Neuropathological Hallmarks of Alzheimer's Disease

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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 (Aβ) 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

Alzheimer's disease Amyloid Beta protein Tau proteins

1. The Role of Aβ and Neurofibrillary Tau Tangle in AD

The proteins Aβ 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 Aβ and the neurofibrillary tangles (NFTs) for tau. The soluble forms of Aβ and tau are also found to be increased in the brains of AD patients [1]. In healthy individuals, Aβ is naturally produced and eliminated from the brain at rates of 7.6% and 8.3% of total Aβ every hour, respectively. However, in late-onset AD (LOAD) this percentage is reduced by around 30% [2][3][4]. As a result of Aβ buildup, microglia and astrocytes are activated as part of the inflammatory response in an attempt to remove the plaque [5][6], 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 [5].

1.1. The Effects of Aβ in AD

Mitochondria are the main energy source for brain cells to function properly. Aβ 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. Aβ 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 [7][8][9][10][11]. Cognitive impairments correlate with synaptic damage in AD [12]. It has been suggested that mitochondrial dysfunction and Aβ buildup at synapses can cause synaptic injury, impaired neurotransmission, and cognitive decline in aging and AD patients [13]. Malfunctioning mitochondria have been shown to increase Aβ generation from APP, and Aβ causes mitochondrial dysfunction [14]. P-glycoprotein (P-gp) is essential for the regular clearance of Aβ across the BBB and plays a crucial gatekeeping role. Endogenous Aβ

peptide release from the brain is part of this process. Emerging evidence supports the hypothesis that defective P-gp activity promotes Aβ accumulation and contributes to the pathophysiology of AD [2][15]. Aβ 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 Aβ oligomers [2][16][17]. It has been proposed that the combination of anti-inflammatory and anti-oxidant drugs may be a useful strategy for treating AD [18]. Heme, a key functional form of iron in cells that is synthesized in mitochondria, binds to Aβ to form the Aβ–heme complex [19], which inhibits Aβ accumulation and results in heme deficiency. Heme shortage reduces mitochondrial complex IV's activity and protein content, causing oxidative stress and disrupting Ca^{2+} homeostasis. Heme deficiency also affects zinc and iron homeostasis, APP, mitochondrial complex IV, and NO synthase (NOS) [20][21][22]. 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 [22]. **Table 1** summarizes the effects of Aβ.

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

Biomarkers	Effects	References
Aβ	results in heme deficiency, which changes: •Homeostasis of zinc, iron, and Ca^{2+}; •APP; •NOS. causes oxidative stress and inflammation and vice versa produces hyperphosphorylated tau develops mitochondrial dysfunction and vice versa results in neurodegeneration	Atamna et al. 2002, [21] Chai et al. 2020, [2] Gotz et al. 2004, [23]; Ittner et al. 2011, [24] Morley et al. 2014, [14] Wang et al. 2020, [25]
Tau	NFTs build up instability of microtubule causes oxidative stress and vice versa results in neurodegeneration buildup of tau tangle results in: •Neuroinflammation; •impaired synaptic function; •dysfunctional autophagy; •dysfunctional mitochondria.	Miao et al. 2019, [26] Brion 1998, [27] Rawat et al. 2022, [28] Eckert et al. 2011, [29] Rawat et al. 2022, [28]

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 [30]. 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 [26]. 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 [31][32]. NFT-bearing neurons showed lower tubulin transcription, which might have a role in the reduced number of microtubules in these cells [32]. 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 [33]. 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 [27][34][35]. 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 [36]. 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 [28][37][38][39]. Calafate et al. [40] 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. [41] 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 [29]. A summary of the effects of tau can be seen in **Table 1**.

