyman, B.T. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann. Neurol.* **1997**, *41*, 17–24. [[CrossRef](#)] [[PubMed](#)]
287. Spires-Jones, T.L.; Hyman, B.T. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* **2014**, *82*, 756–771. [[CrossRef](#)]
288. Terry, R.D.; Masliah, E.; Salmon, D.P.; Butters, N.; DeTeresa, R.; Hill, R.; Hansen, L.A.; Katzman, R. Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* **1991**, *30*, 572–580. [[CrossRef](#)] [[PubMed](#)]
289. de Wilde, M.C.; Overk, C.R.; Sijben, J.W.; Masliah, E. Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability. *Alzheimers Dement.* **2016**, *12*, 633–644. [[CrossRef](#)]
290. Bai, Y.; Li, M.; Zhou, Y.; Ma, L.; Qiao, Q.; Hu, W.; Li, W.; Wills, Z.P.; Gan, W.B. Abnormal dendritic calcium activity and synaptic depotentiation occur early in a mouse model of Alzheimer's disease. *Mol. Neurodegener.* **2017**, *12*, 86. [[CrossRef](#)] [[PubMed](#)]
291. Forner, S.; Baglietto-Vargas, D.; Martini, A.C.; Trujillo-Estrada, L.; LaFerla, F.M. Synaptic Impairment in Alzheimer's Disease: A Dysregulated Symphony. *Trends Neurosci.* **2017**, *40*, 347–357. [[CrossRef](#)]
292. Pozueta, J.; Lefort, R.; Shelanski, M.L. Synaptic changes in Alzheimer's disease and its models. *Neuroscience* **2013**, *251*, 51–65. [[CrossRef](#)] [[PubMed](#)]
293. Spires-Jones, T.; Knafo, S. Spines, plasticity, and cognition in Alzheimer's model mice. *Neural Plast.* **2012**, *2012*, 319836. [[CrossRef](#)]
294. Stephen, T.L.; Tamagnini, F.; Piegsa, J.; Sung, K.; Harvey, J.; Oliver-Evans, A.; Murray, T.K.; Ahmed, Z.; Hutton, M.L.; Randall, A.; et al. Imbalance in the response of pre- and post-synaptic components to amyloidopathy. *Sci. Rep.* **2019**, *9*, 14837. [[CrossRef](#)]
295. Berezcki, E.; Francis, P.T.; Howlett, D.; Pereira, J.B.; Hoglund, K.; Bogstedt, A.; Cedazo-Minguez, A.; Baek, J.H.; Hortobagyi, T.; Attems, J.; et al. Synaptic proteins predict cognitive decline in Alzheimer's disease and Lewy body dementia. *Alzheimers Dement.* **2016**, *12*, 1149–1158. [[CrossRef](#)] [[PubMed](#)]
296. Berezcki, E.; Branca, R.M.; Francis, P.T.; Pereira, J.B.; Baek, J.H.; Hortobagyi, T.; Winblad, B.; Ballard, C.; Lehtio, J.; Aarsland, D. Synaptic markers of cognitive decline in neurodegenerative diseases: A proteomic approach. *Brain* **2018**, *141*, 582–595. [[CrossRef](#)]
297. Mecca, A.P.; O'Dell, R.S.; Sharp, E.S.; Banks, E.R.; Bartlett, H.H.; Zhao, W.; Lipior, S.; Diepenbrock, N.G.; Chen, M.K.; Naganawa, M.; et al. Synaptic density and cognitive performance in Alzheimer's disease: A PET imaging study with [(11)C]UCB-J. *Alzheimers Dement.* **2022**, *18*, 2527–2536. [[CrossRef](#)]
298. Scheff, S.W.; Price, D.A. Synaptic pathology in Alzheimer's disease: A review of ultrastructural studies. *Neurobiol. Aging* **2003**, *24*, 1029–1046. [[CrossRef](#)] [[PubMed](#)]
299. Coleman, P.D.; Flood, D.G. Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiol. Aging* **1987**, *8*, 521–545. [[CrossRef](#)]
300. DeTure, M.A.; Dickson, D.W. The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegener.* **2019**, *14*, 32. [[CrossRef](#)]
301. Hof, P.R.; Morrison, J.H. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. *J. Comp. Neurol.* **1990**, *301*, 55–64. [[CrossRef](#)]
302. Arendt, T.; Bruckner, M.K.; Morawski, M.; Jager, C.; Gertz, H.J. Early neurone loss in Alzheimer's disease: Cortical or subcortical? *Acta Neuropathol. Commun.* **2015**, *3*, 10. [[CrossRef](#)] [[PubMed](#)]
303. Gomez-Isla, T.; Price, J.L.; McKeel, D.W., Jr.; Morris, J.C.; Growdon, J.H.; Hyman, B.T. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J. Neurosci.* **1996**, *16*, 4491–4500. [[CrossRef](#)]
304. West, M.J.; Coleman, P.D.; Flood, D.G.; Troncoso, J.C. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet* **1994**, *344*, 769–772. [[CrossRef](#)]
305. Mountjoy, C.Q.; Roth, M.; Evans, N.J.; Evans, H.M. Cortical neuronal counts in normal elderly controls and demented patients. *Neurobiol. Aging* **1983**, *4*, 1–11. [[CrossRef](#)] [[PubMed](#)]
306. Andrade-Moraes, C.H.; Oliveira-Pinto, A.V.; Castro-Fonseca, E.; da Silva, C.G.; Guimaraes, D.M.; Szczupak, D.; Parente-Bruno, D.R.; Carvalho, L.R.; Polichiso, L.; Gomes, B.V.; et al. Cell number changes in Alzheimer's disease relate to dementia, not to plaques and tangles. *Brain* **2013**, *136*, 3738–3752. [[CrossRef](#)] [[PubMed](#)]
307. Giannakopoulos, P.; Herrmann, F.R.; Bussiere, T.; Bouras, C.; Kovari, E.; Perl, D.P.; Morrison, J.H.; Gold, G.; Hof, P.R. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology* **2003**, *60*, 1495–1500. [[CrossRef](#)]
308. Casas, C.; Sergeant, N.; Itier, J.M.; Blanchard, V.; Wirths, O.; van der Kolk, N.; Vingtdoux, V.; van de Steeg, E.; Ret, G.; Canton, T.; et al. Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated Abeta42 accumulation in a novel Alzheimer transgenic model. *Am. J. Pathol.* **2004**, *165*, 1289–1300. [[CrossRef](#)] [[PubMed](#)]
309. Oakley, H.; Cole, S.L.; Logan, S.; Maus, E.; Shao, P.; Craft, J.; Guillozet-Bongaarts, A.; Ohno, M.; Disterhoft, J.; Van Eldik, L.; et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: Potential factors in amyloid plaque formation. *J. Neurosci.* **2006**, *26*, 10129–10140. [[CrossRef](#)] [[PubMed](#)]
310. Ribe, E.M.; Perez, M.; Puig, B.; Gich, I.; Lim, F.; Cuadrado, M.; Sesma, T.; Catena, S.; Sanchez, B.; Nieto, M.; et al. Accelerated amyloid deposition, neurofibrillary degeneration and neuronal loss in double mutant APP/tau transgenic mice. *Neurobiol. Dis.* **2005**, *20*, 814–822. [[CrossRef](#)]
311. Schmitz, C.; Rutten, B.P.; Pielen, A.; Schafer, S.; Wirths, O.; Tremp, G.; Czech, C.; Blanchard, V.; Multhaup, G.; Rezaie, P.; et al. Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. *Am. J. Pathol.* **2004**, *164*, 1495–1502. [[CrossRef](#)] [[PubMed](#)]

312. Ugolini, F.; Lana, D.; Nardiello, P.; Nosi, D.; Pantano, D.; Casamenti, F.; Giovannini, M.G. Different Patterns of Neurodegeneration and Glia Activation in CA1 and CA3 Hippocampal Regions of TgCRND8 Mice. *Front. Aging Neurosci.* **2018**, *10*, 372. [[CrossRef](#)] [[PubMed](#)]
313. Cline, E.N.; Bicca, M.A.; Viola, K.L.; Klein, W.L. The Amyloid-beta Oligomer Hypothesis: Beginning of the Third Decade. *J. Alzheimer's Dis.* **2018**, *64*, S567–S610. [[CrossRef](#)]
314. Esparza, T.J.; Zhao, H.; Cirrito, J.R.; Cairns, N.J.; Bateman, R.J.; Holtzman, D.M.; Brody, D.L. Amyloid-beta oligomerization in Alzheimer dementia versus high-pathology controls. *Ann. Neurol.* **2013**, *73*, 104–119. [[CrossRef](#)]
315. Lambert, M.P.; Barlow, A.K.; Chromy, B.A.; Edwards, C.; Freed, R.; Liosatos, M.; Morgan, T.E.; Rozovsky, I.; Trommer, B.; Viola, K.L.; et al. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6448–6453. [[CrossRef](#)] [[PubMed](#)]
316. Shankar, G.M.; Li, S.; Mehta, T.H.; Garcia-Munoz, A.; Shepardson, N.E.; Smith, I.; Brett, F.M.; Farrell, M.A.; Rowan, M.J.; Lemere, C.A.; et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* **2008**, *14*, 837–842. [[CrossRef](#)] [[PubMed](#)]
317. Walsh, D.M.; Klyubin, I.; Fadeeva, J.V.; Cullen, W.K.; Anwyl, R.; Wolfe, M.S.; Rowan, M.J.; Selkoe, D.J. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* **2002**, *416*, 535–539. [[CrossRef](#)]
318. Cisse, M.; Halabisky, B.; Harris, J.; Devidze, N.; Dubal, D.B.; Sun, B.; Orr, A.; Lotz, G.; Kim, D.H.; Hamto, P.; et al. Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature* **2011**, *469*, 47–52. [[CrossRef](#)]
319. Smith, L.M.; Strittmatter, S.M. Binding Sites for Amyloid-beta Oligomers and Synaptic Toxicity. *Cold Spring Harb. Perspect. Med.* **2017**, *7*, a024075. [[CrossRef](#)]
320. Koffie, R.M.; Meyer-Luehmann, M.; Hashimoto, T.; Adams, K.W.; Mielke, M.L.; Garcia-Alloza, M.; Micheva, K.D.; Smith, S.J.; Kim, M.L.; Lee, V.M.; et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4012–4017. [[CrossRef](#)]
321. Koffie, R.M.; Hashimoto, T.; Tai, H.C.; Kay, K.R.; Serrano-Pozo, A.; Joyner, D.; Hou, S.; Kopeikina, K.J.; Frosch, M.P.; Lee, V.M.; et al. Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. *Brain* **2012**, *135*, 2155–2168. [[CrossRef](#)]
322. Guerrero-Munoz, M.J.; Gerson, J.; Castillo-Carranza, D.L. Tau Oligomers: The Toxic Player at Synapses in Alzheimer's Disease. *Front. Cell. Neurosci.* **2015**, *9*, 464. [[CrossRef](#)] [[PubMed](#)]
323. Augustinack, J.C.; Schneider, A.; Mandelkow, E.M.; Hyman, B.T. Specific tau phosphorylation sites correlate with severity of neuronal cytopathology in Alzheimer's disease. *Acta Neuropathol.* **2002**, *103*, 26–35. [[CrossRef](#)] [[PubMed](#)]
324. De Vos, S.L.; Miller, R.L.; Schoch, K.M.; Holmes, B.B.; Kebodeaux, C.S.; Wegener, A.J.; Chen, G.; Shen, T.; Tran, H.; Nichols, B.; et al. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. *Sci. Transl. Med.* **2017**, *9*, eaag0481. [[CrossRef](#)] [[PubMed](#)]
325. Fein, J.A.; Sokolow, S.; Miller, C.A.; Vinters, H.V.; Yang, F.; Cole, G.M.; Gyllys, K.H. Co-localization of amyloid beta and tau pathology in Alzheimer's disease synaptosomes. *Am. J. Pathol.* **2008**, *172*, 1683–1692. [[CrossRef](#)]
326. Tai, H.C.; Wang, B.Y.; Serrano-Pozo, A.; Frosch, M.P.; Spires-Jones, T.L.; Hyman, B.T. Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and postsynaptic terminals in Alzheimer's disease. *Acta Neuropathol. Commun.* **2014**, *2*, 146. [[CrossRef](#)] [[PubMed](#)]
327. Zhou, L.; McInnes, J.; Wierda, K.; Holt, M.; Herrmann, A.G.; Jackson, R.J.; Wang, Y.C.; Swerts, J.; Beyens, J.; Miskiewicz, K.; et al. Tau association with synaptic vesicles causes presynaptic dysfunction. *Nat. Commun.* **2017**, *8*, 15295. [[CrossRef](#)]
