

Review

# Proteostasis and Neuroinflammation in Alzheimer's Disease

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Academic Editor: Gernot Riedel

Submitted: 28 February 2025 Revised: 24 May 2025 Accepted: 11 June 2025 Published: 18 September 2025

## Abstract

Alzheimer's disease (AD) is the most common cause of dementia in older adults, marked by a gradual and irreversible deterioration of cognitive abilities, including memory and thinking skills. AD is highly heterogeneous, with variations in amyloid and tau pathology, symptoms, proteostasis, neuroinflammation, and genetics. Dysregulated proteostasis and neuroinflammation, though usually protective, contribute significantly to disease progression. Proteostasis refers to the network that maintains the integrity of both intracellular and extracellular proteins, while neuroinflammation is the biological response to harmful stimuli. Proteostasis stress can activate immune responses and cause excessive inflammation, while impaired microglia and astrocyte function can further disrupt proteostasis and worsen disease progression. While numerous reviews on AD exist, this review focuses on the complex interplay between proteostasis and neuroinflammation in AD and their integral roles in disease pathology. Additionally, we will explore current and promising therapeutics targeting these processes, potential biomarkers, and the clinical trials conducted over the past 5 years, particularly those that address neuroinflammation and proteostasis, as identified through a PubMed search.

**Keywords:** Alzheimer's disease; proteostasis; neuroinflammation; proteotoxic stress; microglia; astrocytes; brain; cognition; inflammation; immunity

## 1. Introduction

Alzheimer's disease (AD), the most common form of dementia in older adults, is a degenerative brain disorder that causes a steady and irreversible loss of memory and cognitive abilities [1,2]. Around 6 million Americans over 65 are living with Alzheimer's, and many younger people are affected too. As more people live longer, that number will likely grow, since age is the biggest risk factor [3]. After the discovery of AD, it was found in 1984 that the amyloid  $\beta$  protein ( $A\beta$ ) is the central component of extracellular amyloid plaques in AD [4]. In the following years,  $A\beta$  has been considered the driver of Alzheimer's pathological processes, and the "amyloid cascade hypothesis" has become a leading theory of AD pathogenesis [5,6]. However, the repetitive failures of  $A\beta$ -targeted clinical trials have cast considerable doubt on this hypothesis and have led investigators to explore other possible mechanisms [5].

Recent investigation supports that overactivated inflammatory responses in the brain, abnormal mitochondria, and impaired protein turnover are connected to AD [7]. Genome-wide association studies have established a link between AD risk genes and innate immune function, including microglia and inflammatory signaling molecules, suggesting a key role for neuroinflammation in AD [8]. Microglia are macrophage-like innate immune cells in the central nervous system (CNS) that can respond to disease progression by altering their physiological functions and inducing the activation of inflammatory pathways [9]. Microglia

exist in different subtypes and can interact with various CNS cells, including astrocytes, oligodendrocytes, and neurons [10]. Their activation and inflammatory response are crucial for neuroprotection. However, persistent and prolonged microglial activation and associated neuroinflammation are central pathological features of AD [11].

Neuroinflammation can have both helpful and harmful effects. It plays a protective role by activating immune responses, where astrocytes and microglia carry out phagocytosis to clear pathogens and debris. However, if this process becomes dysregulated, it may contribute to disease progression [12]. The dual nature of neuroinflammation becomes apparent when the negative effects of this process, causing harmful consequences for neurons in the patient's brain, were observed [11,13]. In each type of inflammatory reaction, the moment that marks the end of its duration is very important. It is an active process supervised by specialized mediators acting as regulators. Numerous studies have demonstrated a reduced concentration of neuroinflammation suppression regulators, which may be related to amyloid deposits present in the brain of AD patients, driving the inflammation process [14,15].

Proteostasis is the maintenance of protein balance in the brain, a complex system crucial for cell function and survival. It includes the ubiquitin-proteasome system (UPS), endoplasmic reticulum (ER) and the autophagolysosomal system which are responsible for the degradation of aberrant proteins under physiological conditions [16–19]. AD is characterized by the accumulation of aberrant



proteins, which signals a severe disturbance in the proteostasis network [17,19]. Under normal conditions, the proteostasis network controls protein quality to prevent aggregation. However, if this system is disrupted, misfolded proteins build up, clump together, and form structured aggregates [20–22]. While AD has been proven to be heterogeneous and has many factors that can contribute to it, this review will be largely focused on the influence of neuroinflammation and aberrant proteostasis, the complex interplay between both in the pathogenesis and progression of the disease, and the recent therapeutic considerations involving neuroinflammation and proteostasis in the management and possible treatment of AD.

## 2. Neuroinflammation and Its Crosstalk With Proteostasis in AD

### 2.1 Inflammatory System in AD

Under physiological conditions, inflammation is considered a beneficial physiological response within the brain and spinal cord, promoting clearance of neuronal debris, misfolded protein, and assisting in tissue repair [23]. However, when inflammation becomes prolonged and sustained, it contributes to a variety of chronic inflammatory diseases. In the central nervous system, brain-residing microglia and astrocytes are the primary sources of inflammation. Therefore, inflammation has been considered as a contributor to neurodegeneration, together with glial activation and peripheral immune infiltration, and proteostasis [24,25]. Inflammation is a key part of AD pathophysiology, with astrocytes and microglia—which release chemokines and cytokines—being the first cells to respond [26,27]. According to Paolicelli *et al.* [28], microglia exist in a dynamic continuum of transcriptional and functional states rather than simplistic binary categories such as “resting” or “activated”. This heterogeneity is shaped by age, brain region, sex, disease context, and environmental stimuli. The paper advocates for a refined nomenclature grounded in multi-omic characterizations—integrating transcriptomic, proteomic, epigenetic, and spatial data—to capture the full complexity of microglial biology. It also highlights the need for standardized reference atlases and cross-species comparisons to clarify distinctions between microglial states observed in health and disease, particularly neurodegenerative conditions such as Alzheimer’s disease, where microglia may have both protective and pathogenic roles. Similarly, Fumagalli *et al.* [29] utilized advanced single-cell RNA sequencing and computational modeling to identify a continuum of microglial states, termed the microglial state continuum (MSC), which reflects varying degrees of activation and functional specialization. They showed that this continuum is influenced by brain region, developmental stage, and disease state. In neurodegenerative contexts, particularly Alzheimer’s disease, microglia exhibit shifts towards less active or dys-

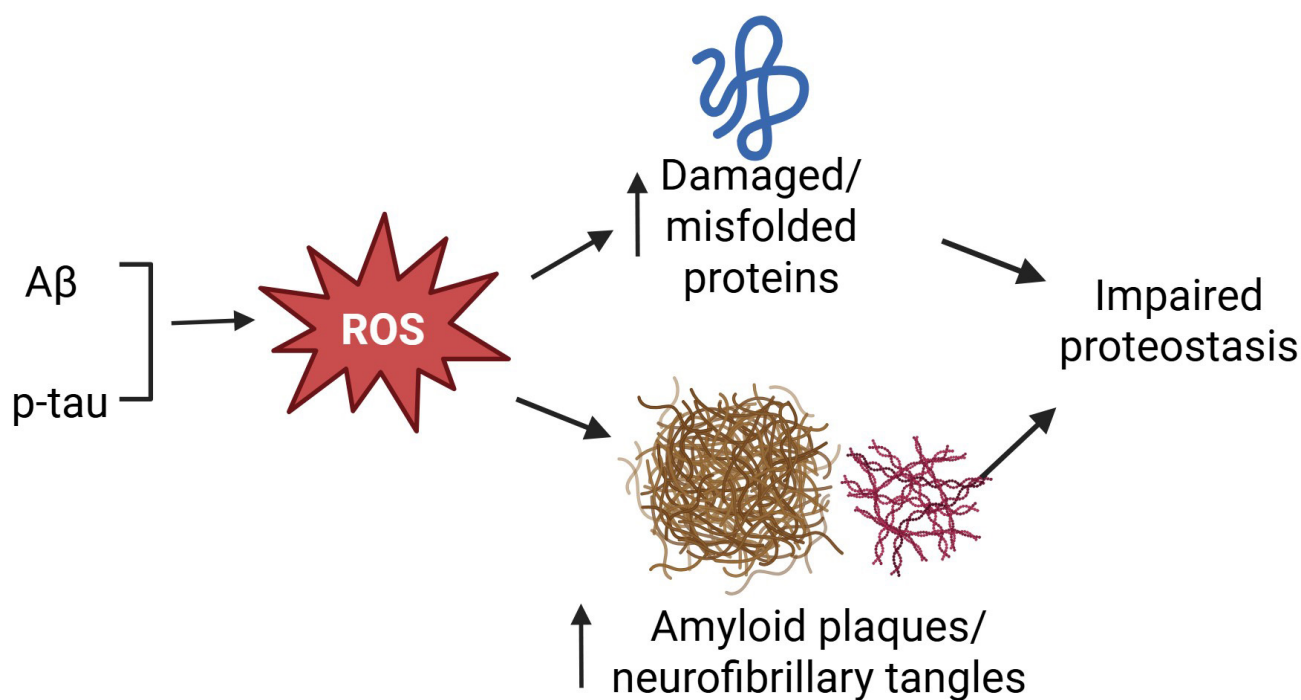
functional states, which may impair their ability to maintain homeostasis. The study also introduces tools for annotating microglial cell states based on gene expression profiles, offering a framework for future research into microglial function and pathology.

An inflammatory response usually begins with overexpression of interleukin (IL-1), monocyte-attracting chemokines, macrophage inflammatory proteins, prostaglandins (PG), factors of coagulation, reactive oxygen species, nitric oxide (NO), complement factors, proteases, and pentraxins, which in turn activate other processes and finally lead to a vicious circle that has a key role in the accumulation of amyloid plaques and neuronal death [27,30]. As mentioned earlier, activated microglia trigger a cascade of signaling pathways, including the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, which regulates inflammation and apoptosis, and the nuclear transcription factor  $\kappa$ B (NF- $\kappa$ B) pathway, which together result in the activation of mammalian target of rapamycin (mTOR) prote [27,31]. The overall action is seen as an increase in cyclooxygenase-2 (Cox-2) and inducible nitric oxide synthase (iNOS). Microglia release inflammatory cytokines by stimulating signaling pathways like Cox-2, Akt/mTOR, NF- $\kappa$ B, caspases, p38 mitogen-activated protein kinases (p38 MAPK), and NO [32–34].

Proinflammatory cytokines and chemokines secreted from microglia, astrocytes, T helper 1 cells, CD4<sup>+</sup> cells, and dendritic cells regulate growth, differentiation, and cell activation. The major proinflammatory cytokines are interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [35,36]. In contrast, anti-inflammatory cytokines, including IL-4, play a crucial role in counteracting the neuroinflammatory response seen in the brains of AD patients [37]. IL-4 has been shown to increase microglia clearance in cell culture studies by enhancing the activity of A $\beta$ -degrading enzymes and promoting CD36 expression [38,39]. Moreover, IL-4 impairs monocyte differentiation into macrophages and reduces their ability to uptake pathological forms of A $\beta$  [40].

### 2.2 Oxidative and ER Stress as Bridging Mechanisms

Oxidative stress (OS) occurs when the production of reactive oxygen and nitrogen species (ROS/RNS) exceeds the capacity of the cell’s antioxidant defenses. OS plays a detrimental role in the pathogenesis of AD as neurons are particularly susceptible to OS due to their high oxygen utilization, weak antioxidant system, and high polyunsaturated fatty acid content in membranes [41,42]. Studies show that antioxidant levels in the brain decline with age, thereby affecting the proteostasis of the brain by increasing susceptibility to protein misfolding [43]. OS results from the accumulation of oxidized and damaged macromolecules that are not efficiently removed and renewed. Proteins are highly susceptible to oxidative damage that in-



**Fig. 1. Oxidative stress impairs proteostasis in AD.** Increased production of amyloid peptides and phosphorylated tau (p-tau) enhances the generation of ROS to damage intracellular proteins and increase the accumulation of amyloid plaques and neurofibrillary tangles, leading to impaired proteostasis. AD, Alzheimer's disease; ROS, reactive oxygen species;  $A\beta$ , amyloid  $\beta$  protein.  $\uparrow$ , increase. Created with <https://www.biorender.com/>.

evitably affects the secondary and tertiary structure, causing an irreversible modification of protein structure and function [44,45].