1.3. Aβ and tau Interplay

While Aβ and tau cause toxicity via different pathways, in vitro and in vivo research suggests that they can interact in three different ways [23][24][42][43]. The first mode of interaction is that Aβ drives tau pathology. In APP transgenic mice, Aβ deposition leads to hyperphosphorylated tau, whereas tau transgenic mice do not have observable Aβ plaque pathology [23][24]. It has been reported that mitochondrial malfunction and a lack of energy are early signs of AD [44][45]. In the second mode of interaction, both Aβ and tau contribute to interactive toxicity, damaging mitochondrial respiration in triple transgenic mice (triple AD mice), which show combined Aβ 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 [24][42]. In previous studies [42][46], 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 Aβ, whereas the deregulation of complex I was dependent on tau According to Vossel et al. [43], in the third mode of interaction, Aβ disrupts axonal transport, which is essential for neuronal activity. Aβ-induced axonal transport impairments are prevented by a decrease in tau.

2. Neuroinflammation

Another underlying mechanism of AD pathology is neuroinflammation [47][48][49][50]. Inflammation is essential for repair processes in the brain, but prolonged inflammation can impair brain function [51][52][53]. The molecular mechanisms underlying the progression from chronic, low-grade systemic inflammation to neurodegeneration are still not fully understood [54]. Neuroinflammation is most likely the result of AD pathologies and risk factors, and it exacerbates the disease severity [55]. AD brains show elevated levels of proinflammatory cytokines and inflammatory markers, possibly as a response to the Aβ plaques and NFT deposition, which induce neuronal damage or death [54][56]. Aβ deposition activates the complement system, microglia, and astrocytes, and induces the secretion of inflammatory mediators such as IL-1α, IL-1β, IL-6, and TNF-α, and reactive oxygen and nitrogen species, which lower phagocytosis and prolong neuroinflammation [55][56]. Proinflammatory mediators activate microglia during the AD pre-symptomatic stage, leading to synaptic dysfunction and neuronal death [55]. This implies that neuroinflammation is an early event in the development of AD pathology [51][57]. 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 [51][55]. 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 Aβ from APP by β- and γ-secretase [58][59]. IL-1 also elevates tau phosphorylation by the p38-MAPK pathway [59][60]. IL-1β 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 [56][61]. 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 [62]. Chemokines can also attract microglia to the periphery of Aβ 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 [63]. On the other hand, SDF-1/CXCR4 chemokine can activate microglia and reduce Aβ 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 [57][64]. Some other chemokines found to be elevated in the blood of AD patients are IP-10, IL-13, IL-8, MIP-1α, and fractalkine; however, RANTES levels were found to be decreased in a previous study [57]. 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 [65][66][67]. 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 [51][68]. Other proteins that have been found to be dysregulated in AD are CSF1R, COX-1, COX-2, CB_2R, P2X7, and P2Y12 receptors [69][70][71][72][73][74][75][76][77][78][79]. Radiotracers for these proteins have been developed; however, further studies are required to determine their utilization as potential

imaging biomarkers to detect neuroinflammation [68]. 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 [57][80][81]. Moreover, the acute-phase inflammatory protein C-reactive protein (CRP) may promote $A\beta_{42}$ 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 [82][83][84]. This controversy is likely due to the changes in its levels as the disease progresses [57]. 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 [85], can enhance brain amyloid accumulation, tau protein phosphorylation, systemic inflammation, and the impairment of memory, learning, and cognitive functions [54][86][87][88][89][90]. 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, Treml2, Tyrobp, CX3CR1, Ccl3*) and markers of phagocytic microglial cells (Iba1, CD68, TREM2) around the Aβ plaques [91][92][93]. WD-induced neuroinflammation seems to occur earlier, before Aβ 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 [54].

Several studies demonstrated a link between diet, obesity, and AD [54][94][95][96][97][98][99][100]. Obesity increases the risk of cognitive decline and AD development six-fold in adulthood and midlife [54][101]. Obese individuals have an increased brain atrophy rate, decreased cortical and hippocampal volume, low performance in memory tasks, and deficits in executive functioning [102][103][104][105][106]. Diet-induced obesity has been associated with increased APP, p-tau levels, and hippocampal Aβ, decreased hippocampal neurogenesis, and cognitive tasks deficit in AD animal models [107][108][109]. Diet-induced hypercholesterolemia experiments in mice showed the exacerbated neuroinflammatory response, increased p-tau levels, and the generation and deposition of toxic Aβ in neurons and astrocytes, leading to impaired cognition [110][111][112]. 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 [54][113][114]. Furthermore, diverse studies have suggested that type 2 diabetes mellitus (T2DM) is a major vascular risk factor, and contributes to AD development [95][115][116][117][118]. Patients with T2DM have a two-fold higher risk of developing AD than healthy individuals [94][119][120][121]. Future studies should address the influence and interaction of environmental and genetic risk factors in AD development and progression.