328. Ghag, G.; Bhatt, N.; Cantu, D.V.; Guerrero-Munoz, M.J.; Ellsworth, A.; Sengupta, U.; Kaye, R. Soluble tau aggregates, not large fibrils, are the toxic species that display seeding and cross-seeding behavior. *Protein Sci.* **2018**, *27*, 1901–1909. [[CrossRef](#)]
329. Jin, M.; Shepardson, N.; Yang, T.; Chen, G.; Walsh, D.; Selkoe, D.J. Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 5819–5824. [[CrossRef](#)]
330. Kopeikina, K.J.; Hyman, B.T.; Spires-Jones, T.L. Soluble forms of tau are toxic in Alzheimer's disease. *Transl. Neurosci.* **2012**, *3*, 223–233. [[CrossRef](#)]
331. Sealey, M.A.; Vourkou, E.; Cowan, C.M.; Bossing, T.; Quraishe, S.; Grammenoudi, S.; Skoulakis, E.M.C.; Mudher, A. Distinct phenotypes of three-repeat and four-repeat human tau in a transgenic model of tauopathy. *Neurobiol. Dis.* **2017**, *105*, 74–83. [[CrossRef](#)]
332. Szabo, L.; Eckert, A.; Grimm, A. Insights into Disease-Associated Tau Impact on Mitochondria. *Int. J. Mol. Sci.* **2020**, *21*, 6344. [[CrossRef](#)] [[PubMed](#)]
333. Kopeikina, K.J.; Carlson, G.A.; Pitstick, R.; Ludvigson, A.E.; Peters, A.; Luebke, J.I.; Koffie, R.M.; Frosch, M.P.; Hyman, B.T.; Spires-Jones, T.L. Tau accumulation causes mitochondrial distribution deficits in neurons in a mouse model of tauopathy and in human Alzheimer's disease brain. *Am. J. Pathol.* **2011**, *179*, 2071–2082. [[CrossRef](#)]
334. Pickett, E.K.; Rose, J.; McCrory, C.; McKenzie, C.A.; King, D.; Smith, C.; Gillingwater, T.H.; Henstridge, C.M.; Spires-Jones, T.L. Region-specific depletion of synaptic mitochondria in the brains of patients with Alzheimer's disease. *Acta Neuropathol.* **2018**, *136*, 747–757. [[CrossRef](#)] [[PubMed](#)]

335. McGeer, P.L.; McGeer, E.G. The inflammatory response system of brain: Implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res. Brain Res. Rev.* **1995**, *21*, 195–218. [[CrossRef](#)] [[PubMed](#)]
336. Davies, C.; Spires-Jones, T.L. Complementing Tau: New Data Show that the Complement System Is Involved in Degeneration in Tauopathies. *Neuron* **2018**, *100*, 1267–1269. [[CrossRef](#)]
337. Henstridge, C.M.; Hyman, B.T.; Spires-Jones, T.L. Beyond the neuron-cellular interactions early in Alzheimer disease pathogenesis. *Nat. Rev. Neurosci.* **2019**, *20*, 94–108. [[CrossRef](#)] [[PubMed](#)]
338. Goel, P.; Chakrabarti, S.; Goel, K.; Bhutani, K.; Chopra, T.; Bali, S. Neuronal cell death mechanisms in Alzheimer's disease: An insight. *Front. Mol. Neurosci.* **2022**, *15*, 937133. [[CrossRef](#)]
339. Rosenberg, G.A. Neurological diseases in relation to the blood-brain barrier. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 1139–1151. [[CrossRef](#)] [[PubMed](#)]
340. Erickson, M.A.; Banks, W.A. Blood-brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *J. Cereb. Blood Flow Metab.* **2013**, *33*, 1500–1513. [[CrossRef](#)] [[PubMed](#)]
341. Sweeney, M.D.; Sagare, A.P.; Zlokovic, B.V. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat. Rev. Neurol.* **2018**, *14*, 133–150. [[CrossRef](#)] [[PubMed](#)]
342. Zhao, Z.; Nelson, A.R.; Betsholtz, C.; Zlokovic, B.V. Establishment and Dysfunction of the Blood-Brain Barrier. *Cell* **2015**, *163*, 1064–1078. [[CrossRef](#)]
343. Michalicova, A.; Majerova, P.; Kovac, A. Tau Protein and Its Role in Blood-Brain Barrier Dysfunction. *Front. Mol. Neurosci.* **2020**, *13*, 570045. [[CrossRef](#)] [[PubMed](#)]
344. Rapic, S.; Backes, H.; Viel, T.; Kummer, M.P.; Monfared, P.; Neumaier, B.; Vollmar, S.; Hoehn, M.; Van der Linden, A.; Heneka, M.T.; et al. Imaging microglial activation and glucose consumption in a mouse model of Alzheimer's disease. *Neurobiol. Aging* **2013**, *34*, 351–354. [[CrossRef](#)] [[PubMed](#)]
345. Zhao, Y.; Wu, X.; Li, X.; Jiang, L.L.; Gui, X.; Liu, Y.; Sun, Y.; Zhu, B.; Pina-Crespo, J.C.; Zhang, M.; et al. TREM2 Is a Receptor for beta-Amyloid that Mediates Microglial Function. *Neuron* **2018**, *97*, 1023–1031.e1027. [[CrossRef](#)]
346. Ries, M.; Sastre, M. Mechanisms of Abeta Clearance and Degradation by Glial Cells. *Front. Aging Neurosci.* **2016**, *8*, 160. [[CrossRef](#)]
347. Tahara, K.; Kim, H.D.; Jin, J.J.; Maxwell, J.A.; Li, L.; Fukuchi, K. Role of toll-like receptor signalling in Abeta uptake and clearance. *Brain* **2006**, *129*, 3006–3019. [[CrossRef](#)]
348. Reed-Geaghan, E.G.; Savage, J.C.; Hise, A.G.; Landreth, G.E. CD14 and toll-like receptors 2 and 4 are required for fibrillar Abeta-stimulated microglial activation. *J. Neurosci.* **2009**, *29*, 11982–11992. [[CrossRef](#)]
349. Kim, K.; Wang, X.; Ragonaud, E.; Bodogai, M.; Illouz, T.; DeLuca, M.; McDevitt, R.A.; Gusev, F.; Okun, E.; Rogaeve, E.; et al. Therapeutic B-cell depletion reverses progression of Alzheimer's disease. *Nat. Commun.* **2021**, *12*, 2185. [[CrossRef](#)]
350. Marsh, S.E.; Abud, E.M.; Lakatos, A.; Karimzadeh, A.; Yeung, S.T.; Davtyan, H.; Fote, G.M.; Lau, L.; Weinger, J.G.; Lane, T.E.; et al. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E1316–E1325. [[CrossRef](#)]
351. Maftei, M.; Thurm, F.; Schnack, C.; Tumani, H.; Otto, M.; Elbert, T.; Kolassa, I.T.; Przybylski, M.; Manea, M.; von Arnim, C.A. Increased levels of antigen-bound beta-amyloid autoantibodies in serum and cerebrospinal fluid of Alzheimer's disease patients. *PLoS ONE* **2013**, *8*, e68996. [[CrossRef](#)] [[PubMed](#)]
352. Prieto, J.M.B.; Felipe, M.J.B. Development, phenotype, and function of non-conventional B cells. *Comp. Immunol. Microbiol. Infect. Dis.* **2017**, *54*, 38–44. [[CrossRef](#)] [[PubMed](#)]
353. Plantone, D.; Pardini, M.; Locci, S.; Nobili, F.; De Stefano, N. B Lymphocytes in Alzheimer's Disease—A Comprehensive Review. *J. Alzheimers Dis.* **2022**, *88*, 1241–1262. [[CrossRef](#)] [[PubMed](#)]
354. Afsar, A.C.; Xuan, M.; Xuan, Z.; Li, Z. A Glance through the Effects of CD4⁺ T Cells, CD8⁺ T Cells, and Cytokines on Alzheimer's Disease. *Comput. Struct. Biotechnol. J. (CSBJ)* **2023**. (submitted).
355. Parachikova, A.; Agadjanyan, M.G.; Cribbs, D.H.; Blurton-Jones, M.; Perreau, V.; Rogers, J.; Beach, T.G.; Cotman, C.W. Inflammatory changes parallel the early stages of Alzheimer disease. *Neurobiol. Aging* **2007**, *28*, 1821–1833. [[CrossRef](#)] [[PubMed](#)]
356. Hickey, W.F.; Hsu, B.L.; Kimura, H. T-lymphocyte entry into the central nervous system. *J. Neurosci. Res.* **1991**, *28*, 254–260. [[CrossRef](#)]
357. Merlini, M.; Kirabali, T.; Kulic, L.; Nitsch, R.M.; Ferretti, M.T. Extravascular CD3⁺ T Cells in Brains of Alzheimer Disease Patients Correlate with Tau but Not with Amyloid Pathology: An Immunohistochemical Study. *Neurodegener. Dis.* **2018**, *18*, 49–56. [[CrossRef](#)]
358. Laurent, C.; Dorothee, G.; Hunot, S.; Martin, E.; Monnet, Y.; Duchamp, M.; Dong, Y.; Legeron, F.P.; Lebourcier, A.; Burnouf, S.; et al. Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. *Brain* **2017**, *140*, 184–200. [[CrossRef](#)]
359. Monsonego, A.; Zota, V.; Karni, A.; Krieger, J.I.; Bar-Or, A.; Bitan, G.; Budson, A.E.; Sperling, R.; Selkoe, D.J.; Weiner, H.L. Increased T cell reactivity to amyloid beta protein in older humans and patients with Alzheimer disease. *J. Clin. Investig.* **2003**, *112*, 415–422. [[CrossRef](#)]
360. Ciccocioppo, F.; Lanuti, P.; Pierdomenico, L.; Simeone, P.; Bologna, G.; Ercolino, E.; Buttari, F.; Fantozzi, R.; Thomas, A.; Onofri, M.; et al. The Characterization of Regulatory T-Cell Profiles in Alzheimer's Disease and Multiple Sclerosis. *Sci. Rep.* **2019**, *9*, 8788. [[CrossRef](#)]

361. Dansokho, C.; Ait Ahmed, D.; Aid, S.; Toly-Ndour, C.; Chaigneau, T.; Calle, V.; Cagnard, N.; Holzenberger, M.; Piaggio, E.; Aucouturier, P.; et al. Regulatory T cells delay disease progression in Alzheimer-like pathology. *Brain* **2016**, *139*, 1237–1251. [[CrossRef](#)] [[PubMed](#)]
362. Machhi, J.; Kevadiya, B.D.; Muhammad, I.K.; Herskovitz, J.; Olson, K.E.; Mosley, R.L.; Gendelman, H.E. Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. *Mol. Neurodegener.* **2020**, *15*, 32. [[CrossRef](#)]
363. Mosmann, T.R.; Cherwinski, H.; Bond, M.W.; Giedlin, M.A.; Coffman, R.L. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol.* **1986**, *136*, 2348–2357. [[CrossRef](#)] [[PubMed](#)]
364. Harrington, L.E.; Hatton, R.D.; Mangan, P.R.; Turner, H.; Murphy, T.L.; Murphy, K.M.; Weaver, C.T. Interleukin 17-producing CD4⁺ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.* **2005**, *6*, 1123–1132. [[CrossRef](#)] [[PubMed](#)]
365. Cao, C.; Arendash, G.W.; Dickson, A.; Mamcarz, M.B.; Lin, X.; Ethell, D.W. Abeta-specific Th2 cells provide cognitive and pathological benefits to Alzheimer's mice without infiltrating the CNS. *Neurobiol. Dis.* **2009**, *34*, 63–70. [[CrossRef](#)]
366. Unger, M.S.; Li, E.; Scharnagl, L.; Poupardin, R.; Altendorfer, B.; Mrowetz, H.; Hutter-Paier, B.; Weiger, T.M.; Heneka, M.T.; Attems, J.; et al. CD8(+) T-cells infiltrate Alzheimer's disease brains and regulate neuronal- and synapse-related gene expression in APP-PS1 transgenic mice. *Brain Behav. Immun.* **2020**, *89*, 67–86. [[CrossRef](#)]
367. Cacquevel, M.; Lebeurrier, N.; Cheenne, S.; Vivien, D. Cytokines in neuroinflammation and Alzheimer's disease. *Curr. Drug Targets* **2004**, *5*, 529–534. [[CrossRef](#)]
368. Holmlund, L.; Cortes Toro, V.; Iverfeldt, K. Additive effects of amyloid beta fragment and interleukin-1beta on interleukin-6 secretion in rat primary glial cultures. *Int. J. Mol. Med.* **2002**, *10*, 245–250.