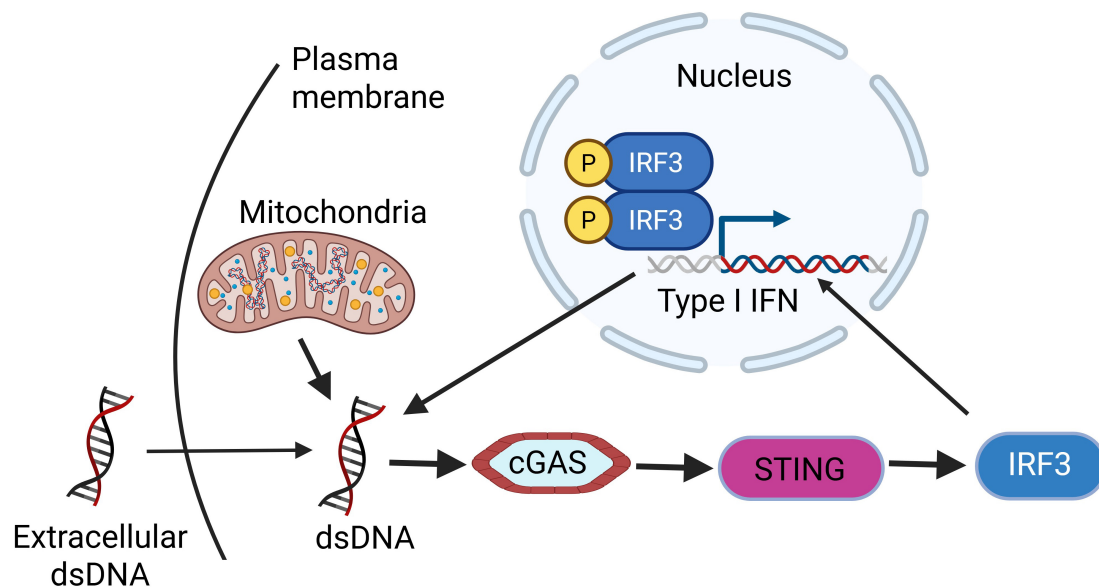
Many studies have shown links between protein homeostasis and OS. As mentioned above, during aging, the capacity of cells to maintain homeostasis and proteostasis decreases, leaving the organism susceptible to AD as proteins are irreversibly oxidized and cannot be efficiently degraded [46–48]. Considering these findings, the formation of toxic and large protein aggregates is a major consequence of protein oxidation and poor proteostasis. Insoluble aggregates can be formed as a result of covalent cross-links among peptide chains, as in the case of  $A\beta$  peptides and neurofibrillary tangles (NFTs) in AD [46,49]. Indeed, OS enhances  $\gamma$ -secretase and  $\beta$ -secretase (BACE-1) activity and  $A\beta$  production in neurons, which opines a direct relationship between amyloidogenic processing of amyloid precursor protein (APP) and OS [50,51] (Fig. 1).

### 2.3 Mitochondrial Dysfunction in AD and cGAS–STING: An Inflammatory and Proteostatic Nexus

While mitochondrial dysfunction spans metabolic, oxidative, and proteostatic roles, one critical consequence is the leakage of mitochondrial DNA, which activates the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS–STING) pathway—linking mitochondrial damage to neuroinflammation in AD. Mitochondrial dysfunction is a key feature of AD pathology, which is character-

ized by altered cellular metabolism [52–54]. Mitochondria are present in all human body cell types (except mature red blood cells) to perform important cell fate-determining functions, and their abundance depends on the role of the cell. Under physiological conditions, mitochondria are well equipped with antioxidants like cytochrome c to mop up ROS, but during aging and in AD, these systems become dysfunctional [55]. Specifically, studies have shown that complex I and complex II are altered during aging and AD [56–58]. On the other hand, protein buildup within mitochondria impairs the electron transport chain's function. It is noted that  $A\beta$  oligomers can enter mitochondria to disrupt their functions. There are two ways by which  $A\beta$  enters mitochondria: (1) through direct transport across the outer membrane via translocase of the outer/inner mitochondrial membrane (TOM/TIM) complex, and (2) through enhanced interaction with the ER facilitated by the mitochondria-associated membranes where  $A\beta$  can be generated and then transported into the mitochondria. This can further increase the buildup of OS [59,60].

The cGAS–STING pathway functions as a DNA detector in the cytosol to identify damage-associated molecular patterns (DAMPs), and to trigger the inflammatory reactions through STING. Mitochondrial dysfunction has been recognized as a key contributor of AD, and when their damages occur, mitochondrial DNA (mtDNA) is released into the cytosol, where the leaked mtDNA serves as a damage-



**Fig. 2. dsDNA activates cGAS-STING signaling pathway to transcribe type I IFNs and trigger inflammation.** Created with <https://www.biorender.com/>. dsDNA, double stranded DNA; IFNs, interferons; IRF3, interferon regulatory factor 3; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

associated molecular pattern (DAMP) to activate the cGAS-STING pathway, resulting in neuroinflammation [61–63].

The cGAS is a ~522 amino acid-long protein that contains two domains, a basic domain [61,64]. In mammalian cells, the activation of cGAS and its downstream STING pathway leads to the generation of type I interferons (IFNs) and pro-inflammatory cytokines (Fig. 2). The cGAS-STING signaling pathway has recently been recognized as a key mechanism in triggering innate immune responses to double-stranded DNA. Research indicates that this pathway is activated in many neurodegenerative diseases [65]. Given that reduced proteasome activity is often seen in neurodegenerative diseases, one study showed that dysfunction of the 26S proteasome can activate the cGAS-STING pathway, ultimately causing neuronal death by triggering necroptosis [66]. However, mounting evidence indicates that autophagy also plays an important role in regulating cGAS–STING signaling to maintain immune homeostasis [67,68], indicating that impaired protein degradation and the accumulation of misfolded proteins may function as a generalized inducer of the pathway likely through enhanced OS and mitochondrial damage (Fig. 2). It is noted that marked activation of cGAS-STING occurs in the hippocampus of AD mice, which is associated with the expression of IL-6, deposition of A $\beta$  plaques, and neuroinflammation [69]. These AD-related effects appear to rely on mtDNA, as neither A $\beta$  nor the mitochondrial-targeted A $\beta$ -precursor protein intracellular domain induces notable cellular damage in the absence of mtDNA [53], suggesting a significant role of mtDNA in AD-associated neuroinflammation.

### 3. Impaired Proteostasis in AD

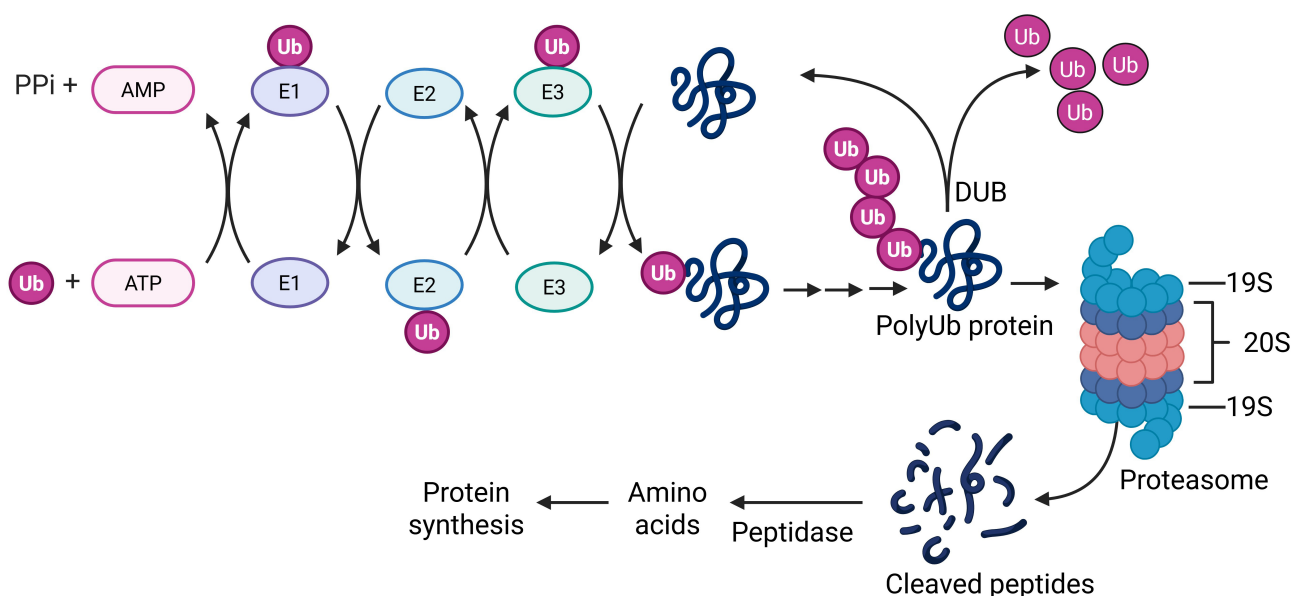
Mammalian cells contain many distinct proteins that vary from cell to cell depending on the type, function, and status of the cell at various times [70,71]. Proteostasis, or protein homeostasis, refers to maintaining a proper balance between protein production and breakdown, ensuring proteins are correctly synthesized, folded, and cleared when damaged or no longer needed. Proteostasis is essential in maintaining human cells' healthy, as 33–35% of newly synthesized proteins are prone to misfolding under physiological conditions. Hence, it becomes crucial during aging as the activity of proteostasis machinery is reduced, causing aggregation and accumulation of damaged/aberrant proteins [72,73].

Maintenance of protein homeostasis is important for cell function, fitness, and survival. As such, cellular integrity relies on proteolytic systems that not only maintain the proper concentration of regulatory and structural proteins but also scavenge damaged and misfolded proteins [3,74]. The two main protein degradation systems are the evolutionarily conserved UPS, which is responsible for the degradation of both functional and dysfunctional short-lived proteins coupled with poly-ubiquitin molecules, and the autophagy-lysosomal system that degrades long-lived proteins, large aggregates of proteins, cellular components, and organelles [75,76]. Proteostasis can be modified by pathogens, aging, environmental changes, cellular stress, and a host of other factors [77,78].

#### 3.1 Ubiquitin-Proteasome System (UPS)

The UPS consists of the ubiquitin conjugation system and the proteasome, working together to degrade intracel-





**Fig. 3. UPS pathway.** In the presence of ATP and the three ubiquitin enzymes (E1, E2, and E3), a Ub is covalently added to a substrate protein. Repeat ubiquitination leads to a polyUb chain attached to the protein to mediate the substrate protein interacting with the proteasome for degradation. A DUB reverses the ubiquitination process to stabilize the substrate protein. Created with <https://www.biorender.com/>. UPS, ubiquitin proteasome system; Ub, ubiquitin; DUB, deubiquitinating enzymes.

lular proteins. Ubiquitination or polyubiquitination serves as a tagging mechanism, marking proteins for destruction, while the proteasome carries out the actual degradation process. Together, they help cells maintain proteostasis [79–81]. Through the UPS pathway, potentially toxic proteins marked for degradation are broken down into small peptides, which can then be recycled to restore intracellular amino acid levels [82] (Fig. 3).