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 [54]. 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 [54][57].

The loss of BBB integrity combined with the migration of immune cells into brain vessels may exacerbate inflammation and neurodegeneration in patients with AD [94]. Some pathological features of BBB breakdown in AD brains include the extravasation of blood-derived proteins (fibrinogen, thrombin, plasminogen, immunoglobin 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 [54][95].

Diverse studies demonstrated that increased Aβ production and deposition induce BBB disruption [122][123][124][125]. Disfunction of the BBB impairs Aβ clearance, and can promote or escalate Aβ production [122]. Thus, a vicious cycle between BBB damage and Aβ accumulation can be established, resulting in neuronal damage and a loss of neuronal networks [122][126]. BBB dysfunction can also induce tau hyperphosphorylation, and tau pathology can trigger BBB damage [122][127][128][129]. Moreover, BBB permeability was found to be increased in APOE4 carriers [130][131][132][133], which show accelerated pericyte degeneration and BBB breakdown [134]. The loss of pericytes in AD is associated with fibrinogen leakage, reduced oxygenation, and fibrillar Aβ accumulation [135]. Additionally, astrocytic dysfunction and reactive astrocytes may induce increased generation of Aβ [122][136]. Another common event in AD is the loss of tight junctions, which is associated with insoluble $A\beta_{40}$ and synaptic dysfunction. Cortical tight junction proteins such as claudin-5 and occludin have been found to be decreased in AD brains [137]. Targeting the BBB and its components can result in a promising strategy to treat AD.

4. Cholinergic Neurons in AD

Cholinergic neurons are nerve cells that secrete the major brain neurotransmitter acetylcholine [138]. Early studies in rodent models and humans delineated the importance of acetylcholine and cholinergic neurons in memory function [139][140]. 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 [141][142][143][144]. Acetylcholine released by the cholinergic system modulates behavioral flexibility [145][146][147], attention [148][149], and arousal [150][151][152]. Of particular interest are the basal forebrain cholinergic neurons, which are essential for cognitive and memory function [153]. These basal forebrain cholinergic neurons form the major projection into the cerebral cortex and hippocampus [154][155][156][157]. These central cholinergic neurons display age-related dysfunction, leading to mild cognitive impairment [158][159][160].

The selective reduction in pre-synaptic cholinergic enzyme activity in specific brain regions of AD patients was first reported in the 1970s [161]. 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 [162][163][164]. 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 [165][166]. This hypothesis was further strengthened after it was

shown that treatment with an acetylcholinesterase inhibitor, tetrahydroaminoacridine (THA, Tacrine), produced clinical improvements in AD patients [167]. 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 [168][169].

Acetylcholine impairment is the most widespread and important neurotransmitter alteration in AD [170]. Acetylcholinesterase hydrolyses acetylcholine to choline and acetate, and is an essential enzyme of the neuronal cholinergic system [171][172]. 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 [173][174]. In addition to these three, only two other treatments (Memantine and Aducanumab) have been approved for AD [175]. 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 [176][177]. 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 [178][179][180].

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 [181][182]. 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 [183]. 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 [184], while there is an increase in the levels of its precursor, proNGF [185][186]. However, evidence has implicated an altered NGF signaling system and interaction with BFCN in AD [187][188]. Dysfunction in the NGF pathway seemed to be due to impaired retrograde transport and maturation of NGF [189]. Genetic delivery of NGF to the brain of AD patients has been used to activate the neuronal trophic response [190]. NGF-based therapy seeking to boost NGF trophic activity should be explored to halt BFCN atrophy, especially in early stages of AD.