369. Eriksson, G.; Zetterstrom, M.; Cortes Toro, V.; Bartfai, T.; Iverfeldt, K. Hypersensitive cytokine response to beta-amyloid 25-35 in astroglial cells from IL-1 receptor type I-deficient mice. *Int. J. Mol. Med.* **1998**, *1*, 201–206. [[CrossRef](#)]
370. Aloisi, F.; Care, A.; Borsellino, G.; Gallo, P.; Rosa, S.; Bassani, A.; Cabibbo, A.; Testa, U.; Levi, G.; Peschle, C. Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1 beta and tumor necrosis factor-alpha. *J. Immunol.* **1992**, *149*, 2358–2366. [[CrossRef](#)]
371. Di Santo, E.; Sironi, M.; Pozzi, P.; Gnocchi, P.; Isetta, A.M.; Delvaux, A.; Goldman, M.; Marchant, A.; Ghezzi, P. Interleukin-10 inhibits lipopolysaccharide-induced tumor necrosis factor and interleukin-1 beta production in the brain without affecting the activation of the hypothalamus-pituitary-adrenal axis. *Neuroimmunomodulation* **1995**, *2*, 149–154. [[CrossRef](#)] [[PubMed](#)]
372. Frenkel, D.; Puckett, L.; Petrovic, S.; Xia, W.; Chen, G.; Vega, J.; Dembinsky-Vaknin, A.; Shen, J.; Plante, M.; Burt, D.S.; et al. A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. *Ann. Neurol.* **2008**, *63*, 591–601. [[CrossRef](#)] [[PubMed](#)]
373. Kiyota, T.; Ingraham, K.L.; Swan, R.J.; Jacobsen, M.T.; Andrews, S.J.; Ikezu, T. AAV serotype 2/1-mediated gene delivery of anti-inflammatory interleukin-10 enhances neurogenesis and cognitive function in APP+PS1 mice. *Gene Ther.* **2012**, *19*, 724–733. [[CrossRef](#)] [[PubMed](#)]
374. Kiyota, T.; Okuyama, S.; Swan, R.J.; Jacobsen, M.T.; Gendelman, H.E.; Ikezu, T. CNS expression of anti-inflammatory cytokine interleukin-4 attenuates Alzheimer's disease-like pathogenesis in APP+PS1 bigenic mice. *FASEB J.* **2010**, *24*, 3093–3102. [[CrossRef](#)] [[PubMed](#)]
375. Zhang, J.; Ke, K.F.; Liu, Z.; Qiu, Y.H.; Peng, Y.P. Th17 cell-mediated neuroinflammation is involved in neurodegeneration of abeta1-42-induced Alzheimer's disease model rats. *PLoS ONE* **2013**, *8*, e75786. [[CrossRef](#)]
376. Zhang, L.; Xu, J.; Gao, J.; Chen, P.; Yin, M.; Zhao, W. Decreased immunoglobulin G in brain regions of elder female APOE4-TR mice accompany with Abeta accumulation. *Immun. Ageing* **2019**, *16*, 2. [[CrossRef](#)]
377. Wei, L.; Laurence, A.; Elias, K.M.; O'Shea, J.J. IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. *J. Biol. Chem.* **2007**, *282*, 34605–34610. [[CrossRef](#)]
378. Miossec, P.; Korn, T.; Kuchroo, V.K. Interleukin-17 and type 17 helper T cells. *N. Engl. J. Med.* **2009**, *361*, 888–898. [[CrossRef](#)]
379. Saresella, M.; Calabrese, E.; Marventano, I.; Piancone, F.; Gatti, A.; Alberoni, M.; Nemni, R.; Clerici, M. Increased activity of Th-17 and Th-9 lymphocytes and a skewing of the post-thymic differentiation pathway are seen in Alzheimer's disease. *Brain Behav. Immun.* **2011**, *25*, 539–547. [[CrossRef](#)]
380. Schuler, T.; Qin, Z.; Ibe, S.; Noben-Trauth, N.; Blankenstein, T. T helper cell type 1-associated and cytotoxic T lymphocyte-mediated tumor immunity is impaired in interleukin 4-deficient mice. *J. Exp. Med.* **1999**, *189*, 803–810. [[CrossRef](#)]
381. Garg, S.K.; Kipnis, J.; Banerjee, R. IFN-gamma and IL-4 differentially shape metabolic responses and neuroprotective phenotype of astrocytes. *J. Neurochem.* **2009**, *108*, 1155–1166. [[CrossRef](#)] [[PubMed](#)]
382. Bate, C.; Kempster, S.; Last, V.; Williams, A. Interferon-gamma increases neuronal death in response to amyloid-beta1-42. *J. Neuroinflammation* **2006**, *3*, 7. [[CrossRef](#)] [[PubMed](#)]
383. Gimsa, U.; Wolf, S.A.; Haas, D.; Bechmann, I.; Nitsch, R. Th2 cells support intrinsic anti-inflammatory properties of the brain. *J. Neuroimmunol.* **2001**, *119*, 73–80. [[CrossRef](#)]
384. Chen, G.F.; Xu, T.H.; Yan, Y.; Zhou, Y.R.; Jiang, Y.; Melcher, K.; Xu, H.E. Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacol. Sin.* **2017**, *38*, 1205–1235. [[CrossRef](#)] [[PubMed](#)]
385. Makin, S. The amyloid hypothesis on trial. *Nature* **2018**, *559*, S4–S7. [[CrossRef](#)] [[PubMed](#)]
386. Vidal, C.; Zhang, L. An Analysis of the Neurological and Molecular Alterations Underlying the Pathogenesis of Alzheimer's Disease. *Cells* **2021**, *10*, 546. [[CrossRef](#)] [[PubMed](#)]

387. Wilkins, H.M.; Swerdlow, R.H. Amyloid precursor protein processing and bioenergetics. *Brain Res. Bull.* **2017**, *133*, 71–79. [[CrossRef](#)] [[PubMed](#)]
388. Siegel, G.; Gerber, H.; Koch, P.; Bruestle, O.; Fraering, P.C.; Rajendran, L. The Alzheimer's Disease gamma-Secretase Generates Higher 42:40 Ratios for beta-Amyloid Than for p3 Peptides. *Cell Rep.* **2017**, *19*, 1967–1976. [[CrossRef](#)]
389. Belloy, M.E.; Napolioni, V.; Greicius, M.D. A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward. *Neuron* **2019**, *101*, 820–838. [[CrossRef](#)]
390. Xiao, X.; Liu, H.; Liu, X.; Zhang, W.; Zhang, S.; Jiao, B. APP, PSEN1, and PSEN2 Variants in Alzheimer's Disease: Systematic Re-evaluation According to ACMG Guidelines. *Front. Aging Neurosci.* **2021**, *13*, 695808. [[CrossRef](#)]
391. Chen, Y.; Strickland, M.R.; Soranno, A.; Holtzman, D.M. Apolipoprotein E: Structural Insights and Links to Alzheimer Disease Pathogenesis. *Neuron* **2021**, *109*, 205–221. [[CrossRef](#)] [[PubMed](#)]
392. Martens, Y.A.; Zhao, N.; Liu, C.C.; Kanekiyo, T.; Yang, A.J.; Goate, A.M.; Holtzman, D.M.; Bu, G. ApoE Cascade Hypothesis in the pathogenesis of Alzheimer's disease and related dementias. *Neuron* **2022**, *110*, 1304–1317. [[CrossRef](#)] [[PubMed](#)]
393. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* **2022**, *18*, 700–789. [[CrossRef](#)]
394. Kamboh, M.I.; Demirci, F.Y.; Wang, X.; Minster, R.L.; Carrasquillo, M.M.; Pankratz, V.S.; Younkin, S.G.; Saykin, A.J.; Alzheimer's Disease Neuroimaging, I.; Jun, G.; et al. Genome-wide association study of Alzheimer's disease. *Transl. Psychiatry* **2012**, *2*, e117. [[CrossRef](#)]
395. Bertram, L.; Tanzi, R.E. Genome-wide association studies in Alzheimer's disease. *Hum. Mol. Genet.* **2009**, *18*, R137–R145. [[CrossRef](#)]
396. Tanzi, R.E. The genetics of Alzheimer disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, 1–10. [[CrossRef](#)] [[PubMed](#)]
397. Harold, D.; Abraham, R.; Hollingworth, P.; Sims, R.; Gerrish, A.; Hamshere, M.L.; Pahwa, J.S.; Moskvin, V.; Dowzell, K.; Williams, A.; et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet.* **2009**, *41*, 1088–1093. [[CrossRef](#)] [[PubMed](#)]
398. Lambert, J.C.; Ibrahim-Verbaas, C.A.; Harold, D.; Naj, A.C.; Sims, R.; Bellenguez, C.; DeStafano, A.L.; Bis, J.C.; Beecham, G.W.; Grenier-Boley, B.; et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* **2013**, *45*, 1452–1458. [[CrossRef](#)]
399. Pimenova, A.A.; Raj, T.; Goate, A.M. Untangling Genetic Risk for Alzheimer's Disease. *Biol. Psychiatry* **2018**, *83*, 300–310. [[CrossRef](#)]
400. Zhao, Z.; Sagare, A.P.; Ma, Q.; Halliday, M.R.; Kong, P.; Kisler, K.; Winkler, E.A.; Ramanathan, A.; Kanekiyo, T.; Bu, G.; et al. Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance. *Nat. Neurosci.* **2015**, *18*, 978–987. [[CrossRef](#)]
401. Bell, R.D.; Sagare, A.P.; Friedman, A.E.; Bedi, G.S.; Holtzman, D.M.; Deane, R.; Zlokovic, B.V. Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. *J. Cereb. Blood Flow Metab.* **2007**, *27*, 909–918. [[CrossRef](#)] [[PubMed](#)]
402. Qi, X.M.; Wang, C.; Chu, X.K.; Li, G.; Ma, J.F. Intraventricular infusion of clusterin ameliorated cognition and pathology in Tg6799 model of Alzheimer's disease. *BMC Neurosci.* **2018**, *19*, 2. [[CrossRef](#)] [[PubMed](#)]
403. Rovelet-Lecrux, A.; Legallic, S.; Wallon, D.; Flaman, J.M.; Martinaud, O.; Bombois, S.; Rollin-Sillaire, A.; Michon, A.; Le Ber, I.; Pariente, J.; et al. A genome-wide study reveals rare CNVs exclusive to extreme phenotypes of Alzheimer disease. *Eur. J. Hum. Genet.* **2012**, *20*, 613–617. [[CrossRef](#)] [[PubMed](#)]
404. Wu, Z.; Guo, H.; Chow, N.; Sallstrom, J.; Bell, R.D.; Deane, R.; Brooks, A.I.; Kanagala, S.; Rubio, A.; Sagare, A.; et al. Role of the MEOX2 homeobox gene in neurovascular dysfunction in Alzheimer disease. *Nat. Med.* **2005**, *11*, 959–965. [[CrossRef](#)]
405. Atagi, Y.; Liu, C.C.; Painter, M.M.; Chen, X.F.; Verbeeck, C.; Zheng, H.; Li, X.; Rademakers, R.; Kang, S.S.; Xu, H.; et al. Apolipoprotein E Is a Ligand for Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). *J. Biol. Chem.* **2015**, *290*, 26043–26050. [[CrossRef](#)]
406. Bailey, C.C.; DeVaux, L.B.; Farzan, M. The Triggering Receptor Expressed on Myeloid Cells 2 Binds Apolipoprotein E. *J. Biol. Chem.* **2015**, *290*, 26033–26042. [[CrossRef](#)]
407. Suarez-Calvet, M.; Kleinberger, G.; Araque Caballero, M.A.; Brendel, M.; Rominger, A.; Alcolea, D.; Fortea, J.; Lleó, A.; Blesa, R.; Gispert, J.D.; et al. sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. *EMBO Mol. Med.* **2016**, *8*, 466–476. [[CrossRef](#)]
408. Colonna, M.; Wang, Y. TREM2 variants: New keys to decipher Alzheimer disease pathogenesis. *Nat. Rev. Neurosci.* **2016**, *17*, 201–207. [[CrossRef](#)]