Protein degradation via the UPS pathway starts with ubiquitin (Ub) [83]. Downstream of the ubiquitination reaction is the degradation of polyUb-tagged proteins by proteasome, a multiple-protein assembled large complex composed of two particles: the regulatory 19S complex which aids substrate recognition, deubiquitinating, unfolding of protein and uncoiling of protein for degradation, and the 26S catalytic complex which is hollow, cylindrical, composed of two inner and two outer rings responsible for the actual degradation of substrate protein [84,85] (Fig. 3). Extensive research has demonstrated that the UPS plays a vital role in eliminating AD-related pathological proteins, and its impairment is associated with increased severity of Alzheimer's disease pathology. Tau is degraded by 26S proteasome in a ubiquitin- and ATP-dependent manner because phosphorylated and non-phosphorylated tau proteins are the substrate of ATP/Mg<sup>2+</sup>-dependent proteasome [86]. In contrast, when UPS is disrupted, accumulation of non-degraded protein and neuroinflammation will occur.

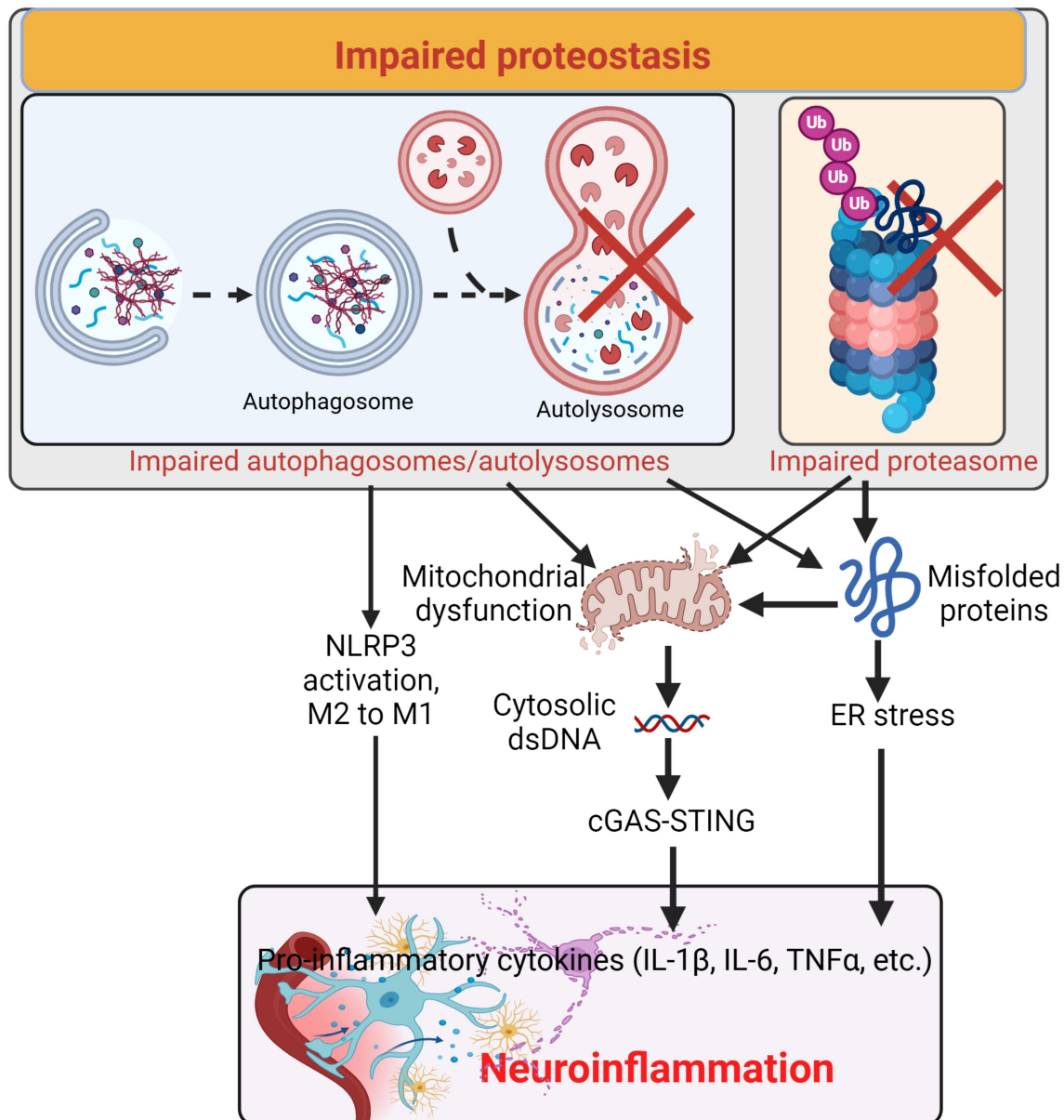
### 3.2 Autophagy-Lysosome Pathways (ALPs)

Autophagy is a major proteolytic system in the cytoplasm and removes aggregates by lysosomal degradation

[87]. Under physiological conditions, there is usually no buildup of aberrant protein as the clearance rate is always higher than the production rate. Autophagy, also known as autophagocytosis, is one of the ways that the brain ensures this happens; it is a self-eating process that delivers cytoplasmic cargo to the lysosome for degradation [5,18]. The autophagy-lysosome pathway (ALP) involves the biogenesis of a unique organelle enclosed by a double lipid bilayer, named the autophagosome. During autophagy, autophagosomes fuse with lysosomes, where protein-containing vacuoles are broken down by hydrolytic enzymes. Age-related, stochastic, non-enzymatic, post-translational modifications, as well as macromolecules, cytosolic portions, and entire organelles, are usually degraded by the ALPs via lysosomes [88,89].

### 3.3 Neurovascular Unit (NVU) Dysfunction and the Glymphatic System in AD

Neurovascular unit (NVU) dysfunction and the glymphatic system have been implicated in neuroinflammation and proteostasis in AD. NVU plays an important role in maintaining homeostasis of the brain microenvironment and the accelerated aging of NVU cells may directly impair NVU function and contribute to AD pathogenesis [90]. Thus, rescuing NVU dysfunction might be a viable approach to AD treatments [91]. One study has showed that the diameter of microvessels and PV (Parvalbumin) neuron numbers were decreased, the microglial number was increased, and spatial learning was deficient in the hippocampus at 24 months of age, suggesting that the impairment of the hippocampal neuro-vascular unit precedes changes in



**Fig. 4. Impaired proteostasis induces neuroinflammation.** Impaired proteasome and autophagy cause accumulation of misfolded proteins and mitochondrial dysfunction, leading to ER stress and release of dsDNA from the mitochondria and/or nuclei to activate the cGAS-STING pathway inducing neuroinflammation. Additionally, impaired autophagy also activates the NLRP3 and facilitates the conversion from M2 to M1 of microglia, enhancing neuroinflammation. Created with <https://www.biorender.com/>. ER, endoplasmic reticulum; NLRP3, nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing 3; ×, impairment.

spatial cognition in naturally aged rats [92]. In addition, single-nucleus transcriptome analysis identified eight main cell types and the expression patterns of aging-related genes in NVU cells of AD [90].

The glymphatic system is considered to be associated with the pathogenesis of AD, although the alterations of the glymphatic system along the AD continuum are still unknown, it is suggested that cognitive dysfunction is closely associated with the activity of the glymphatic system [93]. Evidence showed lower diffusion tensor image analysis along the perivascular space (DTI-ALPS) index was found

in patients with AD dementia, which may suggest impaired glymphatic system function [94]. A new small molecule, OAB-14, enhances the clearance of brain A $\beta$  via the glymphatic system and improves cognitive function [95]. Taken together, while NVU dysfunction is connected to neuroinflammation, the glymphatic system is connected to proteostasis. While more information is needed on their exact mechanisms of action in AD, it may be beneficial to consider these systems together with neuroinflammation and proteostasis in the management of AD.

## 4. Relationship Between Proteostasis and Neuroinflammation in AD

Extracellular A $\beta$  deposition and aggregation are the hallmarks of AD. These deposited A $\beta$  plaques cause microglial inflammatory activation, migration, and phagocytosis [38,96]. Exacerbation of AD pathology is observed as a result of this because the primary immune response to the buildup of A $\beta$  is sustained microglia activation leading to reactive microgliosis and decreased microglial capacity to phagocytose A $\beta$  and pro-inflammatory cytokine release [24,97]. Another hallmark of AD pathology, tauopathy, has been demonstrated to spread between the brain cells by direct secretion, ectosomal, and exosomal mechanisms [98,99]. In tauopathy, microglia play a key role in propagating tau-related pathology through exosome release [100,101].

### 4.1 Impaired Proteostasis Triggers Neuroinflammation

The cellular stress response is a major regulator of the proteostasis network in various scenarios of induced imbalance in proteostasis. Previous data show that impaired proteostasis leads to toxic protein buildup and mitochondrial dysfunction, triggering an immune response; when excessive, this inflammation can contribute to neuronal dysfunction [102,103]. For instance, when the neuronal proteasome function is disrupted, this causes mitochondrial DNA to be released into the cytosol, activating the cGAS-STING pathway and triggering neuroinflammation and necroptosis in the animal brain (Fig. 4). Likewise, autophagy and mitophagy dysfunctions are found in most AD cases, likely caused by A $\beta$  and p-tau aggregates and toxic effects. When autophagy is disrupted, it activates the nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome, leading to increased production of pro-inflammatory cytokines (Fig. 4).

Inflammasomes are multiprotein complexes present in microglia, astrocytes, neurons, endothelial cells, and macrophages within the CNS; they are part of the innate immune system that recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [103,104]. The activation of inflammasomes, such as the NLRP3 which is a key component of inflammasomes, has been reported in several neurodegenerative diseases because they activate caspase-1 and the subsequent release of pro-inflammatory cytokines IL-1 and IL-18 [103].

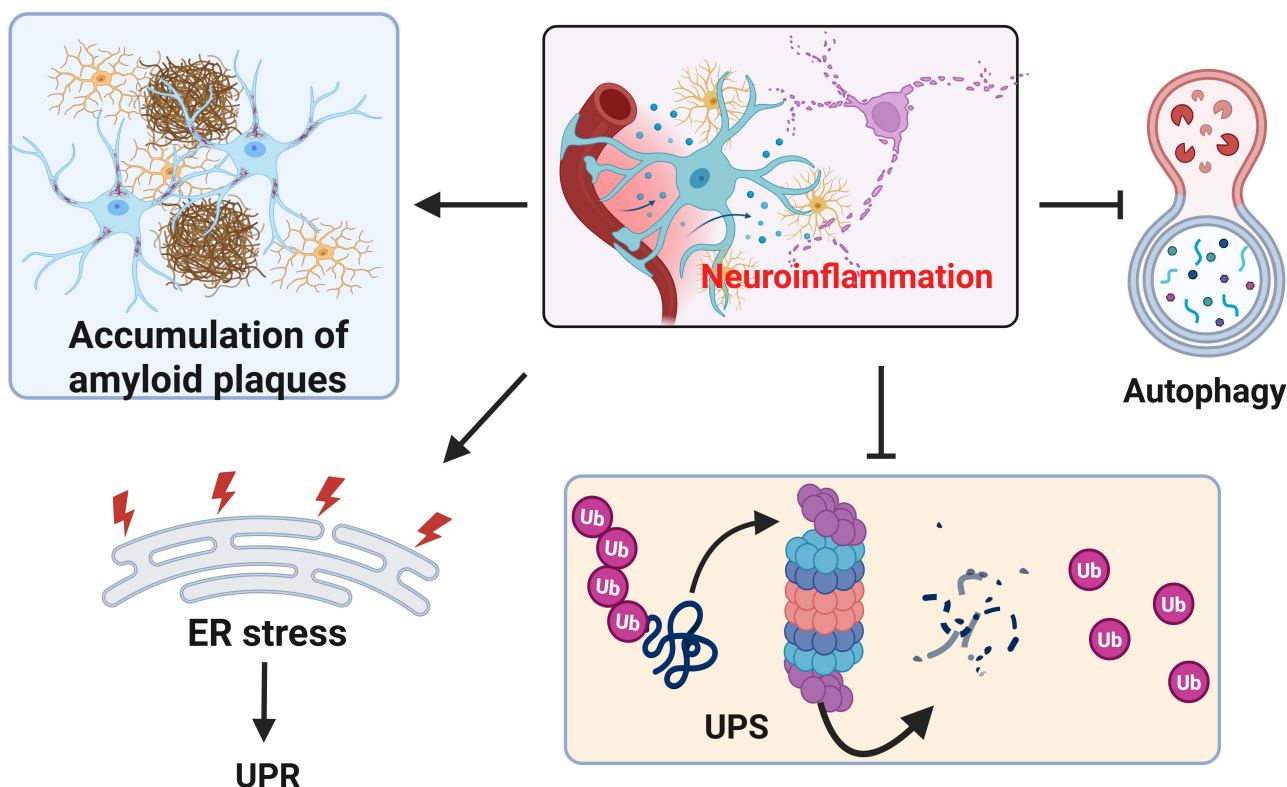
Amyloid- $\beta$  peptides were able to activate the NLRP3 inflammasome in microglia, and IL-1 $\beta$  secretion occurred in a purine receptor (P2X7) receptor-independent manner. Thus, microglia-dependent inflammasome activation by protein aggregates can play an important role in the brain and especially in neuroinflammatory conditions [105]. Available research have found that exposure to A $\beta$  significantly increases the expression of F-box and WD-40 domain protein 11 (FBXW11) in microglia, provid-