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 [191][192][193][194][195]. 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 [196][197][198][199]. Microglia are also involved in synaptic formation and remodeling [200][201][202]. As part of the complement cascade of the CNS innate immune system, macroglia engulf and prune synapses [203][204][205]. 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 [206][207]. 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 [208][209][210][211][212]. 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.

5.1. Astrocytes

Astrocytes are the most prevalent glial cells, and constitute about a third of cells in the human central nervous system [193][194]. 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 [213][214][215][216]. Reactive astrogliosis has been reported in the brains of mouse models of AD and AD patients. Astrocytes become more reactive and associate with Aβ plaques in the AD brain [215][217][218]. 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 [219][220][221]. Aβ can activate astrocyte reactivity, upregulate the release of pro-inflammatory cytokines [222][223][224][225], and alter astrocyte-Ca^{2+} homeostasis [226][227][228]. Impaired calcium signaling mediated by astrocytes, especially increased Ca^{2+} activity leading to the hyperactivation of Ca^{2+}-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 [226][229][230].

Atrophic astrocytes have been documented in both mouse models of AD and the post-mortem brains of AD patients [231][232][233]. 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 [232][234]. 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 Aβ [235][236]. A defective astrocyte might not be able to effectively clear Aβ. In the later stages of neurodegeneration, as Aβ 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.

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 [237][238][239]. 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 [237][240][241]. Reactive microglia are a neuropathological hallmark of AD brain response to amyloid deposition, neurofibrillary tau tangles, and neuronal death [242][243][244]. 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.

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 [245]. The *APOE4* allele is a major genetic risk factor for LOAD [246]. *APOE* is involved in amyloid clearance and plaque formation. The *APOE4* allele seems to reduce amyloid removal and elevate amyloid deposition in plaques [247][248][249]. *APOE4* has been reported to alter lipid homeostasis in glia cells [250] and promote dysfunctional microglia phenotypes in neurodegeneration [251]. TREM2 is a surface receptor expressed on myeloid cells including microglia. TREM2 is involved in the clearance of Aβ, the removal of cell debris, and microglial survival [252][253][254][255]. 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.

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 [256]. Some genes, such as *CR1*, involved in the complement system, are genetic risk factors for AD development [257][258]. 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 [203][257].

6. Synaptic and Neuronal Loss in AD

A progressive decline in cognitive function is a major symptom and hallmark of AD [259][260]. Cognitive deficit has been reported to be present at early stages of the disease and decades before amyloid deposition [261][262]. 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 [263][264][265][266][267][268]. Synaptic dysfunction and loss have been extensively reported in animal models of AD [269][270][271][272][273]. The correlation between synapse loss and cognitive defects has been demonstrated using various methods and models [274][275][276][277].

Neuronal loss is a canonical neuropathological feature of AD [278][279][280]. The loss of neurons starts at early stages and accelerates as the disease progresses [281][282][283]. There is a pronounced loss of neurons in the entorhinal cortex and hippocampus compared to other brain regions [282][283][284]. Neuronal loss in these regions closely correlates with cognitive impairments [285][286]. Various AD transgenic mouse models replicate the neuronal loss seen in AD [287][288][289][290][291].

Mechanisms of Synaptic Loss and Neuronal Loss

Aβ is connected to synaptic dysfunction in AD. However, it is the soluble oligomeric Aβ 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. [292][293][294][295][296]. The mechanism of Aβ-induced damage possibly involves the binding of Aβ to synaptic-associated proteins [297][298]. Advanced imaging techniques have been used to show the presence of soluble amyloid species in synapses [297][299]. 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 [300].

The accumulation of tau proteins correlates with cognitive decline and clinical symptoms in AD [301]. Although tau is found in healthy and AD synapses, there are higher levels of hyperphosphorylated tau in the synapses of the AD brain [302][303][304][305][306]. Tau toxicity to synapses and neurons seems to be mediated by soluble, hyperphosphorylated, oligomer forms [307][308][309][310]. Normal tau protein is involved in the axonal transport of mitochondria and other important molecules to synapses [311]. 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 [43][305][312][313].

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 [6][314]. 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 [315][316].

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 [317].

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