409. Guerreiro, R.; Wojtas, A.; Bras, J.; Carrasquillo, M.; Rogaeva, E.; Majounie, E.; Cruchaga, C.; Sassi, C.; Kauwe, J.S.; Younkin, S.; et al. TREM2 variants in Alzheimer's disease. *N. Engl. J. Med.* **2013**, *368*, 117–127. [[CrossRef](#)]
410. Bradshaw, E.M.; Chibnik, L.B.; Keenan, B.T.; Ottoboni, L.; Raj, T.; Tang, A.; Rosenkrantz, L.L.; Imboya, S.; Lee, M.; Von Korff, A.; et al. CD33 Alzheimer's disease locus: Altered monocyte function and amyloid biology. *Nat. Neurosci.* **2013**, *16*, 848–850. [[CrossRef](#)]
411. Lambert, J.C.; Heath, S.; Even, G.; Champion, D.; Sleegers, K.; Hiltunen, M.; Combarros, O.; Zelenika, D.; Bullido, M.J.; Tavernier, B.; et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet.* **2009**, *41*, 1094–1099. [[CrossRef](#)]

412. Zhang, G.; Zhang, Y.; Shen, Y.; Wang, Y.; Zhao, M.; Sun, L. The Potential Role of Ferroptosis in Alzheimer's Disease. *J. Alzheimers Dis.* **2021**, *80*, 907–925. [[CrossRef](#)] [[PubMed](#)]
413. Uchida, Y.; Kan, H.; Sakurai, K.; Horimoto, Y.; Hayashi, E.; Iida, A.; Okamura, N.; Oishi, K.; Matsukawa, N. APOE varepsilon4 dose associates with increased brain iron and beta-amyloid via blood-brain barrier dysfunction. *J. Neurol. Neurosurg. Psychiatry* **2022**, *93*, 772–778. [[CrossRef](#)] [[PubMed](#)]
414. Nir, T.M.; Zhu, A.H.; Gari, I.B.; Dixon, D.; Islam, T.; Villalon-Reina, J.E.; Medland, S.E.; Thompson, P.M.; Jahanshad, N. Effects of ApoE4 and ApoE2 genotypes on subcortical magnetic susceptibility and microstructure in 27,535 participants from the UK Biobank. *Pac. Symp. Biocomput.* **2022**, *27*, 121–132. [[PubMed](#)]
415. Peters, D.G.; Connor, J.R.; Meadowcroft, M.D. The relationship between iron dyshomeostasis and amyloidogenesis in Alzheimer's disease: Two sides of the same coin. *Neurobiol. Dis.* **2015**, *81*, 49–65. [[CrossRef](#)]
416. Spotorno, N.; Acosta-Cabronero, J.; Stomrud, E.; Lampinen, B.; Strandberg, O.T.; van Westen, D.; Hansson, O. Relationship between cortical iron and tau aggregation in Alzheimer's disease. *Brain* **2020**, *143*, 1341–1349. [[CrossRef](#)]
417. Ramos, P.; Santos, A.; Pinto, N.R.; Mendes, R.; Magalhaes, T.; Almeida, A. Iron levels in the human brain: A post-mortem study of anatomical region differences and age-related changes. *J. Trace Elem. Med. Biol.* **2014**, *28*, 13–17. [[CrossRef](#)]
418. Connor, J.R.; Menzies, S.L.; St Martin, S.M.; Mufson, E.J. A histochemical study of iron, transferrin, and ferritin in Alzheimer's diseased brains. *J. Neurosci. Res.* **1992**, *31*, 75–83. [[CrossRef](#)]
419. Raha, A.A.; Vaishnav, R.A.; Friedland, R.P.; Bomford, A.; Raha-Chowdhury, R. The systemic iron-regulatory proteins hepcidin and ferroportin are reduced in the brain in Alzheimer's disease. *Acta Neuropathol. Commun.* **2013**, *1*, 55. [[CrossRef](#)]
420. Crespo, A.C.; Silva, B.; Marques, L.; Marcelino, E.; Maruta, C.; Costa, S.; Timoteo, A.; Vilares, A.; Couto, F.S.; Faustino, P.; et al. Genetic and biochemical markers in patients with Alzheimer's disease support a concerted systemic iron homeostasis dysregulation. *Neurobiol. Aging* **2014**, *35*, 777–785. [[CrossRef](#)]
421. Ashraf, A.; Jeandriens, J.; Parkes, H.G.; So, P.W. Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Alzheimer's disease: Evidence of ferroptosis. *Redox Biol.* **2020**, *32*, 101494. [[CrossRef](#)] [[PubMed](#)]
422. Ayton, S.; Wang, Y.; Diouf, I.; Schneider, J.A.; Brockman, J.; Morris, M.C.; Bush, A.I. Brain iron is associated with accelerated cognitive decline in people with Alzheimer pathology. *Mol. Psychiatry* **2020**, *25*, 2932–2941. [[CrossRef](#)] [[PubMed](#)]
423. McIntosh, A.; Mela, V.; Harty, C.; Minogue, A.M.; Costello, D.A.; Kerskens, C.; Lynch, M.A. Iron accumulation in microglia triggers a cascade of events that leads to altered metabolism and compromised function in APP/PS1 mice. *Brain Pathol.* **2019**, *29*, 606–621. [[CrossRef](#)] [[PubMed](#)]
424. Van Landeghem, G.F.; Sikstrom, C.; Beckman, L.E.; Adolfsson, R.; Beckman, L. Transferrin C2, metal binding and Alzheimer's disease. *Neuroreport* **1998**, *9*, 177–179. [[CrossRef](#)] [[PubMed](#)]
425. van Rensburg, S.J.; Carstens, M.E.; Potocnik, F.C.; Aucamp, A.K.; Taljaard, J.J. Increased frequency of the transferrin C2 subtype in Alzheimer's disease. *Neuroreport* **1993**, *4*, 1269–1271. [[CrossRef](#)]
426. Ashraf, A.; Stosnach, H.; Parkes, H.G.; Hye, A.; Powell, J.; So, P.-W.; For the AddNeuroMed consortium. Pattern of Altered Plasma Elemental Phosphorus, Calcium, Zinc, and Iron in Alzheimer's Disease. *Sci. Rep.* **2019**, *9*, 3147. [[CrossRef](#)] [[PubMed](#)]
427. Bao, W.D.; Pang, P.; Zhou, X.T.; Hu, F.; Xiong, W.; Chen, K.; Wang, J.; Wang, F.; Xie, D.; Hu, Y.Z.; et al. Loss of ferroportin induces memory impairment by promoting ferroptosis in Alzheimer's disease. *Cell Death Differ.* **2021**, *28*, 1548–1562. [[CrossRef](#)]
428. Connor, J.R.; Tucker, P.; Johnson, M.; Snyder, B. Ceruloplasmin levels in the human superior temporal gyrus in aging and Alzheimer's disease. *Neurosci. Lett.* **1993**, *159*, 88–90. [[CrossRef](#)] [[PubMed](#)]
429. Guerreiro, C.; Silva, B.; Crespo, A.C.; Marques, L.; Costa, S.; Timoteo, A.; Marcelino, E.; Maruta, C.; Vilares, A.; Matos, M.; et al. Decrease in APP and CP mRNA expression supports impairment of iron export in Alzheimer's disease patients. *Biochim. Biophys. Acta* **2015**, *1852*, 2116–2122. [[CrossRef](#)]
430. Xu, H.; Perreau, V.M.; Dent, K.A.; Bush, A.I.; Finkelstein, D.I.; Adlard, P.A. Iron Regulates Apolipoprotein E Expression and Secretion in Neurons and Astrocytes. *J. Alzheimers Dis.* **2016**, *51*, 471–487. [[CrossRef](#)]
431. Rogers, J.T.; Randall, J.D.; Cahill, C.M.; Eder, P.S.; Huang, X.; Gunshin, H.; Leiter, L.; McPhee, J.; Sarang, S.S.; Utsuki, T.; et al. An iron-responsive element type II in the 5'-untranslated region of the Alzheimer's amyloid precursor protein transcript. *J. Biol. Chem.* **2002**, *277*, 45518–45528. [[CrossRef](#)]
432. Amit, T.; Bar-Am, O.; Mechlovich, D.; Kupersmidt, L.; Youdim, M.B.H.; Weinreb, O. The novel multitarget iron chelating and propargylamine drug M30 affects APP regulation and processing activities in Alzheimer's disease models. *Neuropharmacology* **2017**, *123*, 359–367. [[CrossRef](#)] [[PubMed](#)]
433. Ayton, S.; Faux, N.G.; Bush, A.I. Association of Cerebrospinal Fluid Ferritin Level With Preclinical Cognitive Decline in APOE-epsilon4 Carriers. *JAMA Neurol.* **2017**, *74*, 122–125. [[CrossRef](#)] [[PubMed](#)]
434. Connor, J.R. CSF ferritin predicts CSF A-beta decline in biomarker-determined Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **2018**, *89*, 445. [[CrossRef](#)] [[PubMed](#)]
435. Tao, Y.; Wang, Y.; Rogers, J.T.; Wang, F. Perturbed iron distribution in Alzheimer's disease serum, cerebrospinal fluid, and selected brain regions: A systematic review and meta-analysis. *J. Alzheimer's Dis.* **2014**, *42*, 679–690. [[CrossRef](#)] [[PubMed](#)]
436. Choi, Y.K.; Kim, Y.M. Beneficial and Detrimental Roles of Heme Oxygenase-1 in the Neurovascular System. *Int. J. Mol. Sci.* **2022**, *23*, 7041. [[CrossRef](#)]
437. Chiabrando, D.; Fiorito, V.; Petrillo, S.; Tolosano, E. Unraveling the Role of Heme in Neurodegeneration. *Front. Neurosci.* **2018**, *12*, 712. [[CrossRef](#)]

438. Chua, J.J.E. HEBP1—An early trigger for neuronal cell death and circuit dysfunction in Alzheimer’s disease. *Semin. Cell Dev. Biol.* **2023**, *139*, 102–110. [[CrossRef](#)]
439. Flemmig, J.; Zamocky, M.; Alia, A. Amyloid beta and free heme: Bloody new insights into the pathogenesis of Alzheimer’s disease. *Neural Regen. Res.* **2018**, *13*, 1170–1174. [[CrossRef](#)]
440. Cullen, K.M.; Kocsi, Z.; Stone, J. Microvascular pathology in the aging human brain: Evidence that senile plaques are sites of microhaemorrhages. *Neurobiol. Aging* **2006**, *27*, 1786–1796. [[CrossRef](#)]
441. Holtzman, D.M.; Morris, J.C.; Goate, A.M. Alzheimer’s disease: The challenge of the second century. *Sci. Transl. Med.* **2011**, *3*, 77sr71. [[CrossRef](#)] [[PubMed](#)]
442. Hui, Y.; Wang, D.; Li, W.; Zhang, L.; Jin, J.; Ma, N.; Zhou, L.; Nakajima, O.; Zhao, W.; Gao, X. Long-term overexpression of heme oxygenase 1 promotes tau aggregation in mouse brain by inducing tau phosphorylation. *J. Alzheimer’s Dis.* **2011**, *26*, 299–313. [[CrossRef](#)] [[PubMed](#)]
443. Wang, D.; Hui, Y.; Peng, Y.; Tang, L.; Jin, J.; He, R.; Li, Y.; Zhang, S.; Li, L.; Zhou, Y.; et al. Overexpression of heme oxygenase 1 causes cognitive decline and affects pathways for tauopathy in mice. *J. Alzheimer’s Dis.* **2015**, *43*, 519–534. [[CrossRef](#)] [[PubMed](#)]
444. Cimini, F.A.; Perluigi, M.; Barchetta, I.; Cavallo, M.G.; Barone, E. Role of Biliverdin Reductase A in the Regulation of Insulin Signaling in Metabolic and Neurodegenerative Diseases: An Update. *Int. J. Mol. Sci.* **2022**, *23*, 5574. [[CrossRef](#)] [[PubMed](#)]