ing insight into the mechanisms of microglial activation. Moreover, FBXW11 deletion considerably ameliorated the inflammatory response in A $\beta$ -incubated microglial cells through suppressing NF- $\kappa$ B signaling. Similar research showed that when microglia were incubated with A $\beta$ 42, microglia cell morphology changed, the expression level of inflammatory factors increased, cell apoptosis was promoted, and the expression of microtubule-associated protein (Tau protein) and related proteins increased [106]. Additional research indicates A $\beta$ -induced activation of the NLRP3 inflammasome in microglia occurs via the toll-like receptor 4 (TLR4) pathway [107]. Additionally, A $\beta$  treatment also induced a high level of caspase-1 and IL-1 in the brain tissue of AD mice [108,109], while inhibition of either NLRP3 or caspase-1 increased the clearance of A $\beta$  by microglia, reduced the A $\beta$  deposition, and improved cognitive impairment [110]. Inhibition of the NLRP3 increased the endothelial properties and survival, suggesting a role of NLRP3 in blood-brain barrier dysfunction in AD.

### 4.2 Increased Neuroinflammation Enhances Protein Misfolding and Disrupts Proteostasis

As mentioned above, microglia are one of the first immune cells that get activated and recruited to the site of infection or injury as an inflammatory response [111]. It is noted that microglia express the purinergic receptors that act as ATP-activated ion channels abundantly present on the surface of microglia and play a role in immune response [112,113]. One type of purinergic receptor is called the P2 receptor, which can be activated by metabolites and A $\beta$ , thereby causing microglia to activate their phagocytic capacity. Several receptors, such as the toll-like receptors, act as important bridges that connect the innate and adaptive immune response and through recognition receptors like TLR2, TLR4, and myeloid cell 2 (TREM2)—found on myeloid cells—they play a key role in the clearance of A $\beta$  aggregates [114,115]. When these receptors are activated by metabolites and A $\beta$ , phagosomes form, which subsequently fuse with the lysosomes within microglia cells to form phagolysosomes [116]. The endocytosed substances in the phagolysosomes are then degraded by various hydrolases and cathepsins [117,118].

However, the challenge lies in the fact that overstimulating these receptors can lead to excessive production of inflammatory factors such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 which in turn promotes inflammation. They have been implicated in the accumulation of A $\beta$  and hyperphosphorylation of tau, contributing to the activation of microglia and astrocytes and the formation and release of exosomes that help spread the aggregates to other cells [119,120]. For example, TREM2 has been reported to promote the conversion of microglia to the disease-associated microglia phenotype, responsible for A $\beta$  phagocytosis [121]. Microglia could also drive tau spreading and toxicity by promoting neuroinflammation, such as activating the NLRP3 inflam-



**Fig. 5. Neuroinflammation impairs proteostasis.** In presence of neuroinflammation, the accumulation of amyloid plaques and p-tau (not shown) increases (upper left). In addition to inducing ER stress and unfolded protein response (UPR) in the ER, neuroinflammation also inhibits UPS and autophagy. Created with <https://www.biorender.com/>.

masome. Microglial autophagy deficiency can lead to dysregulation of lipid metabolism, induce microglia into a pro-inflammatory state, and as a result, enhance intraneuronal tau pathology and its spreading [122]. It is evident that microglia-mediated neuroinflammation accelerates A $\beta$  and tau pathology in AD (Fig. 5). On the other hand, A $\beta$  promotes neuroinflammation in glia.

$\alpha$ 1-Antitrypsin (A1AT) reduces A $\beta$ 42-induced inflammation in microglial cells and protects neurons from glutamate-induced toxicity [123]. Neuroinflammation disrupts experience-dependent structural plasticity of dendritic spines in preclinical stages of AD [124], while A $\beta$  pathology profoundly affects human astrocytes and changes their entire energy metabolism, which could result in disturbed brain homeostasis and aggravated disease progression [125]. Studies have reported profound astrogliosis in the brain of animal models of AD and AD patients [126,127]. When astrocytes are activated by A $\beta$ , injury, or signal of damage, they also participate in the secretion of inflammatory cytokines, including IL-1, IL-6, and TNF- $\alpha$ , thereby promoting A $\beta$  aggregation and the neurodegenerative processes in AD [127,128] (Fig. 5). Although the precise mechanism behind astrocyte-induced protein aggregation is not fully understood, activation of astrocyte receptors such as lipoprotein receptor-related proteins (LRPs), scavenger receptor-like receptors, membrane-associated proteo-

glycans, and the advanced glycation end products receptor (RAGE) which contributes to A $\beta$  aggregation by recognizing and binding to A $\beta$  [129]. In addition to promoting the accumulation of immune cells in senile plaques, A $\beta$  also contributes substantially to the inflammatory processes mediated by astrocytes [130,131]. Taking all that has been highlighted above together, it can be concluded that neuroinflammation and protein dysfunction go hand in hand, and it will be of therapeutic benefit to have formulations that target both axes.

## 5. Neuroinflammation and Proteostasis as Potential Targets for AD Treatment

AD is a heterogeneous condition, characterized by variability in amyloid composition, tau distribution, the relationship between amyloid and tau, clinical symptoms, neuroinflammation, age, and genetic background. This complexity has led to the development of multiple research and treatment strategies targeting different aspects of the disease, such as oxidative stress, genetic mutations, gut microbiome disruption, protein homeostasis (or proteostasis), neuroinflammation, and more. Here, we focus specifically on research and therapeutic strategies targeting neuroinflammation, proteostasis, and their interplay in the management of AD.



**Table 1. Therapeutic agents targeting neuroinflammation and proteostasis in clinical trial.**

S/N	Agent	Route	Target	AD Stage	Phase	Reference
1	Hydromethylthionine Mesylate	Oral	Tau aggregation inhibitor	Mild cognitive impairment (MCI)-AD	III	[134,135]
2	Buntanetap	Oral	Neuroinflammation, A $\beta$ and Tau aggregation	Mild AD	I	[136]
3	AADvac1 (active peptide vaccine)	IV	Tau aggregation	Mild AD	II	[137]
4	Gosuranemab (anti-tau monoclonal antibody)	IV	Tau aggregation	Mild AD	II	[138]
5	Semorinemab	IV	Tau aggregation and microglia activation (neuroinflammation)	Mild-Moderate AD	II	[139–141]
6	MAPTRx (Tau-targeting antisense oligonucleotide)	IV	Tau aggregation	Mild AD	Ib	[142]
7	Tilavonemab	IV	Tau aggregation	Mild AD	II	[143]
8	NPT088	IV	A $\beta$ and Tau aggregation	Mild-Moderate AD	Initial	[144]
9	Neflamapimod (p38 $\alpha$ kinase inhibitor)	Oral	A $\beta$ and Tau aggregation	Mild AD	II	[145]
10	Lecanemab (humanized IgG1 monoclonal antibody)	IV	A $\beta$	Mild AD	III	[146–148]
11	Donanemab	IV	A $\beta$	Mild AD	II	[149]
12	Gantenerumab (anti-A $\beta$ IgG1 monoclonal antibody)	IV	A $\beta$	Mild AD	III	[150]
13	Aducanumab (human monoclonal antibody)	IV	A $\beta$	Mild AD	III	[151]
14	Aducanumab (Japanese subgroup Analysis)	IV	A $\beta$	Mild cognitive impairment-AD (MCI-AD)	III	[152]
15	CT1812 (modulator of the sigma-2 receptor (S2R))	Oral	A $\beta$	Mild-Moderate AD	II	[153]
16	CT1812 (modulator of the sigma-2 receptor (S2R))	Indwelling cerebrospinal fluid (CSF) catheter	A $\beta$	Mild-Moderate AD	Ib	[154]
17	Atabecestat (JNJ-54861911)	Oral	$\beta$ APP-cleaving enzyme 1 (BACE1) inhibitor	Mild AD	II	[155]
18	Verubecestat	Oral	BACE1 inhibitor	Mild-Moderate AD	III	[156]
19	Hydralazine	Oral	Mitochondrial function SIRT1/SIRT5 axis and NRF2 signaling pathway (Neuroinflammation and Oxidative stress)	Mild-Moderate AD	III	[157]
20	NeuroEPO plus (NeuralCIM®)	Oral	Oxidative damage and neuroinflammation	Mild-Moderate AD	II-III	[158]
21	GRF6019	IV	Neuroinflammation, cognition and synaptic plasticity	Severe AD	II	[159]
22	Semaglutide (glucagon-like peptide-1 receptor agonist)	Oral	Neuroinflammation	Mild AD	III	[160]
23	Masitinib (tyrosine kinase inhibitor)	Oral	Neuroinflammation (Mast cells and Microglia)- Adjunct treatment	Mild to Moderate	III	[161]
24	AL002 (engineered, humanized monoclonal immunoglobulin G1 (IgG1) antibody)	IV	Neuroinflammation (Microglia, triggering receptor expressed on myeloid cells 2 (TREM2) agonistic)	Mild AD	I	[162,163]

### 5.1 Current and Potential Therapeutic Strategies

Current drugs used in the management of AD either target cholinergic or glutamatergic neurotransmission, which only relieve the symptoms. There is no curative medication available, though there are many ongoing clinical trials for such drugs. Some newly developed agents target the amyloid and tau proteins [132]. Donepezil, galantamine, and rivastigmine are the current three acetylcholinesterase inhibitors that have been approved by the Food and Drug Administration, and they act via modification of the cholinergic system. They are usually used for mild to moderate AD, while Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist of the glutamatergic system, was approved in 2003 for moderate to severe AD. These drugs improve cognition in the patient and ease the social and economic burden [133]. A lot of reviews have done a deep dive into the above medications, so we will not dwell on them here. Researchers are developing various agents with the hopes of finding a lasting solution to AD. The list of such drugs that are in clinical trials is long, and those related to neuroinflammation and proteostasis mechanisms in the past five years (2019 till date) using PubMed search are mentioned in Table 1 (Ref. [134–163]).

While some act on tau, such as donanemab (The trailblazer-ALZ 2 randomized clinical trial), which significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population [149]. Similarly, gosuranemab had an acceptable safety profile and was generally well tolerated. At week 76, all doses caused significant reductions in the cerebrospinal fluid levels of unbound N-terminal tau compared to placebo [138]. Tilavonemab was generally well tolerated, although it did not demonstrate efficacy in treating patients with early AD. Thus, further investigation of tilavonemab in early AD is not warranted [143]. Some therapeutics target both proteostasis and inflammation, such as buntanetap, which was safe and well tolerated. Biomarker data during the trial indicated a trend in lowering the levels of neurotoxic proteins and inflammatory factors and improving axonal integrity and synaptic function in both AD and PD cohorts [164].