445. Vidal, C.; Daescu, K.; Fitzgerald, K.E.; Starokadomska, A.; Bezprozvanny, I.; Zhang, L. Amyloid beta perturbs elevated heme flux induced with neuronal development. *Alzheimer’s Dement.* **2019**, *5*, 27–37. [[CrossRef](#)]
446. Veinbergs, I.; Everson, A.; Sagara, Y.; Maslah, E. Neurotoxic effects of apolipoprotein E4 are mediated via dysregulation of calcium homeostasis. *J. Neurosci. Res.* **2002**, *67*, 379–387. [[CrossRef](#)] [[PubMed](#)]
447. Barger, S.W.; Mattson, M.P. Isoform-specific modulation by apolipoprotein E of the activities of secreted beta-amyloid precursor protein. *J. Neurochem.* **1997**, *69*, 60–67. [[CrossRef](#)]
448. Calvo-Rodriguez, M.; Hou, S.S.; Snyder, A.C.; Kharitonova, E.K.; Russ, A.N.; Das, S.; Fan, Z.; Muzikansky, A.; Garcia-Alloza, M.; Serrano-Pozo, A.; et al. Increased mitochondrial calcium levels associated with neuronal death in a mouse model of Alzheimer’s disease. *Nat. Commun.* **2020**, *11*, 2146. [[CrossRef](#)]
449. Calvo-Rodriguez, M.; Bacskai, B.J. Mitochondria and Calcium in Alzheimer’s Disease: From Cell Signaling to Neuronal Cell Death. *Trends Neurosci.* **2021**, *44*, 136–151. [[CrossRef](#)]
450. Scheiber, I.F.; Mercer, J.F.; Dringen, R. Metabolism and functions of copper in brain. *Prog. Neurobiol.* **2014**, *116*, 33–57. [[CrossRef](#)]
451. Lutsenko, S.; Bhattacharjee, A.; Hubbard, A.L. Copper handling machinery of the brain. *Metallomics* **2010**, *2*, 596–608. [[CrossRef](#)]
452. Hunt, D.M. Copper and neurological function. *Biol. Roles Copp.* **1980**, *79*, 247–266. [[CrossRef](#)]
453. Mercer, S.W.; Wang, J.; Burke, R. In Vivo Modeling of the Pathogenic Effect of Copper Transporter Mutations That Cause Menkes and Wilson Diseases, Motor Neuropathy, and Susceptibility to Alzheimer’s Disease. *J. Biol. Chem.* **2017**, *292*, 4113–4122. [[CrossRef](#)]
454. Bucossi, S.; Polimanti, R.; Mariani, S.; Ventriglia, M.; Bonvicini, C.; Migliore, S.; Manfellotto, D.; Salustri, C.; Vernieri, F.; Rossini, P.M.; et al. Association of K832R and R952K SNPs of Wilson’s disease gene with Alzheimer’s disease. *J. Alzheimers Dis.* **2012**, *29*, 913–919. [[CrossRef](#)]
455. Bayer, T.A.; Schafer, S.; Simons, A.; Kemmling, A.; Kamer, T.; Tepest, R.; Eckert, A.; Schussel, K.; Eikenberg, O.; Sturchler-Pierrat, C.; et al. Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Abeta production in APP23 transgenic mice. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 14187–14192. [[CrossRef](#)]
456. Atwood, C.S.; Moir, R.D.; Huang, X.; Scarpa, R.C.; Bacarra, N.M.; Romano, D.M.; Hartshorn, M.A.; Tanzi, R.E.; Bush, A.I. Dramatic aggregation of Alzheimer abeta by Cu(II) is induced by conditions representing physiological acidosis. *J. Biol. Chem.* **1998**, *273*, 12817–12826. [[CrossRef](#)]
457. Huang, X.; Cuajungco, M.P.; Atwood, C.S.; Hartshorn, M.A.; Tyndall, J.D.; Hanson, G.R.; Stokes, K.C.; Leopold, M.; Multhaup, G.; Goldstein, L.E.; et al. Cu(II) potentiation of alzheimer abeta neurotoxicity. Correlation with cell-free hydrogen peroxide production and metal reduction. *J. Biol. Chem.* **1999**, *274*, 37111–37116. [[CrossRef](#)]
458. Rottkamp, C.A.; Raina, A.K.; Zhu, X.; Gaier, E.; Bush, A.I.; Atwood, C.S.; Chevion, M.; Perry, G.; Smith, M.A. Redox-active iron mediates amyloid-beta toxicity. *Free Radic. Biol. Med.* **2001**, *30*, 447–450. [[CrossRef](#)]
459. Milton, N.G. Role of hydrogen peroxide in the aetiology of Alzheimer’s disease: Implications for treatment. *Drugs Aging* **2004**, *21*, 81–100. [[CrossRef](#)]
460. Bellingham, S.A.; Lahiri, D.K.; Maloney, B.; La Fontaine, S.; Multhaup, G.; Camakaris, J. Copper depletion down-regulates expression of the Alzheimer’s disease amyloid-beta precursor protein gene. *J. Biol. Chem.* **2004**, *279*, 20378–20386. [[CrossRef](#)]
461. Armendariz, A.D.; Gonzalez, M.; Loguinov, A.V.; Vulpe, C.D. Gene expression profiling in chronic copper overload reveals upregulation of Prnp and App. *Physiol. Genom.* **2004**, *20*, 45–54. [[CrossRef](#)]
462. Cater, M.A.; McInnes, K.T.; Li, Q.X.; Volitakis, I.; La Fontaine, S.; Mercer, J.F.; Bush, A.I. Intracellular copper deficiency increases amyloid-beta secretion by diverse mechanisms. *Biochem. J.* **2008**, *412*, 141–152. [[CrossRef](#)]
463. Gerber, H.; Wu, F.; Dimitrov, M.; Garcia Osuna, G.M.; Fraering, P.C. Zinc and Copper Differentially Modulate Amyloid Precursor Protein Processing by gamma-Secretase and Amyloid-beta Peptide Production. *J. Biol. Chem.* **2017**, *292*, 3751–3767. [[CrossRef](#)]
464. Phinney, A.L.; Drisaldi, B.; Schmidt, S.D.; Lugowski, S.; Coronado, V.; Liang, Y.; Horne, P.; Yang, J.; Sekoulidis, J.; Coomaraswamy, J.; et al. In vivo reduction of amyloid-beta by a mutant copper transporter. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 14193–14198. [[CrossRef](#)]

465. Hu, X.; Zhang, Q.; Wang, W.; Yuan, Z.; Zhu, X.; Chen, B.; Chen, X. Tripeptide GGH as the Inhibitor of Copper-Amyloid-beta-Mediated Redox Reaction and Toxicity. *ACS Chem. Neurosci.* **2016**, *7*, 1255–1263. [[CrossRef](#)]
466. Perrone, L.; Mothes, E.; Vignes, M.; Mockel, A.; Figueroa, C.; Miquel, M.C.; Maddelein, M.L.; Faller, P. Copper transfer from Cu-Abeta to human serum albumin inhibits aggregation, radical production and reduces Abeta toxicity. *Chembiochem* **2010**, *11*, 110–118. [[CrossRef](#)]
467. Puglielli, L.; Friedlich, A.L.; Setchell, K.D.; Nagano, S.; Opazo, C.; Cherny, R.A.; Barnham, K.J.; Wade, J.D.; Melov, S.; Kovacs, D.M.; et al. Alzheimer disease beta-amyloid activity mimics cholesterol oxidase. *J. Clin. Investig.* **2005**, *115*, 2556–2563. [[CrossRef](#)]
468. Reybier, K.; Ayala, S.; Alies, B.; Rodrigues, J.V.; Bustos Rodriguez, S.; La Penna, G.; Collin, F.; Gomes, C.M.; Hureau, C.; Faller, P. Free Superoxide is an Intermediate in the Production of H₂O₂ by Copper(I)-Abeta Peptide and O₂. *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 1085–1089. [[CrossRef](#)]
469. Opazo, C.; Huang, X.; Cherny, R.A.; Moir, R.D.; Roher, A.E.; White, A.R.; Cappai, R.; Masters, C.L.; Tanzi, R.E.; Inestrosa, N.C.; et al. Metalloenzyme-like activity of Alzheimer's disease beta-amyloid. Cu-dependent catalytic conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H₂O(2). *J. Biol. Chem.* **2002**, *277*, 40302–40308. [[CrossRef](#)]
470. Greenough, M.A.; Volitakis, I.; Li, Q.X.; Laughton, K.; Evin, G.; Ho, M.; Dalziel, A.H.; Camakaris, J.; Bush, A.I. Presenilins promote the cellular uptake of copper and zinc and maintain copper chaperone of SOD1-dependent copper/zinc superoxide dismutase activity. *J. Biol. Chem.* **2011**, *286*, 9776–9786. [[CrossRef](#)]
471. Ma, Q.; Li, Y.; Du, J.; Liu, H.; Kanazawa, K.; Nemoto, T.; Nakanishi, H.; Zhao, Y. Copper binding properties of a tau peptide associated with Alzheimer's disease studied by CD, NMR, and MALDI-TOF MS. *Peptides* **2006**, *27*, 841–849. [[CrossRef](#)] [[PubMed](#)]
472. Su, X.Y.; Wu, W.H.; Huang, Z.P.; Hu, J.; Lei, P.; Yu, C.H.; Zhao, Y.F.; Li, Y.M. Hydrogen peroxide can be generated by tau in the presence of Cu(II). *Biochem. Biophys. Res. Commun.* **2007**, *358*, 661–665. [[CrossRef](#)]
473. Sayre, L.M.; Perry, G.; Harris, P.L.; Liu, Y.; Schubert, K.A.; Smith, M.A. In situ oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease: A central role for bound transition metals. *J. Neurochem.* **2000**, *74*, 270–279. [[CrossRef](#)] [[PubMed](#)]
474. Danscher, G.; Stoltenberg, M. Zinc-specific autometallographic in vivo selenium methods: Tracing of zinc-enriched (ZEN) terminals, ZEN pathways, and pools of zinc ions in a multitude of other ZEN cells. *J. Histochem. Cytochem.* **2005**, *53*, 141–153. [[CrossRef](#)] [[PubMed](#)]
475. Vogt, K.; Mellor, J.; Tong, G.; Nicoll, R. The actions of synaptically released zinc at hippocampal mossy fiber synapses. *Neuron* **2000**, *26*, 187–196. [[CrossRef](#)] [[PubMed](#)]
476. Bush, A.I.; Pettingell, W.H., Jr.; Paradis, M.D.; Tanzi, R.E. Modulation of A beta adhesiveness and secretase site cleavage by zinc. *J. Biol. Chem.* **1994**, *269*, 12152–12158. [[CrossRef](#)] [[PubMed](#)]
477. Oh, S.B.; Kim, J.A.; Park, S.; Lee, J.Y. Associative Interactions among Zinc, Apolipoprotein E, and Amyloid-beta in the Amyloid Pathology. *Int. J. Mol. Sci.* **2020**, *21*, 802. [[CrossRef](#)] [[PubMed](#)]
478. Esler, W.P.; Stimson, E.R.; Jennings, J.M.; Ghilardi, J.R.; Mantyh, P.W.; Maggio, J.E. Zinc-induced aggregation of human and rat beta-amyloid peptides in vitro. *J. Neurochem.* **1996**, *66*, 723–732. [[CrossRef](#)]
479. Palmiter, R.D.; Cole, T.B.; Quaife, C.J.; Findley, S.D. ZnT-3, a putative transporter of zinc into synaptic vesicles. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14934–14939. [[CrossRef](#)]
480. Adlard, P.A.; Parncutt, J.M.; Finkelstein, D.I.; Bush, A.I. Cognitive loss in zinc transporter-3 knock-out mice: A phenocopy for the synaptic and memory deficits of Alzheimer's disease? *J. Neurosci.* **2010**, *30*, 1631–1636. [[CrossRef](#)]