While some drugs, such as Tilavonemab, did not move further because of efficacy and toxicity, others have continued through various clinical trial phases and gotten approved, such as Aduhelm (aducanumab), which was approved using the accelerated approval pathway in 2021, lecanemab, approved in 2023, and Eli Lilly's Kisunla (Donanemab), recently approved in 2024 [4]. It is important to highlight that most drugs in clinical trials target tau and/or  $A\beta$ , despite the well-established significant role of neuroinflammation in both the development and progression of AD. Having drugs that target both axes may yield better therapeutic outcomes for patients.

### 5.2 Neuroinflammation-Related Biomarkers for AD

A biomarker is an indicator considered for the evaluation of any normal biological as well as pathogenic processes and pharmacological effects of any therapy. In the case of AD, a biomarker can be used to assess the overall health and disease condition of aged patients [165]. An extracellular deposition of amyloid- $\beta$  ( $A\beta$ ) protein and an aggregated form of hyperphosphorylated tau protein in the brain are two main pathological characteristics of AD [166]. During diagnosis, increased retention of  $A\beta$  tracers in the brain and diminished concentrations of  $A\beta$ 42 in CSF have been considered early biomarkers of AD [167] (Table 2, Ref. [168–176]). Both  $A\beta$  and hyperphosphorylated tau have been demonstrated to have high diagnostic and prognostic value as they start changing decades before the onset of dementia symptoms.

Elevated pTau181 in the plasma identifies participants more likely to progress to AD [168] and is a suitable method for enrichment in AD clinical trials. A study by [169] showed CSF-soluble platelet-derived growth factor receptor beta (sPDGFR $\beta$ ) is associated with BBB leakage in the early cognitive impairment stage of AD, which may contribute to cognitive impairment in AD progression. Similarly, glial fibrillary acidic protein (GFAP), neurofilament light chain (NF-L), and p-tau181 were identified as the biomarkers that are significantly associated with disease progression in both CSF and plasma, thereby suggesting that both CSF and plasma measurement of NF-L, p-tau181, and GFAP may play a significant role in disease staging and monitoring [177]. Furthermore, p-tau217 and the p-tau217/ $A\beta$ 40 ratios showed robust correlations with cerebrospinal fluid biomarkers and positron emission tomography amyloid standardized uptake value ratios, underscoring their value as non-invasive diagnostic alternatives [170,171]. Using a risk prediction model, seven protein signatures (APOE, CGA, CRP, CCL26, CCL20, NRCAM, and PYY) have been identified that could independently predict AD incidence in the future [172]. Extracellular vesicles (EVs) have also been explored as possible biomarkers. Preliminary data suggest that plasma-derived EV S100A8 might be a potential biomarker of AD [178] (Table 2).

Circulating long noncoding RNAs (lncRNAs) might serve as biomarkers for different pathological conditions. BACE1-antisense (BACE1-AS) lncRNA is upregulated in the AD brain and might be detected in the bloodstream (Table 2). The BACE1-AS level was low in the pre-AD subgroup but was high in full-AD people compared to the healthy controls. Therefore, BACE1-AS lncRNA may discriminate pre-AD and healthy control (75% sensitivity and 100% specificity), full-AD and healthy control (68% sensitivity and 100% specificity), and pre-AD and full-AD subgroups (78% sensitivity and 100% specificity), highlighting its potential as a biomarker for AD development [173]. Also in agreement with the above data is the research that suggests lncRNA MALAT1 (CSF but not plasma lncRNA-

**Table 2. Identified biomarkers for AD.**

Biomarkers	Source	References
A $\beta$ 42	Brain, CSF	[168]
pTau181	Plasma	[169]
NF-L, p-tau181, and GFAP	Plasma, CSF	[170]
p-tau217 and p-tau217/A $\beta$ 1-42 ratio	Plasma	[171,172]
EV S100A8	Plasma	[173]
lncRNAs, BACE1-AS	Plasma	[174,175]
A $\beta$ 40/A $\beta$ 42 ratio and type 1 T-helper cells	Plasma	[176]

NF-L, neurofilament light chain; GFAP, glial fibrillary acidic protein; CSF, cerebrospinal fluid; lncRNAs, circulating long noncoding RNAs; BACE1-AS, BACE1-antisense; EV, extracellular vesicles.

MALAT1) targeted miR-125b as potential biomarkers for AD, as they could predict the MMSE score decline at 1, 2, and 3 years in AD patients [174].

Inflammatory cells have also been explored as possible biomarkers. FP40/FP42 and type 1 T-helper cells can accurately predict the pathological changes of late mild cognitive impairment [175] (Table 2). The inflammatory biomarker, GFAP, is a more sensitive marker of the inflammatory process in response to the A $\beta$  misfolding and aggregation, which has been increasingly used as an indicator for A $\beta$ 42 levels in the CSF [136].

## 6. Conclusion and Future Directions

AD is a multifactorial neurodegenerative disorder with complex pathogenic mechanisms that go far beyond amyloid- $\beta$  (A $\beta$ ) accumulation and tau hyperphosphorylation. Among the many disrupted cellular processes in AD, impaired proteostasis—particularly involving the ubiquitin-proteasome system and autophagy-lysosome pathway—has emerged as a consistent and critical feature in both experimental models and human pathology [176,179]. Studies have confirmed that both A $\beta$  and aggregated tau proteins can directly inhibit proteasome function, leading to the buildup of misfolded or damaged proteins and subsequent cellular toxicity. However, due to the intricate structure and regulation of the proteasome machinery, efforts to modulate its activity *in vivo* have faced significant technical and biological challenges. Beyond the impairment of protein clearance, neuroinflammation has gained attention as a key contributor to the onset and progression of AD. However, it is essential to interpret the role of inflammatory mediators with caution, as these immune pathways are not unique to AD. Many of the same microglial and astrocytic responses are implicated in a range of neurodegenerative and neuroinflammatory diseases, including Parkinson's disease, Huntington's disease, cerebral ischemia-reperfusion injury, and autoimmune encephalomyelitis. Hence, it is important to interpret this cautiously, as many of these cells are also implicated in other neurodegenerative diseases [180].

Relying solely on targeting neuroinflammation is unlikely to resolve the underlying proteostasis dysregulation in AD. Rather, a combinatorial therapeutic strategy is required—one that addresses both neuroinflammatory responses and proteostatic collapse simultaneously. The development of preclinical models that more accurately reflect the human disease, especially in terms of inflammation-proteostasis interactions, remains a priority. Many current transgenic or knock-in models fail to capture the full scope of proteostasis disturbances and chronic inflammation seen in human AD brains, thereby limiting translational success.

Recent technological advances offer hope for overcoming these barriers. Tools such as single-cell RNA sequencing have revolutionized our ability to dissect cellular heterogeneity within the brain, especially among microglial subpopulations. These tools allow for the identification of disease-associated microglial states and the mapping of their transcriptional dynamics across disease stages. Additionally, organoid models of the human brain, particularly those incorporating immune components such as microglia, present promising platforms for studying drug responses in a more physiologically relevant context. The application of cerebral organoids, combined with advanced transcriptomics and proteomics, could pave the way for identifying more precise therapeutic targets and predicting human responses more effectively.

Current Food and Drug Administration (FDA)-approved therapies for AD—such as aducanumab, lecanemab, and donanemab—are largely focused on reducing A $\beta$  burden. While these monoclonal antibodies demonstrate some ability to slow the progression of early-stage AD, they are effective in only a subset (approximately 20–30%) of patients and do not halt or reverse disease progression. Moreover, most of these therapies offer limited benefits to individuals in the later stages of the disease, who represent a significant proportion of the patient population. This therapeutic gap emphasizes the urgent need for interventions that go beyond A $\beta$  targeting.

There is growing consensus in the field that addressing multiple pathological pathways simultaneously—such as combining anti-inflammatory agents, proteostasis enhancers, mitochondrial stabilizers, and synaptic modulators—may produce synergistic effects and yield better clinical outcomes. The future of AD therapy will likely hinge on the integration of multi-target approaches tailored to disease stage and patient-specific pathophysiological profiles. Personalized medicine strategies, possibly guided by biomarkers of proteostasis and inflammation, hold promise in optimizing these combination therapies.

In conclusion, advancing AD treatment requires a paradigm shift toward holistic, multi-modal strategies that address the disease's complex molecular underpinnings. This includes prioritizing research into proteostasis-inflammation crosstalk, investing in the development of

more representative disease models, and embracing the power of emerging technologies in neuroscience. Only through such an integrative approach can we hope to develop effective therapies that not only delay disease progression but also improve the quality of life for patients across all stages of AD.

## Abbreviations

AD, Alzheimer's disease; A $\beta$ , amyloid beta; APP, amyloid precursor protein; ATF4, activating transcription factor 4; APP-CTFs, amyloid precursor protein-derived C-terminal fragments; ALPs, Autophagy-Lysosome pathways; RAGE, advanced glycation end products; BACE-1,  $\beta$ -secretase; Cox-2, cyclooxygenase-2; cGAS, Cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase; CHOP, C/EBP-homologous protein; DAMPs, damage-associated molecular patterns; ds-DNA, double stranded DNA; ER, endoplasmic reticulum; ERAD, ER-associated degradation; eIF2, E74-like factor 2; GSH, glutathione; Grp78, glucose-related protein 78; GFAP, Glial fibrillary acidic protein; IL-1, interleukin; IFNs, Interferons; lncRNAs, Circulating long noncoding RNAs; mTOR, mammalian target of rapamycin; mtDNA, mitochondrial DNA; miR-214-3p/ATG5, microRNA-214-3p/autophagy-related protein 5; MAP2, microtubule-associated protein; MAPT/TAU, microtubule-associated protein tau; TREM2, myeloid cell 2; NO, nitric oxide; NF- $\kappa$ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NFTs, Neurofibrillary tangles; hNmnat1, Nicotinamide mononucleotide adenylyltransferase 1; NAD<sup>+</sup>, nicotinamide adenine dinucleotide; NVU, Neurovascular unit; NLRP3, nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing (NLRP) 3; OS, oxidative stress; PG, prostaglandin; Akt/mTOR, Protein kinase B/mammalian target of rapamycin; p38 MAPK, p38 mitogen-activated protein kinases; PINK1-Parkin, PTEN-induced kinase 1-Parkin; PS1, Presenilin 1; ROS, reactive oxygen species; RNS, Reactive nitrogen species; raw IOP, raw inonotus obliquus polysaccharide; TNF- $\alpha$ , Tumor necrosis factor; TBN, tetramethylpyrazine nitrene; TFEB, transcriptional factor EB; TLR4, Toll-like receptor 4; UPS, ubiquitin proteasome system; UPR, Unfolded protein response; vATPase, vacuolar-type ATPase.

## Author Contributions

AP and HW designed the research work; AP wrote the first draft; HW edited the manuscript. AP made tables, and HW prepared figures. Both authors searched references. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This work was supported by the NIH/NIA RF1 AG072510. Any opinions, findings, conclusions, or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of NIH.