481. Hoke, D.E.; Tan, J.L.; Ilaya, N.T.; Culvenor, J.G.; Smith, S.J.; White, A.R.; Masters, C.L.; Evin, G.M. In vitro gamma-secretase cleavage of the Alzheimer's amyloid precursor protein correlates to a subset of presenilin complexes and is inhibited by zinc. *FEBS J.* **2005**, *272*, 5544–5557. [[CrossRef](#)]
482. Xu, H.; Gupta, V.B.; Martins, I.J.; Martins, R.N.; Fowler, C.J.; Bush, A.I.; Finkelstein, D.I.; Adlard, P.A. Zinc affects the proteolytic stability of Apolipoprotein E in an isoform-dependent way. *Neurobiol. Dis.* **2015**, *81*, 38–48. [[CrossRef](#)]
483. Boom, A.; Authelet, M.; Dedecker, R.; Frederick, C.; Van Heurck, R.; Daubie, V.; Leroy, K.; Pochet, R.; Brion, J.P. Bimodal modulation of tau protein phosphorylation and conformation by extracellular Zn²⁺ in human-tau transfected cells. *Biochim. Biophys. Acta* **2009**, *1793*, 1058–1067. [[CrossRef](#)]
484. Zhou, F.; Chen, S.; Xiong, J.; Li, Y.; Qu, L. Luteolin reduces zinc-induced tau phosphorylation at Ser262/356 in an ROS-dependent manner in SH-SY5Y cells. *Biol. Trace Elem. Res.* **2012**, *149*, 273–279. [[CrossRef](#)]
485. Craven, K.M.; Kochen, W.R.; Hernandez, C.M.; Flinn, J.M. Zinc Exacerbates Tau Pathology in a Tau Mouse Model. *J. Alzheimers Dis.* **2018**, *64*, 617–630. [[CrossRef](#)]
486. Gwon, A.R.; Park, J.S.; Park, J.H.; Baik, S.H.; Jeong, H.Y.; Hyun, D.H.; Park, K.W.; Jo, D.G. Selenium attenuates A beta production and A beta-induced neuronal death. *Neurosci. Lett.* **2010**, *469*, 391–395. [[CrossRef](#)]
487. Cardoso, B.R.; Hare, D.J.; Bush, A.I.; Roberts, B.R. Glutathione peroxidase 4: A new player in neurodegeneration? *Mol. Psychiatry* **2017**, *22*, 328–335. [[CrossRef](#)]
488. Yang, W.S.; SriRamaratnam, R.; Welsch, M.E.; Shimada, K.; Skouta, R.; Viswanathan, V.S.; Cheah, J.H.; Clemons, P.A.; Shamji, A.F.; Clish, C.B.; et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell* **2014**, *156*, 317–331. [[CrossRef](#)]
489. Cardoso, B.R.; Ong, T.P.; Jacob-Filho, W.; Jaluul, O.; Freitas, M.I.; Cozzolino, S.M. Nutritional status of selenium in Alzheimer's disease patients. *Br. J. Nutr.* **2010**, *103*, 803–806. [[CrossRef](#)]

490. Olde Rikkert, M.G.; Verhey, F.R.; Sijben, J.W.; Bouwman, F.H.; Dautzenberg, P.L.; Lansink, M.; Sipers, W.M.; van Asselt, D.Z.; van Hees, A.M.; Stevens, M.; et al. Differences in nutritional status between very mild Alzheimer's disease patients and healthy controls. *J. Alzheimers Dis.* **2014**, *41*, 261–271. [[CrossRef](#)]
491. Cardoso, B.R.; Hare, D.J.; Lind, M.; McLean, C.A.; Volitakis, I.; Laws, S.M.; Masters, C.L.; Bush, A.I.; Roberts, B.R. The APOE epsilon4 Allele Is Associated with Lower Selenium Levels in the Brain: Implications for Alzheimer's Disease. *ACS Chem. Neurosci.* **2017**, *8*, 1459–1464. [[CrossRef](#)]
492. Varikasuvu, S.R.; Prasad, V.S.; Kothapalli, J.; Manne, M. Brain Selenium in Alzheimer's Disease (BRAIN SEAD Study): A Systematic Review and Meta-Analysis. *Biol. Trace Elem. Res.* **2019**, *189*, 361–369. [[CrossRef](#)]
493. Berr, C.; Balansard, B.; Arnaud, J.; Rousset, A.M.; Alperovitch, A. Cognitive decline is associated with systemic oxidative stress: The EVA study. *Etude du Vieillissement Arteriel. J. Am. Geriatr. Soc.* **2000**, *48*, 1285–1291. [[CrossRef](#)]
494. Benzi, G.; Moretti, A. Are reactive oxygen species involved in Alzheimer's disease? *Neurobiol. Aging* **1995**, *16*, 661–674. [[CrossRef](#)]
495. Pratico, D. Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy: Lights and shadows. *Ann. N. Y. Acad. Sci.* **2008**, *1147*, 70–78. [[CrossRef](#)]
496. Markesbery, W.R. Oxidative stress hypothesis in Alzheimer's disease. *Free Radic. Biol. Med.* **1997**, *23*, 134–147. [[CrossRef](#)]
497. Castellani, R.; Hirai, K.; Aliev, G.; Drew, K.L.; Nunomura, A.; Takeda, A.; Cash, A.D.; Obrenovich, M.E.; Perry, G.; Smith, M.A. Role of mitochondrial dysfunction in Alzheimer's disease. *J. Neurosci. Res.* **2002**, *70*, 357–360. [[CrossRef](#)]
498. Gibson, G.E.; Sheu, K.F.; Blass, J.P. Abnormalities of mitochondrial enzymes in Alzheimer disease. *J. Neural Transm.* **1998**, *105*, 855–870. [[CrossRef](#)]
499. Sochocka, M.; Koutsouraki, E.S.; Gasiorowski, K.; Leszek, J. Vascular oxidative stress and mitochondrial failure in the pathobiology of Alzheimer's disease: A new approach to therapy. *CNS Neurol. Disord. Drug Targets* **2013**, *12*, 870–881. [[CrossRef](#)]
500. Vakifahmetoglu-Norberg, H.; Ouchida, A.T.; Norberg, E. The role of mitochondria in metabolism and cell death. *Biochem. Biophys. Res. Commun.* **2017**, *482*, 426–431. [[CrossRef](#)]
501. Cadonic, C.; Sabbir, M.G.; Albensi, B.C. Mechanisms of Mitochondrial Dysfunction in Alzheimer's Disease. *Mol. Neurobiol.* **2016**, *53*, 6078–6090. [[CrossRef](#)] [[PubMed](#)]
502. Reddy, P.H.; Tripathi, R.; Troung, Q.; Tirumala, K.; Reddy, T.P.; Anekonda, V.; Shirendeb, U.P.; Calkins, M.J.; Reddy, A.P.; Mao, P.; et al. Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: Implications to mitochondria-targeted antioxidant therapeutics. *Biochim. Biophys. Acta* **2012**, *1822*, 639–649. [[CrossRef](#)] [[PubMed](#)]
503. Piaceri, I.; Rinnoci, V.; Bagnoli, S.; Failli, Y.; Sorbi, S. Mitochondria and Alzheimer's disease. *J. Neurol. Sci.* **2012**, *322*, 31–34. [[CrossRef](#)]
504. Sorbi, S.; Bird, E.D.; Blass, J.P. Decreased pyruvate dehydrogenase complex activity in Huntington and Alzheimer brain. *Ann. Neurol.* **1983**, *13*, 72–78. [[CrossRef](#)] [[PubMed](#)]
505. Curti, D.; Rognoni, F.; Gasparini, L.; Cattaneo, A.; Paolillo, M.; Racchi, M.; Zani, L.; Bianchetti, A.; Trabucchi, M.; Bergamaschi, S.; et al. Oxidative metabolism in cultured fibroblasts derived from sporadic Alzheimer's disease (AD) patients. *Neurosci. Lett.* **1997**, *236*, 13–16. [[CrossRef](#)] [[PubMed](#)]
506. Gibson, G.E.; Sheu, K.F.; Blass, J.P.; Baker, A.; Carlson, K.C.; Harding, B.; Perrino, P. Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. *Arch. Neurol.* **1988**, *45*, 836–840. [[CrossRef](#)]
507. Gella, A.; Durany, N. Oxidative stress in Alzheimer disease. *Cell Adhes. Migr.* **2009**, *3*, 88–93. [[CrossRef](#)]
508. Barbagallo, M.; Marotta, F.; Dominguez, L.J. Oxidative stress in patients with Alzheimer's disease: Effect of extracts of fermented papaya powder. *Mediat. Inflamm.* **2015**, *2015*, 624801. [[CrossRef](#)]
509. Pacheris, M.; Beretta, S.; Ferrarese, C. Peripheral markers of oxidative stress and excitotoxicity in neurodegenerative disorders: Tools for diagnosis and therapy? *J. Alzheimers Dis.* **2004**, *6*, 177–184. [[CrossRef](#)]
510. Galbusera, C.; Facheris, M.; Magni, F.; Galimberti, G.; Sala, G.; Tremolada, L.; Isella, V.; Guerini, F.R.; Appollonio, I.; Galli-Kienle, M.; et al. Increased susceptibility to plasma lipid peroxidation in Alzheimer disease patients. *Curr. Alzheimer Res.* **2004**, *1*, 103–109. [[CrossRef](#)]
511. Butterfield, D.A.; Drake, J.; Pocernich, C.; Castegna, A. Evidence of oxidative damage in Alzheimer's disease brain: Central role for amyloid beta-peptide. *Trends Mol. Med.* **2001**, *7*, 548–554. [[CrossRef](#)] [[PubMed](#)]
512. Butterfield, D.A. beta-Amyloid-associated free radical oxidative stress and neurotoxicity: Implications for Alzheimer's disease. *Chem. Res. Toxicol.* **1997**, *10*, 495–506. [[CrossRef](#)] [[PubMed](#)]
513. Varadarajan, S.; Yatin, S.; Aksenova, M.; Butterfield, D.A. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *J. Struct. Biol.* **2000**, *130*, 184–208. [[CrossRef](#)]
514. Yatin, S.M.; Yatin, M.; Varadarajan, S.; Ain, K.B.; Butterfield, D.A. Role of spermine in amyloid beta-peptide-associated free radical-induced neurotoxicity. *J. Neurosci. Res.* **2001**, *63*, 395–401. [[CrossRef](#)] [[PubMed](#)]
515. Yatin, S.M.; Varadarajan, S.; Link, C.D.; Butterfield, D.A. In vitro and in vivo oxidative stress associated with Alzheimer's amyloid beta-peptide (1-42). *Neurobiol. Aging* **1999**, *20*, 325–330; discussion 339–342. [[CrossRef](#)]
516. Yatin, S.M.; Varadarajan, S.; Butterfield, D.A. Vitamin E Prevents Alzheimer's Amyloid beta-Peptide (1-42)-Induced Neuronal Protein Oxidation and Reactive Oxygen Species Production. *J. Alzheimers Dis.* **2000**, *2*, 123–131. [[CrossRef](#)]
517. Butterfield, D.A.; Lauderback, C.M. 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.* **2002**, *32*, 1050–1060. [[CrossRef](#)]

518. Daniels, W.M.; van Rensburg, S.J.; van Zyl, J.M.; Taljaard, J.J. Melatonin prevents beta-amyloid-induced lipid peroxidation. *J. Pineal Res.* **1998**, *24*, 78–82. [[CrossRef](#)]
519. Bruce-Keller, A.J.; Begley, J.G.; Fu, W.; Butterfield, D.A.; Bredesen, D.E.; Hutchins, J.B.; Hensley, K.; Mattson, M.P. Bcl-2 protects isolated plasma and mitochondrial membranes against lipid peroxidation induced by hydrogen peroxide and amyloid beta-peptide. *J. Neurochem.* **1998**, *70*, 31–39. [[CrossRef](#)]
520. Mecocci, P.; MacGarvey, U.; Kaufman, A.E.; Koontz, D.; Shoffner, J.M.; Wallace, D.C.; Beal, M.F. Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. *Ann. Neurol.* **1993**, *34*, 609–616. [[CrossRef](#)]
521. Markesbery, W.R.; Lovell, M.A. DNA oxidation in Alzheimer's disease. *Antioxid. Redox Signal.* **2006**, *8*, 2039–2045. [[CrossRef](#)] [[PubMed](#)]
522. Pena-Bautista, C.; Tirlle, T.; Lopez-Nogueroles, M.; Vento, M.; Baquero, M.; Chafer-Pericas, C. Oxidative Damage of DNA as Early Marker of Alzheimer's Disease. *Int. J. Mol. Sci.* **2019**, *20*, 6136. [[CrossRef](#)]
523. Moslemnezhad, A.; Mahjoub, S.; Moghadasi, M. Altered plasma marker of oxidative DNA damage and total antioxidant capacity in patients with Alzheimer's disease. *Caspian J. Intern. Med.* **2016**, *7*, 88–92. [[PubMed](#)]
524. Munch, G.; Cunningham, A.M.; Riederer, P.; Braak, E. Advanced glycation endproducts are associated with Hirano bodies in Alzheimer's disease. *Brain Res.* **1998**, *796*, 307–310. [[CrossRef](#)] [[PubMed](#)]
525. Li, X.H.; Lv, B.L.; Xie, J.Z.; Liu, J.; Zhou, X.W.; Wang, J.Z. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. *Neurobiol. Aging* **2012**, *33*, 1400–1410. [[CrossRef](#)]
526. Vitek, M.P.; Bhattacharya, K.; Glendening, J.M.; Stopa, E.; Vlassara, H.; Bucala, R.; Manogue, K.; Cerami, A. Advanced glycation end products contribute to amyloidosis in Alzheimer disease. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4766–4770. [[CrossRef](#)]
527. Wang, X.; Su, B.; Siedlak, S.L.; Moreira, P.I.; Fujioka, H.; Wang, Y.; Casadesus, G.; Zhu, X. Amyloid-beta overproduction causes abnormal mitochondrial dynamics via differential modulation of mitochondrial fission/fusion proteins. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 19318–19323. [[CrossRef](#)]
528. Kandimalla, R.; Reddy, P.H. Multiple faces of dynamin-related protein 1 and its role in Alzheimer's disease pathogenesis. *Biochim. Biophys. Acta* **2016**, *1862*, 814–828. [[CrossRef](#)]
529. Ren, Z.; Zhang, X.; Ding, T.; Zhong, Z.; Hu, H.; Xu, Z.; Deng, J. Mitochondrial Dynamics Imbalance: A Strategy for Promoting Viral Infection. *Front. Microbiol.* **2020**, *11*, 1992. [[CrossRef](#)]
530. Wang, X.; Su, B.; Lee, H.G.; Li, X.; Perry, G.; Smith, M.A.; Zhu, X. Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *J. Neurosci.* **2009**, *29*, 9090–9103. [[CrossRef](#)]
531. Leuner, K.; Schutt, T.; Kurz, C.; Eckert, S.H.; Schiller, C.; Occhipinti, A.; Mai, S.; Jendrach, M.; Eckert, G.P.; Kruse, S.E.; et al. Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation. *Antioxid. Redox Signal.* **2012**, *16*, 1421–1433. [[CrossRef](#)] [[PubMed](#)]
532. Leuner, K.; Schulz, K.; Schutt, T.; Pantel, J.; Prvulovic, D.; Rhein, V.; Savaskan, E.; Czech, C.; Eckert, A.; Muller, W.E. Peripheral mitochondrial dysfunction in Alzheimer's disease: Focus on lymphocytes. *Mol. Neurobiol.* **2012**, *46*, 194–204. [[CrossRef](#)] [[PubMed](#)]
533. Cardoso, S.M.; Santos, S.; Swerdlow, R.H.; Oliveira, C.R. Functional mitochondria are required for amyloid beta-mediated neurotoxicity. *FASEB J.* **2001**, *15*, 1439–1441. [[CrossRef](#)]
534. Swerdlow, R.H.; Khan, S.M. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Med. Hypotheses* **2004**, *63*, 8–20. [[CrossRef](#)] [[PubMed](#)]
535. Moreira, P.I.; Cardoso, S.M.; Santos, M.S.; Oliveira, C.R. The key role of mitochondria in Alzheimer's disease. *J. Alzheimers Dis.* **2006**, *9*, 101–110. [[CrossRef](#)]
536. Moreira, P.I.; Santos, M.S.; Sena, C.; Seica, R.; Oliveira, C.R. Insulin protects against amyloid beta-peptide toxicity in brain mitochondria of diabetic rats. *Neurobiol. Dis.* **2005**, *18*, 628–637. [[CrossRef](#)]
537. Moreira, P.I.; Santos, M.S.; Sena, C.; Nunes, E.; Seica, R.; Oliveira, C.R. CoQ10 therapy attenuates amyloid beta-peptide toxicity in brain mitochondria isolated from aged diabetic rats. *Exp. Neurol.* **2005**, *196*, 112–119. [[CrossRef](#)]
538. Gasparini, L.; Gouras, G.K.; Wang, R.; Gross, R.S.; Beal, M.F.; Greengard, P.; Xu, H. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *J. Neurosci.* **2001**, *21*, 2561–2570. [[CrossRef](#)]
539. Solano, D.C.; Sironi, M.; Bonfini, C.; Solerte, S.B.; Govoni, S.; Racchi, M. Insulin regulates soluble amyloid precursor protein release via phosphatidyl inositol 3 kinase-dependent pathway. *FASEB J.* **2000**, *14*, 1015–1022. [[CrossRef](#)]
540. Cabezas-Opazo, F.A.; Vergara-Pulgar, K.; Perez, M.J.; Jara, C.; Osorio-Fuentealba, C.; Quintanilla, R.A. Mitochondrial Dysfunction Contributes to the Pathogenesis of Alzheimer's Disease. *Oxidative Med. Cell. Longev.* **2015**, *2015*, 509654. [[CrossRef](#)]
541. Johri, A.; Beal, M.F. Mitochondrial dysfunction in neurodegenerative diseases. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 619–630. [[CrossRef](#)] [[PubMed](#)]
542. Cheng, Y.; Bai, F. The Association of Tau With Mitochondrial Dysfunction in Alzheimer's Disease. *Front. Neurosci.* **2018**, *12*, 163. [[CrossRef](#)] [[PubMed](#)]
543. Moreira, P.I.; Carvalho, C.; Zhu, X.; Smith, M.A.; Perry, G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. *Biochim. Biophys. Acta* **2010**, *1802*, 2–10. [[CrossRef](#)]
544. Wallace, D.C. Mitochondrial diseases in man and mouse. *Science* **1999**, *283*, 1482–1488. [[CrossRef](#)] [[PubMed](#)]
545. Bell, R.D.; Winkler, E.A.; Singh, I.; Sagare, A.P.; Deane, R.; Wu, Z.; Holtzman, D.M.; Betsholtz, C.; Armulik, A.; Sallstrom, J.; et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature* **2012**, *485*, 512–516. [[CrossRef](#)]

546. Davies, D.A. The Role of APOE and NF- κ B in Alzheimer's Disease. *Immuno* **2021**, *1*, 391–399. [[CrossRef](#)]
547. Halliday, M.R.; Pomara, N.; Sagare, A.P.; Mack, W.J.; Frangione, B.; Zlokovic, B.V. Relationship between cyclophilin a levels and matrix metalloproteinase 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood-brain barrier breakdown. *JAMA Neurol.* **2013**, *70*, 1198–1200. [[CrossRef](#)] [[PubMed](#)]
548. Berlanga-Acosta, J.; Guillen-Nieto, G.; Rodriguez-Rodriguez, N.; Bringas-Vega, M.L.; Garcia-Del-Barco-Herrera, D.; Berlanga-Saez, J.O.; Garcia-Ojalvo, A.; Valdes-Sosa, M.J.; Valdes-Sosa, P.A. Insulin Resistance at the Crossroad of Alzheimer Disease Pathology: A Review. *Front. Endocrinol.* **2020**, *11*, 560375. [[CrossRef](#)] [[PubMed](#)]
549. Protas, H.D.; Chen, K.; Langbaum, J.B.; Fleisher, A.S.; Alexander, G.E.; Lee, W.; Bandy, D.; de Leon, M.J.; Mosconi, L.; Buckley, S.; et al. Posterior cingulate glucose metabolism, hippocampal glucose metabolism, and hippocampal volume in cognitively normal, late-middle-aged persons at 3 levels of genetic risk for Alzheimer disease. *JAMA Neurol.* **2013**, *70*, 320–325. [[CrossRef](#)]
550. An, Y.; Varma, V.R.; Varma, S.; Casanova, R.; Dammer, E.; Pletnikova, O.; Chia, C.W.; Egan, J.M.; Ferrucci, L.; Troncoso, J.; et al. Evidence for brain glucose dysregulation in Alzheimer's disease. *Alzheimers Dement.* **2018**, *14*, 318–329. [[CrossRef](#)]
551. Arseniou, S.; Siokas, V.; Aloizou, A.M.; Stamati, P.; Mentis, A.A.; Tsouris, Z.; Dastamani, M.; Peristeri, E.; Valotassiou, V.; Bogdanos, D.P.; et al. SLC2A3 rs12842 polymorphism and risk for Alzheimer's disease. *Neurol. Res.* **2020**, *42*, 853–861. [[CrossRef](#)] [[PubMed](#)]
552. Simpson, I.A.; Chundu, K.R.; Davies-Hill, T.; Honer, W.G.; Davies, P. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. *Ann. Neurol.* **1994**, *35*, 546–551. [[CrossRef](#)] [[PubMed](#)]
553. Kulas, J.A.; Weigel, T.K.; Ferris, H.A. Insulin resistance and impaired lipid metabolism as a potential link between diabetes and Alzheimer's disease. *Drug Dev. Res.* **2020**, *81*, 194–205. [[CrossRef](#)] [[PubMed](#)]
554. Wakabayashi, T.; Yamaguchi, K.; Matsui, K.; Sano, T.; Kubota, T.; Hashimoto, T.; Mano, A.; Yamada, K.; Matsuo, Y.; Kubota, N.; et al. Differential effects of diet- and genetically-induced brain insulin resistance on amyloid pathology in a mouse model of Alzheimer's disease. *Mol. Neurodegener.* **2019**, *14*, 15. [[CrossRef](#)] [[PubMed](#)]
555. Spinelli, M.; Fusco, S.; Mainardi, M.; Scala, F.; Natale, F.; Lapenta, R.; Mattera, A.; Rinaudo, M.; Li Puma, D.D.; Ripoli, C.; et al. Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. *Nat. Commun.* **2017**, *8*, 2009. [[CrossRef](#)]
556. Kothari, V.; Luo, Y.; Tornabene, T.; O'Neill, A.M.; Greene, M.W.; Geetha, T.; Babu, J.R. High fat diet induces brain insulin resistance and cognitive impairment in mice. *Biochim. Biophys. Acta Mol. Basis Dis.* **2017**, *1863*, 499–508. [[CrossRef](#)]
557. Ma, Q.L.; Yang, F.; Rosario, E.R.; Ubeda, O.J.; Beech, W.; Gant, D.J.; Chen, P.P.; Hudspeth, B.; Chen, C.; Zhao, Y.; et al. Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: Suppression by omega-3 fatty acids and curcumin. *J. Neurosci.* **2009**, *29*, 9078–9089. [[CrossRef](#)]
558. Bomfim, T.R.; Forny-Germano, L.; Sathler, L.B.; Brito-Moreira, J.; Houzel, J.C.; Decker, H.; Silverman, M.A.; Kazi, H.; Melo, H.M.; McClean, P.L.; et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated A β oligomers. *J. Clin. Investig.* **2012**, *122*, 1339–1353. [[CrossRef](#)]