## Conflict of Interest

The authors declare no conflict of interest. Hongmin Wang is serving as one of the Editorial Board members of this journal. We declare that Hongmin Wang had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

## References

- [1] Abubakar MB, Sanusi KO, Ugusman A, Mohamed W, Kamal H, Ibrahim NH, *et al.* Alzheimer's Disease: An Update and Insights Into Pathophysiology. *Frontiers in Aging Neuroscience*. 2022; 14: 742408. <https://doi.org/10.3389/fnagi.2022.742408>.
- [2] El Kadmiri N, Zaid N, Zaid Y, Tadevosyan A, Hachem A, Dubé MP, *et al.* Novel presenilin mutations within Moroccan patients with Early-Onset Alzheimer's Disease. *Neuroscience*. 2014; 269: 215–222. <https://doi.org/10.1016/j.neuroscience.2014.03.052>.
- [3] Manola MS, Gummi S, Trougakos IP. Differential Dose- and Tissue-Dependent Effects of foxo on Aging, Metabolic and Pro-teostatic Pathways. *Cells*. 2021; 10: 3577. <https://doi.org/10.3390/cells10123577>.
- [4] Behl C. Biochemistry and Genetics Point Out a Prime Suspect for Causing Alzheimer's Disease. In *Alzheimer's Disease Research: What Has Guided Research So Far and Why It Is High Time for a Paradigm Shift* (pp. 109–117). Springer: Cham. 2023. [https://doi.org/10.1007/978-3-031-31570-1\\_7](https://doi.org/10.1007/978-3-031-31570-1_7).
- [5] Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid  $\beta$ -based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduction and Targeted Therapy*. 2023; 8: 248. <https://doi.org/10.1038/s41392-023-01484-7>.
- [6] Rahman MM, Lendel C. Extracellular protein components of amyloid plaques and their roles in Alzheimer's disease pathology. *Molecular Neurodegeneration*. 2021; 16: 59. <https://doi.org/10.1186/s13024-021-00465-0>.
- [7] Le Guen Y, Luo G, Ambati A, Damotte V, Jansen I, Yu E, *et al.* Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by *HLA-DRB1\*04* subtypes. *Proceedings of the National Academy of Sciences of the United States of America*. 2023; 120: e2302720120. <https://doi.org/10.1073/pnas.2302720120>.
- [8] Pan RY, He L, Zhang J, Liu X, Liao Y, Gao J, *et al.* Positive feedback regulation of microglial glucose metabolism by histone H4 lysine 12 lactylation in Alzheimer's disease. *Cell Metabolism*. 2022; 34: 634–648.e6. <https://doi.org/10.1016/j.cmet.2022.02.013>.
- [9] Kalafatakis I, Karagogeos D. Oligodendrocytes and Microglia: Key Players in Myelin Development, Damage and Repair. *Biomolecules*. 2021; 11: 1058. <https://doi.org/10.3390/biom11071058>.



- [10] Hughes AN. Glial Cells Promote Myelin Formation and Elimination. *Frontiers in Cell and Developmental Biology*. 2021; 9: 661486. <https://doi.org/10.3389/fcell.2021.661486>.
- [11] Unger MS, Schernthaner P, Marschallinger J, Mrowetz H, Aigner L. Microglia prevent peripheral immune cell invasion and promote an anti-inflammatory environment in the brain of APP-PS1 transgenic mice. *Journal of Neuroinflammation*. 2018; 15: 274. <https://doi.org/10.1186/s12974-018-1304-4>.
- [12] Cai Y, Liu J, Wang B, Sun M, Yang H. Microglia in the Neuroinflammatory Pathogenesis of Alzheimer's Disease and Related Therapeutic Targets. *Frontiers in Immunology*. 2022; 13: 856376. <https://doi.org/10.3389/fimmu.2022.856376>.
- [13] Twarowski B, Herbet M. Inflammatory Processes in Alzheimer's Disease-Pathomechanism, Diagnosis and Treatment: A Review. *International Journal of Molecular Sciences*. 2023; 24: 6518. <https://doi.org/10.3390/ijms24076518>.
- [14] Weng Y, Xie G. Increased GABBR2 Expression on Cell Membranes Causes Increased Ca<sup>2+</sup> + Inward Flow, Associated with Cognitive Impairment in Early Alzheimer's Disease. *Biochemical Genetics*. 2024. <https://doi.org/10.1007/s10528-024-11004-z>. (online ahead of print)
- [15] Zu HB, Liu XY, Yao K. DHCR24 overexpression modulates microglia polarization and inflammatory response via Akt/GSK3 $\beta$  signaling in A $\beta$ <sub>25–35</sub> treated BV-2 cells. *Life Sciences*. 2020; 260: 118470. <https://doi.org/10.1016/j.lfs.2020.118470>.
- [16] Tecalco-Cruz AC, Pedraza-Chaverri J, Briones-Herrera A, Cruz-Ramos E, López-Canovas L, Zepeda-Cervantes J. Protein degradation-associated mechanisms that are affected in Alzheimer's disease. *Molecular and Cellular Biochemistry*. 2022; 477: 915–925. <https://doi.org/10.1007/s11010-021-04334-8>.
- [17] Schmidt MF, Gan ZY, Komander D, Dewson G. Ubiquitin signalling in neurodegeneration: mechanisms and therapeutic opportunities. *Cell Death and Differentiation*. 2021; 28: 570–590. <https://doi.org/10.1038/s41418-020-00706-7>.
- [18] Zhang W, Xu C, Sun J, Shen HM, Wang J, Yang C. Impairment of the autophagy-lysosomal pathway in Alzheimer's diseases: Pathogenic mechanisms and therapeutic potential. *Acta Pharmaceutica Sinica. B*. 2022; 12: 1019–1040. <https://doi.org/10.1016/j.apsb.2022.01.008>.
- [19] Zhong G, Fang Z, Sun T, Ying M, Wang A, Chen Y, *et al.* Ubiquitin ligase RFWD2 promotes dendritic spine and synapse formation by activating the ERK/PEA3/c-Jun pathway in rat cerebral cortical neurons. *Biochimica et Biophysica Acta. Molecular Basis of Disease*. 2024; 1870: 167319. <https://doi.org/10.1016/j.bbadis.2024.167319>.
- [20] Deleyto-Seldas N, Efeyan A. The mTOR-Autophagy Axis and the Control of Metabolism. *Frontiers in Cell and Developmental Biology*. 2021; 9: 655731. <https://doi.org/10.3389/fcell.2021.655731>.
- [21] Zhao X, Yang J. Amyloid- $\beta$  peptide is a substrate of the human 20S proteasome. *ACS Chemical Neuroscience*. 2010; 1: 655–660. <https://doi.org/10.1021/cn100067e>.
- [22] Hipp MS, Hartl FU. Interplay of Proteostasis Capacity and Protein Aggregation: Implications for Cellular Function and Disease. *Journal of Molecular Biology*. 2024; 436: 168615. <https://doi.org/10.1016/j.jmb.2024.168615>.
- [23] Mayor A, Martinon F, De Smedt T, Pétrilli V, Tschopp J. A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses. *Nature Immunology*. 2007; 8: 497–503. <https://doi.org/10.1038/ni1459>.
- [24] Wang Z, Zhang YH, Guo C, Gao HL, Zhong ML, Huang TT, *et al.* Tetrathiomolybdate Treatment Leads to the Suppression of Inflammatory Responses through the TRAF6/NF $\kappa$ B Pathway in LPS-Stimulated BV-2 Microglia. *Frontiers in Aging Neuro-*
- science*. 2018; 10: 9. <https://doi.org/10.3389/fnagi.2018.00009>.
- [25] Çetin G, Studencka-Turski M, Venz S, Schormann E, Junker H, Hammer E, *et al.* Immunoproteasomes control activation of innate immune signaling and microglial function. *Frontiers in Immunology*. 2022; 13: 982786. <https://doi.org/10.3389/fimmu.2022.982786>.
- [26] Bai Y, Ma X. Chlorzoxazone exhibits neuroprotection against Alzheimer's disease by attenuating neuroinflammation and neurodegeneration in vitro and in vivo. *International Immunopharmacology*. 2020; 88: 106790. <https://doi.org/10.1016/j.intimp.2020.106790>.
- [27] Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH. Neuroinflammation in Alzheimer's Disease: Current Progress in Molecular Signaling and Therapeutics. *Inflammation*. 2023; 46: 1–17. <https://doi.org/10.1007/s10753-022-01721-1>.
- [28] Paolicelli RC, Sierra A, Stevens B, Tremblay ME, Aguzzi A, Ajami B, *et al.* Microglia states and nomenclature: A field at its crossroads. *Neuron*. 2022; 110: 3458–3483. <https://doi.org/10.1016/j.neuron.2022.10.020>.
- [29] Fumagalli L, Nazlie Mohebiany A, Premereur J, Polanco Miquel P, Bijmens B, Van de Walle P, *et al.* Microglia heterogeneity, modeling and cell-state annotation in development and neurodegeneration. *Nature Neuroscience*. 2025. <https://doi.org/10.1038/s41593-025-01931-4>. (online ahead of print)
- [30] Li D, Cui YL, Li H, Huang SL, Fan Y. Resveratrol attenuates inflammation by regulating macrophage polarization via inhibition of toll-like receptor 4/MyD88 signaling pathway. *Pharmacognosy Magazine*. 2021; 17: 321–326. [https://doi.org/10.4103/pm.pm\\_312\\_20](https://doi.org/10.4103/pm.pm_312_20).
- [31] Malayil R, Chhichholiya Y, Vasudeva K, Singh HV, Singh T, Singh S, *et al.* Oncogenic metabolic reprogramming in breast cancer: focus on signaling pathways and mitochondrial genes. *Medical Oncology (Northwood, London, England)*. 2023; 40: 174. <https://doi.org/10.1007/s12032-023-02037-2>.
- [32] Dhapola R, Hota SS, Sarma P, Bhattacharyya A, Medhi B, Reddy DH. Recent advances in molecular pathways and therapeutic implications targeting neuroinflammation for Alzheimer's disease. *Inflammopharmacology*. 2021; 29: 1669–1681. <https://doi.org/10.1007/s10787-021-00889-6>.
- [33] Yeung YT, Aziz F, Guerrero-Castilla A, Arguelles S. Signaling Pathways in Inflammation and Anti-inflammatory Therapies. *Current Pharmaceutical Design*. 2018; 24: 1449–1484. <https://doi.org/10.2174/1381612824666180327165604>.
- [34] Lashgari NA, Roudsari NM, Shamsnia HS, Shayan M, Momtaz S, Abdolghaffari AH. TLR/mTOR inflammatory signaling pathway: novel insight for the treatment of schizophrenia. *Canadian Journal of Physiology and Pharmacology*. 2024; 102: 150–160. <https://doi.org/10.1139/cjpp-2023-0107>.
- [35] Ebrahimi F, Koch M, Pieroh P, Ghadban C, Hobusch C, Bechmann I, *et al.* Time dependent neuroprotection of mycophenolate mofetil: effects on temporal dynamics in glial proliferation, apoptosis, and scar formation. *Journal of Neuroinflammation*. 2012; 9: 89. <https://doi.org/10.1186/1742-2094-9-89>.
- [36] Licastro F, Pedrini S, Caputo L, Annoni G, Davis LJ, Ferri C, *et al.* Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain? *Journal of Neuroimmunology*. 2000; 103: 97–102. [https://doi.org/10.1016/s0165-5728\(99\)00226-x](https://doi.org/10.1016/s0165-5728(99)00226-x).
- [37] Kumari S, Dhapola R, Sharma P, Singh SK, Reddy DH. Implicative role of Cytokines in Neuroinflammation mediated AD and associated signaling pathways: Current Progress in molecular signaling and therapeutics. *Ageing Research Reviews*. 2023; 102098. <https://doi.org/10.1016/j.arr.2023.102098>.
- [38] Lee CYD, Landreth GE. The role of microglia in amyloid clearance from the AD brain. *Journal of Neural Transmission (Vi-*

- enna, Austria: 1996). 2010; 117: 949–960. <https://doi.org/10.1007/s00702-010-0433-4>.
- [39] Ji YF, Wang YJ, Chen SH, Cheng Y. Interleukin-4 promotes the clearance of amyloid- $\beta$  by monocyte through enhancing the recognition and intracellular processing of amyloid- $\beta$ . *Journal of Alzheimer's Disease: JAD*. 2024; 102: 1017–1026. <https://doi.org/10.1177/13872877241295361>.
- [40] Zuroff LR, Torbati T, Hart NJ, Fuchs DT, Sheyn J, Rentsendorj A, *et al.* Effects of IL-34 on Macrophage Immunological Profile in Response to Alzheimer's-Related A $\beta_{42}$  Assemblies. *Frontiers in Immunology*. 2020; 11: 1449. <https://doi.org/10.3389/fimmu.2020.01449>.
- [41] Zhang S, Ye J, Dong G. Neuroprotective effect of baicalein on hydrogen peroxide-mediated oxidative stress and mitochondrial dysfunction in PC12 cells. *Journal of Molecular Neuroscience: MN*. 2010; 40: 311–320. <https://doi.org/10.1007/s12031-009-9285-5>.
- [42] Ataei S, Abaspanah S, Haddadi R, Mohammadi M, Nili-Ahmadabadi A. Therapeutic Potential of Dihydropyridine Calcium Channel Blockers on Oxidative Injury Caused by Organophosphates in Cortex and Cerebellum: An In Vivo Study. *Indian Journal of Clinical Biochemistry: IJCB*. 2020; 35: 339–346. <https://doi.org/10.1007/s12291-019-00830-3>.
- [43] Feng Y, Jiang C, Yang F, Chen Z, Li Z. *Apocynum venetum* leaf extract protects against H<sub>2</sub>O<sub>2</sub>-induced oxidative stress by increasing autophagy in PC12 cells. *Biomedical Reports*. 2020; 13: 6. <https://doi.org/10.3892/br.2020.1313>.
- [44] Lushchak VI. Interplay between bioenergetics and oxidative stress at normal brain aging. Aging as a result of increasing disbalance in the system oxidative stress-energy provision. *Pflügers Archiv: European Journal of Physiology*. 2021; 473: 713–722. <https://doi.org/10.1007/s00424-021-02531-4>.
- [45] Zu G, Sun K, Li L, Zu X, Han T, Huang H. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. *Scientific Reports*. 2021; 11: 22959. <https://doi.org/10.1038/s41598-021-02248-5>.
- [46] Ulfig A, Jakob U. Cellular oxidants and the proteostasis network: balance between activation and destruction. *Trends in Biochemical Sciences*. 2024; 49: 761–774. <https://doi.org/10.1016/j.tibs.2024.07.001>.
- [47] Redza-Dutordoir M, Averill-Bates DA. Interactions between reactive oxygen species and autophagy: Special issue: Death mechanisms in cellular homeostasis. *Biochimica et Biophysica Acta. Molecular Cell Research*. 2021; 1868: 119041. <https://doi.org/10.1016/j.bbamer.2021.119041>.
- [48] Wang H, Wang A, Wang X, Zeng X, Xing H. AMPK/PPAR- $\gamma$ /NF- $\kappa$ B axis participates in ROS-mediated apoptosis and autophagy caused by cadmium in pig liver. *Environmental Pollution (Barking, Essex: 1987)*. 2022; 294: 118659. <https://doi.org/10.1016/j.envpol.2021.118659>.
- [49] Hetz C. Adapting the proteostasis capacity to sustain brain healthspan. *Cell*. 2021; 184: 1545–1560. <https://doi.org/10.1016/j.cell.2021.02.007>.
- [50] Piccini A, Borghi R, Guglielmotto M, Tamagno E, Cirmena G, Garuti A, *et al.*  $\beta$ -amyloid 1-42 induces physiological transcriptional regulation of BACE1. *Journal of Neurochemistry*. 2012; 122: 1023–1031. <https://doi.org/10.1111/j.1471-4159.2012.07834.x>.
- [51] Tamagno E, Guglielmotto M, Monteleone D, Tabaton M. Amyloid- $\beta$  production: major link between oxidative stress and BACE1. *Neurotoxicity Research*. 2012; 22: 208–219. <https://doi.org/10.1007/s12640-011-9283-6>.
- [52] Ashleigh T, Swerdlow RH, Beal MF. The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2023; 19: 333–342. <https://doi.org/10.1002/alz.12683>.
- [53] Sandberg AA, Manning E, Wilkins HM, Mazzarino R, Minckley T, Swerdlow RH, *et al.* Mitochondrial Targeting of Amyloid- $\beta$  Protein Precursor Intracellular Domain Induces Hippocampal Cell Death via a Mechanism Distinct from Amyloid- $\beta$ . *Journal of Alzheimer's Disease: JAD*. 2022; 86: 1727–1744. <https://doi.org/10.3233/JAD-215108>.
- [54] Picone P, Nuzzo D, Caruana L, Scafidi V, Di Carlo M. Mitochondrial dysfunction: different routes to Alzheimer's disease therapy. *Oxidative Medicine and Cellular Longevity*. 2014; 2014: 780179. <https://doi.org/10.1155/2014/780179>.
- [55] Olajide OJ, La Rue C, Bergdahl A, Chapman CA. Inhibiting amyloid beta (1-42) peptide-induced mitochondrial dysfunction prevents the degradation of synaptic proteins in the entorhinal cortex. *Frontiers in Aging Neuroscience*. 2022; 14: 960314. <https://doi.org/10.3389/fnagi.2022.960314>.
- [56] Koopman WJH, Nijtmans LGJ, Dieteren CEJ, Roestenberg P, Valsecchi F, Smeitink JAM, *et al.* Mammalian mitochondrial complex I: biogenesis, regulation, and reactive oxygen species generation. *Antioxidants & Redox Signaling*. 2010; 12: 1431–1470. <https://doi.org/10.1089/ars.2009.2743>.
- [57] Ralph SJ, Moreno-Sánchez R, Neuzil J, Rodríguez-Enríquez S. Inhibitors of succinate: quinone reductase/Complex II regulate production of mitochondrial reactive oxygen species and protect normal cells from ischemic damage but induce specific cancer cell death. *Pharmaceutical Research*. 2011; 28: 2695–2730. <http://doi.org/10.1007/s11095-011-0566-7>.
- [58] Cardoso S, Carvalho C, Correia SC, Moreira PI. Protective effects of 2,4-dinitrophenol in okadaic acid-induced cellular model of Alzheimer's disease. *Biochimica et Biophysica Acta. Molecular Basis of Disease*. 2024; 1870: 167222. <https://doi.org/10.1016/j.bbadis.2024.167222>.
- [59] Farrugia MY, Caruana M, Ghio S, Camilleri A, Farrugia C, Cauchi RJ, *et al.* Toxic oligomers of the amyloidogenic HypF-N protein form pores in mitochondrial membranes. *Scientific Reports*. 2020; 10: 17733. <https://doi.org/10.1038/s41598-020-74841-z>.
- [60] Fernandes T, Resende R, Silva DF, Marques AP, Santos AE, Cardoso SM, *et al.* Structural and Functional Alterations in Mitochondria-Associated Membranes (MAMs) and in Mitochondria Activate Stress Response Mechanisms in an In Vitro Model of Alzheimer's Disease. *Biomedicines*. 2021; 9: 881. <https://doi.org/10.3390/biomedicines9080881>.
- [61] Govindarajulu M, Ramesh S, Beasley M, Lynn G, Wallace C, Labeau S, *et al.* Role of cGAS-Sting Signaling in Alzheimer's Disease. *International Journal of Molecular Sciences*. 2023; 24: 8151. <https://doi.org/10.3390/ijms24098151>.
- [62] Jiang GL, Yang XL, Zhou HJ, Long J, Liu B, Zhang LM, *et al.* cGAS knockdown promotes microglial M2 polarization to alleviate neuroinflammation by inhibiting cGAS-STING signaling pathway in cerebral ischemic stroke. *Brain Research Bulletin*. 2021; 171: 183–195. <https://doi.org/10.1016/j.brainresbu.2021.03.010>.
- [63] Quan S, Fu X, Cai H, Ren Z, Xu Y, Jia L. The neuroimmune nexus: unraveling the role of the mtDNA-cGAS-STING signal pathway in Alzheimer's disease. *Molecular Neurodegeneration*. 2025; 20: 25. <https://doi.org/10.1186/s13024-025-00815-2>.
- [64] Alarcón-Espósito J, Nagiri RK, Gan L, Sinha SC. Identification and development of cGAS inhibitors and their uses to treat Alzheimer's disease. *Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics*. 2025; 22: e00536. <https://doi.org/10.1016/j.neurot.2025.e00536>.
- [65] Huang Y, Liu B, Sinha SC, Amin S, Gan L. Mechanism and therapeutic potential of targeting cGAS-STING signaling in neurological disorders. *Molecular Neurodegeneration*. 2023; 18: 79. <https://doi.org/10.1186/s13024-023-00672-x>.
- [66] Dwamena A, Asadi Y, Gilstrap E, Wang, H. Impaired pro-