559. Femminella, G.D.; Livingston, N.R.; Raza, S.; van der Doef, T.; Frangou, E.; Love, S.; Busza, G.; Calsolaro, V.; Carver, S.; Holmes, C.; et al. Does insulin resistance influence neurodegeneration in non-diabetic Alzheimer's subjects? *Alzheimers Res. Ther.* **2021**, *13*, 47. [[CrossRef](#)]
560. Yadav, Y.; Dey, C.S. PP2C α aggravates neuronal insulin resistance leading to AD-like phenotype in vitro. *Biochem. Biophys. Res. Commun.* **2023**, *644*, 49–54. [[CrossRef](#)]
561. Plaschke, K.; Kopitz, J.; Siegelin, M.; Schliebs, R.; Salkovic-Petrisic, M.; Riederer, P.; Hoyer, S. Insulin-resistant brain state after intracerebroventricular streptozotocin injection exacerbates Alzheimer-like changes in Tg2576 A β PP-overexpressing mice. *J. Alzheimers Dis.* **2010**, *19*, 691–704. [[CrossRef](#)] [[PubMed](#)]
562. Lee, J.H.; Kim, H.J.; Kim, J.U.; Yook, T.H.; Kim, K.H.; Lee, J.Y.; Yang, G. A Novel Treatment Strategy by Natural Products in NLRP3 Inflammasome-Mediated Neuroinflammation in Alzheimer's and Parkinson's Disease. *Int. J. Mol. Sci.* **2021**, *22*, 1324. [[CrossRef](#)] [[PubMed](#)]
563. Dempsey, C.; Rubio Araiz, A.; Bryson, K.J.; Finucane, O.; Larkin, C.; Mills, E.L.; Robertson, A.A.B.; Cooper, M.A.; O'Neill, L.A.J.; Lynch, M.A. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-beta and cognitive function in APP/PS1 mice. *Brain Behav. Immun.* **2017**, *61*, 306–316. [[CrossRef](#)] [[PubMed](#)]
564. Ansari, M.A.; Scheff, S.W. Oxidative stress in the progression of Alzheimer disease in the frontal cortex. *J. Neuropathol. Exp. Neurol.* **2010**, *69*, 155–167. [[CrossRef](#)]
565. Mandal, P.K.; Saharan, S.; Tripathi, M.; Murari, G. Brain glutathione levels—a novel biomarker for mild cognitive impairment and Alzheimer's disease. *Biol. Psychiatry* **2015**, *78*, 702–710. [[CrossRef](#)]
566. Shukla, D.; Mandal, P.K.; Tripathi, M.; Vishwakarma, G.; Mishra, R.; Sandal, K. Quantitation of in vivo brain glutathione conformers in cingulate cortex among age-matched control, MCI, and AD patients using MEGA-PRESS. *Hum. Brain Mapp.* **2020**, *41*, 194–217. [[CrossRef](#)]
567. Jazvinscak Jembrek, M.; Hof, P.R.; Simic, G. Ceramides in Alzheimer's Disease: Key Mediators of Neuronal Apoptosis Induced by Oxidative Stress and A β Accumulation. *Oxidative Med. Cell. Longev.* **2015**, *2015*, 346783. [[CrossRef](#)]
568. Kurz, J.; Parnham, M.J.; Geisslinger, G.; Schiffmann, S. Ceramides as Novel Disease Biomarkers. *Trends Mol. Med.* **2019**, *25*, 20–32. [[CrossRef](#)]

569. Suresh, J.; Khor, I.W.; Kaur, P.; Heng, H.L.; Torta, F.; Dawe, G.S.; Tai, E.S.; Tolwinski, N.S. Shared signaling pathways in Alzheimer's and metabolic disease may point to new treatment approaches. *FEBS J.* **2021**, *288*, 3855–3873. [CrossRef]
570. Costantini, C.; Weindruch, R.; Della Valle, G.; Puglielli, L. A TrkA-to-p75NTR molecular switch activates amyloid beta-peptide generation during aging. *Biochem. J.* **2005**, *391*, 59–67. [CrossRef]
571. Kosicek, M.; Zetterberg, H.; Andreassen, N.; Peter-Katalinic, J.; Hecimovic, S. Elevated cerebrospinal fluid sphingomyelin levels in prodromal Alzheimer's disease. *Neurosci. Lett.* **2012**, *516*, 302–305. [CrossRef] [PubMed]
572. Koal, T.; Klavins, K.; Seppi, D.; Kemmler, G.; Humpel, C. Sphingomyelin SM(d18:1/18:0) is significantly enhanced in cerebrospinal fluid samples dichotomized by pathological amyloid-beta42, tau, and phospho-tau-181 levels. *J. Alzheimers Dis.* **2015**, *44*, 1193–1201. [CrossRef]
573. Kosicek, M.; Kirsch, S.; Bene, R.; Trkanjec, Z.; Titlic, M.; Bindila, L.; Peter-Katalinic, J.; Hecimovic, S. Nano-HPLC-MS analysis of phospholipids in cerebrospinal fluid of Alzheimer's disease patients—a pilot study. *Anal. Bioanal. Chem.* **2010**, *398*, 2929–2937. [CrossRef]
574. Willaime, S.; Vanhoutte, P.; Caboche, J.; Lemaigre-Dubreuil, Y.; Mariani, J.; Brugg, B. Ceramide-induced apoptosis in cortical neurons is mediated by an increase in p38 phosphorylation and not by the decrease in ERK phosphorylation. *Eur. J. Neurosci.* **2001**, *13*, 2037–2046. [CrossRef]
575. Stoica, B.A.; Movsesyan, V.A.; Knoblach, S.M.; Faden, A.I. Ceramide induces neuronal apoptosis through mitogen-activated protein kinases and causes release of multiple mitochondrial proteins. *Mol. Cell Neurosci.* **2005**, *29*, 355–371. [CrossRef]
576. Soeda, S.; Tsuji, Y.; Ochiai, T.; Mishima, K.; Iwasaki, K.; Fujiwara, M.; Yokomatsu, T.; Murano, T.; Shibuya, S.; Shimeno, H. Inhibition of sphingomyelinase activity helps to prevent neuron death caused by ischemic stress. *Neurochem. Int.* **2004**, *45*, 619–626. [CrossRef]
577. Razani, E.; Pourbagheri-Sigaroodi, A.; Safaroghli-Azar, A.; Zoghi, A.; Shanaki-Bavarsad, M.; Bashash, D. The PI3K/Akt signaling axis in Alzheimer's disease: A valuable target to stimulate or suppress? *Cell Stress Chaperones* **2021**, *26*, 871–887. [CrossRef] [PubMed]
578. Kumar, M.; Bansal, N. Implications of Phosphoinositide 3-Kinase-Akt (PI3K-Akt) Pathway in the Pathogenesis of Alzheimer's Disease. *Mol. Neurobiol.* **2022**, *59*, 354–385. [CrossRef]
579. Griffin, R.J.; Moloney, A.; Kelliher, M.; Johnston, J.A.; Ravid, R.; Dockery, P.; O'Connor, R.; O'Neill, C. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. *J. Neurochem.* **2005**, *93*, 105–117. [CrossRef] [PubMed]
580. Park, K.K.; Liu, K.; Hu, Y.; Smith, P.D.; Wang, C.; Cai, B.; Xu, B.; Connolly, L.; Kramvis, I.; Sahin, M.; et al. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. *Science* **2008**, *322*, 963–966. [CrossRef]
581. Fraser, M.M.; Bayazitov, I.T.; Zakharenko, S.S.; Baker, S.J. Phosphatase and tensin homolog, deleted on chromosome 10 deficiency in brain causes defects in synaptic structure, transmission and plasticity, and myelination abnormalities. *Neuroscience* **2008**, *151*, 476–488. [CrossRef] [PubMed]
582. Kwak, Y.D.; Ma, T.; Diao, S.; Zhang, X.; Chen, Y.; Hsu, J.; Lipton, S.A.; Masliah, E.; Xu, H.; Liao, F.F. NO signaling and S-nitrosylation regulate PTEN inhibition in neurodegeneration. *Mol. Neurodegener.* **2010**, *5*, 49. [CrossRef] [PubMed]
583. Ismail, A.; Ning, K.; Al-Hayani, A.; Sharrack, B.; Azzouz, M. PTEN: A molecular target for neurodegenerative disorders. *Transl. Neurosci.* **2012**, *3*, 132–142. [CrossRef]
584. Li, H.; Zhao, H. Mathematical model of Alzheimer's disease with prion proteins interactions and treatment. *Appl. Math. Comput.* **2022**, *433*, 127377. [CrossRef]
585. Dayeh, M.A.; Livadiotis, G.; Elaydi, S. A discrete mathematical model for the aggregation of beta-Amyloid. *PLoS ONE* **2018**, *13*, e0196402. [CrossRef]
586. Pallitto, M.M.; Murphy, R.M. A mathematical model of the kinetics of beta-amyloid fibril growth from the denatured state. *Biophys. J.* **2001**, *81*, 1805–1822. [CrossRef]
587. Craft, D.L.; Wein, L.M.; Selkoe, D.J. A mathematical model of the impact of novel treatments on the A beta burden in the Alzheimer's brain, CSF and plasma. *Bull. Math. Biol.* **2002**, *64*, 1011–1031. [CrossRef]
588. Heller, D. The Spreading Confusion: Rethinking Alzheimer's Disease. Available online: <https://sitn.hms.harvard.edu/flash/2015/the-spreading-confusion-rethinking-alzheimers-disease/> (accessed on 18 January 2023).
589. Gimbel, D.A.; Nygaard, H.B.; Coffey, E.E.; Gunther, E.C.; Lauren, J.; Gimbel, Z.A.; Strittmatter, S.M. Memory impairment in transgenic Alzheimer mice requires cellular prion protein. *J. Neurosci.* **2010**, *30*, 6367–6374. [CrossRef]
590. Hu, J.; Zhang, Q.; Meyer-Baese, A.; Ye, M. Stationary distribution of a stochastic Alzheimer's disease model. *Math. Methods Appl. Sci.* **2020**, *43*, 9706–9718. [CrossRef]
591. Jiang, D.; Liu, Q.; Shi, N.; Hayat, T.; Alsaedi, A.; Xia, P. Dynamics of a stochastic HIV-1 infection model with logistic growth. *Phys. A Stat. Mech. Its Appl.* **2017**, *469*, 706–717. [CrossRef]
592. Dalal, N.; Greenhalgh, D.; Mao, X. A stochastic model for internal HIV dynamics. *J. Math. Anal. Appl.* **2008**, *341*, 1084–1101. [CrossRef]
593. Yusuf, A.A.; Figueiredo, I.P.; Afsar, A.; Burroughs, N.J.; Pinto, A.A.; Oliveira, B.M. The effect of a linear tuning between the antigenic stimulations of CD4⁺ T cells and CD4⁺ Tregs. *Mathematics* **2020**, *8*, 293. [CrossRef]

594. Afsar, A.; Martins, F.; Oliveira, B.M.; Pinto, A.A. A fit of CD4⁺ T cell immune response to an infection by lymphocytic choriomeningitis virus. *Math. Biosci. Eng.* **2019**, *16*, 7009–7021. [[CrossRef](#)] [[PubMed](#)]
595. Afsar, A.; Martins, F.; Oliveira, B.M.; Pinto, A.A. Immune Response Model Fitting to CD4⁺ T Cell Data in Lymphocytic Choriomeningitis Virus LCMV infection. In *Modeling, Dynamics, Optimization and Bioeconomics IV: DGS VI JOLATE, Madrid, Spain, May 2018, and ICABR, Berkeley, USA, May–June 2017—Selected Contributions*; Springer International Publishing: Berlin/Heidelberg, Germany, 2021; pp. 1–10.

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