- teasome induces mitochondrial DNA release to activate the cGAS-STING signaling pathway and cause necroptosis in mouse brain. *bioRxiv*. 2024. <https://doi.org/10.1101/2024.11.13.623442>. (preprint)
- [67] Zhang K, Huang Q, Li X, Zhao Z, Hong C, Sun Z, *et al.* The cGAS-STING pathway in viral infections: a promising link between inflammation, oxidative stress and autophagy. *Frontiers in Immunology*. 2024; 15: 1352479. <https://doi.org/10.3389/fimmu.2024.1352479>.
  - [68] Murthy AMV, Robinson N, Kumar S. Crosstalk between cGAS-STING signaling and cell death. *Cell Death and Differentiation*. 2020; 27: 2989–3003. <https://doi.org/10.1038/s41418-020-00624-8>.
  - [69] Liu M, Pan J, Li X, Zhang X, Tian F, Li M, *et al.* Interleukin-6 deficiency reduces neuroinflammation by inhibiting the STAT3-cGAS-STING pathway in Alzheimer's disease mice. *Journal of Neuroinflammation*. 2024; 21: 282. <https://doi.org/10.1186/s12974-024-03277-3>.
  - [70] Tawo R, Pokrzywa W, Kevei É, Akyuz ME, Balaji V, Adrian S, *et al.* The Ubiquitin Ligase CHIP Integrates Proteostasis and Aging by Regulation of Insulin Receptor Turnover. *Cell*. 2017; 169: 470–482.e13. <https://doi.org/10.1016/j.cell.2017.04.003>.
  - [71] Rebeaud ME, Mallik S, Goloubinoff P, Tawfik DS. On the evolution of chaperones and cochaperones and the expansion of proteomes across the Tree of Life. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2020885118. <https://doi.org/10.1073/pnas.2020885118>.
  - [72] Ruan L, Wang Y, Zhang X, Tomaszewski A, McNamara JT, Li R. Mitochondria-Associated Proteostasis. *Annual Review of Biophysics*. 2020; 49: 41–67. <https://doi.org/10.1146/annurev-biophys-121219-081604>.
  - [73] Elman JA, Panizzon MS, Gustavson DE, Franz CE, Sanderson-Cimino ME, Lyons MJ, *et al.* Amyloid- $\beta$  Positivity Predicts Cognitive Decline but Cognition Predicts Progression to Amyloid- $\beta$  Positivity. *Biological Psychiatry*. 2020; 87: 819–828. <https://doi.org/10.1016/j.biopsych.2019.12.021>.
  - [74] Jayaraj GG, Hipp MS, Hartl FU. Functional Modules of the Proteostasis Network. *Cold Spring Harbor Perspectives in Biology*. 2020; 12: a033951. <https://doi.org/10.1101/cshperspect.a033951>.
  - [75] Calabrese V, Cornelius C, Stella AMG, Calabrese EJ. Cellular stress responses, mitostress and carnitine insufficiencies as critical determinants in aging and neurodegenerative disorders: role of hormesis and vitagenes. *Neurochemical Research*. 2010; 35: 1880–1915. <https://doi.org/10.1007/s11064-010-0307-z>.
  - [76] Nedelsky NB, Todd PK, Taylor JP. Autophagy and the ubiquitin-proteasome system: collaborators in neuroprotection. *Biochimica et Biophysica Acta*. 2008; 1782: 691–699. <https://doi.org/10.1016/j.bbdis.2008.10.002>.
  - [77] Weinberg J, Gaur M, Swaroop A, Taylor A. Proteostasis in aging-associated ocular disease. *Molecular Aspects of Medicine*. 2022; 88: 101157. <https://doi.org/10.1016/j.mam.2022.101157>.
  - [78] Maldonado E, Morales-Pison S, Urbina F, Solari A. Aging Hallmarks and the Role of Oxidative Stress. *Antioxidants (Basel, Switzerland)*. 2023; 12: 651. <https://doi.org/10.3390/antiox12030651>.
  - [79] Meyer-Schwesinger C. The ubiquitin-proteasome system in kidney physiology and disease. *Nature Reviews. Nephrology*. 2019; 15: 393–411. <https://doi.org/10.1038/s41581-019-0148-1>.
  - [80] Riederer BM, Leuba G, Vernay A, Riederer IM. The role of the ubiquitin proteasome system in Alzheimer's disease. *Experimental Biology and Medicine (Maywood, N.J.)*. 2011; 236: 268–276. <https://doi.org/10.1258/ebm.2010.010327>.
  - [81] Blasiak J, Pawlowska E, Szczepanska J, Kaamiranta K. Interplay between Autophagy and the Ubiquitin-Proteasome System and Its Role in the Pathogenesis of Age-Related Macular Degeneration. *International Journal of Molecular Sciences*. 2019; 20: 210. <https://doi.org/10.3390/ijms20010210>.
  - [82] Dagar G, Kumar R, Yadav KK, Singh M, Pandita TK. Ubiquitination and deubiquitination: Implications on cancer therapy. *Biochimica et Biophysica Acta. Gene Regulatory Mechanisms*. 2023; 1866: 194979. <https://doi.org/10.1016/j.bbaggm.2023.194979>.
  - [83] Collins GA, Goldberg AL. The Logic of the 26S Proteasome. *Cell*. 2017; 169: 792–806. <https://doi.org/10.1016/j.cell.2017.04.023>.
  - [84] Bedford L, Lowe J, Dick LR, Mayer RJ, Brownell JE. Ubiquitin-like protein conjugation and the ubiquitin-proteasome system as drug targets. *Nature Reviews. Drug Discovery*. 2011; 10: 29–46. <https://doi.org/10.1038/nrd3321>.
  - [85] Sahu I, Glickman MH. Structural Insights into Substrate Recognition and Processing by the 20S Proteasome. *Biomolecules*. 2021; 11: 148. <https://doi.org/10.3390/biom11020148>.
  - [86] Zhang JY, Liu SJ, Li HL, Wang JZ. Microtubule-associated protein tau is a substrate of ATP/Mg(2+)-dependent proteasome protease system. *Journal of Neural Transmission (Vienna, Austria: 1996)*. 2005; 112: 547–555. <https://doi.org/10.1007/s00702-004-0196-x>.
  - [87] Lehotzky A, Oláh J, Fekete JT, Szénási T, Szabó E, Györfy B, *et al.* Co-Transmission of Alpha-Synuclein and TPPP/p25 Inhibits Their Proteolytic Degradation in Human Cell Models. *Frontiers in Molecular Biosciences*. 2021; 8: 666026. <https://doi.org/10.3389/fmolb.2021.666026>.
  - [88] Filimonenko M, Isakson P, Finley KD, Anderson M, Jeong H, Melia TJ, *et al.* The selective macroautophagic degradation of aggregated proteins requires the PI3P-binding protein Alf1. *Molecular Cell*. 2010; 38: 265–279. <https://doi.org/10.1016/j.molcel.2010.04.007>.
  - [89] Uddin MS, Stachowiak A, Mamun AA, Tzvetkov NT, Takeda S, Atanasov AG, *et al.* Autophagy and Alzheimer's Disease: From Molecular Mechanisms to Therapeutic Implications. *Frontiers in Aging Neuroscience*. 2018; 10: 04. <https://doi.org/10.3389/fnagi.2018.00004>.
  - [90] Zhao Y, Xie YZ, Liu YS. Accelerated aging-related transcriptome alterations in neurovascular unit cells in the brain of Alzheimer's disease. *Frontiers in Aging Neuroscience*. 2022; 14: 949074. <https://doi.org/10.3389/fnagi.2022.949074>.
  - [91] Xia X, Wei Y, Huang Q, Zhou Y, Wang X, Shi Y, *et al.* Counteracting Alzheimer's disease via normalizing neurovascular unit with a self-regulated multi-functional nano-modulator. *Acta Pharmaceutica Sinica. B*. 2024; 14: 5464–5478. <https://doi.org/10.1016/j.apsb.2024.05.017>.
  - [92] Wang N, Tan Y, Zhou Q, Mao R, Yang Y. The impairment of the hippocampal neuro-vascular unit precedes changes in spatial cognition in naturally aged rats. *Neuroscience Letters*. 2022; 776: 136580. <https://doi.org/10.1016/j.neulet.2022.136580>.
  - [93] Zhong J, Wang L, Li Y, Jiang J. A Novel Diffusion Tensor Image Analysis Along the Perivascular Space Method to Evaluate Glymphatic Alterations in Alzheimer's Disease. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*. 2023; 2023: 1–4. <https://doi.org/10.1109/EMBC40787.2023.10340315>.
  - [94] Zhang X, Wang Y, Jiao B, Wang Z, Shi J, Zhang Y, *et al.* Glymphatic system impairment in Alzheimer's disease: associations with perivascular space volume and cognitive function. *European Radiology*. 2024; 34: 1314–1323. <https://doi.org/10.1007/s00330-023-10122-3>.
  - [95] Zhang X, Cao R, Zhu C, Yang L, Zheng N, Ji W, *et al.* Mechanism of anti-AD action of OAB-14 by enhancing the function of glymphatic system. *Neurochemistry International*. 2023;



105633. <https://doi.org/10.1016/j.neuint.2023.105633>.
- [96] Zhang ZY, Harischandra DS, Wang R, Ghaisas S, Zhao JY, McMonagle TP, *et al.* TRIM11 protects against tauopathies and is down-regulated in Alzheimer's disease. *Science* (New York, N.Y.). 2023; 381: eadd6696. <https://doi.org/10.1126/science.ad6696>.
- [97] d'Errico P, Ziegler-Waldkirch S, Aires V, Hoffmann P, Mezö C, Erny D, *et al.* Microglia contribute to the propagation of A $\beta$  into unaffected brain tissue. *Nature Neuroscience*. 2022; 25: 20–25. <https://doi.org/10.1038/s41593-021-00951-0>.
- [98] Pooler AM, Polydoro M, Wegmann S, Nicholls SB, Spire-Jones TL, Hyman BT. Propagation of tau pathology in Alzheimer's disease: identification of novel therapeutic targets. *Alzheimer's Research & Therapy*. 2013; 5: 49. <https://doi.org/10.1186/alzr.t214>.
- [99] Ruan Z, Pathak D, Venkatesan Kalavai S, Yoshii-Kitahara A, Muraoka S, Bhatt N, *et al.* Alzheimer's disease brain-derived extracellular vesicles spread tau pathology in interneurons. *Brain: a Journal of Neurology*. 2021; 144: 288–309. <https://doi.org/10.1093/brain/awaa376>.
- [100] Anand C, Maia PD, Torok J, Mezas C, Raj A. The effects of microglia on tauopathy progression can be quantified using Nexopathy in silico (Nexis) models. *Scientific Reports*. 2022; 12: 21170. <https://doi.org/10.1038/s41598-022-25131-3>.
- [101] Odfalk KF, Bieniek KF, Hopp SC. Microglia: Friend and foe in tauopathy. *Progress in Neurobiology*. 2022; 216: 102306. <https://doi.org/10.1016/j.pneurobio.2022.102306>.
- [102] Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. *Nature Reviews. Neuroscience*. 2018; 19: 610–621. <https://doi.org/10.1038/s41583-018-0055-7>.
- [103] Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nature Reviews. Immunology*. 2016; 16: 407–420. <https://doi.org/10.1038/nri.2016.58>.
- [104] Li Y, Huang H, Liu B, Zhang Y, Pan X, Yu XY, *et al.* Inflammasomes as therapeutic targets in human diseases. *Signal Transduction and Targeted Therapy*. 2021; 6: 247. <https://doi.org/10.1038/s41392-021-00650-z>.
- [105] Gustin A, Kirchmeyer M, Koncina E, Felten P, Losciuto S, Heurtaux T, *et al.* NLRP3 Inflammasome Is Expressed and Functional in Mouse Brain Microglia but Not in Astrocytes. *PloS One*. 2015; 10: e0130624. <https://doi.org/10.1371/journal.pone.0130624>.
- [106] Dou RX, Zhang YM, Hu XJ, Gao FL, Zhang LL, Liang YH, *et al.* A $\beta$ <sub>1–42</sub> promotes microglial activation and apoptosis in the progression of AD by binding to TLR4. *Redox Biology*. 2024; 78: 103428. <https://doi.org/10.1016/j.redox.2024.103428>.
- [107] Zhang YJ, Guo WJ, Tang ZY, Lin HB, Hong P, Wang JW, *et al.* Isoflurane Attenuates Cerebral Ischaemia-Reperfusion Injury via the TLR4-NLRP3 Signalling Pathway in Diabetic Mice. *Oxidative Medicine and Cellular Longevity*. 2022; 2022: 2650693. <https://doi.org/10.1155/2022/2650693>.
- [108] Liang T, Zhang Y, Wu S, Chen Q, Wang L. The Role of NLRP3 Inflammasome in Alzheimer's Disease and Potential Therapeutic Targets. *Frontiers in Pharmacology*. 2022; 13: 845185. <https://doi.org/10.3389/fphar.2022.845185>.
- [109] Johnson NH, Kerr NA, de Rivero Vaccari JP, Bramlett HM, Keane RW, Dietrich WD. Genetic predisposition to Alzheimer's disease alters inflammasome activity after traumatic brain injury. *Translational Research: the Journal of Laboratory and Clinical Medicine*. 2023; 257: 66–77. <https://doi.org/10.1016/j.trsl.2023.02.001>.
- [110] Zhu MJ, Zhang L, Wang CP. Copper Overload Promotes  $\beta$ -amyloid Induced NLRP3/Caspase-1/GSDMD-Mediated Pyroptosis in Alzheimer's Disease. *Journal of Integrative Neuroscience*. 2024; 23: 194. <https://doi.org/10.31083/j.jin2310194>.
- [111] Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. *Journal of Neuroinflammation*. 2022; 19: 206. <https://doi.org/10.1186/s12974-022-02565-0>.
- [112] Rotondo JC, Mazziotta C, Lanzillotti C, Stefani C, Badiale G, Campione G, *et al.* The Role of Purinergic P2X7 Receptor in Inflammation and Cancer: Novel Molecular Insights and Clinical Applications. *Cancers*. 2022; 14: 1116. <https://doi.org/10.3390/cancers14051116>.
- [113] Janks L, Sharma CVR, Egan TM. A central role for P2X7 receptors in human microglia. *Journal of Neuroinflammation*. 2018; 15: 325. <https://doi.org/10.1186/s12974-018-1353-8>.
- [114] Lester SN, Li K. Toll-like receptors in antiviral innate immunity. *Journal of Molecular Biology*. 2014; 426: 1246–1264. <https://doi.org/10.1016/j.jmb.2013.11.024>.
- [115] Pasare C, Medzhitov R. Toll-like receptors: linking innate and adaptive immunity. *Microbes and Infection*. 2004; 6: 1382–1387. <https://doi.org/10.1016/j.micinf.2004.08.018>.
- [116] Perluigi M, Di Domenico F, Giorgi A, Schinà ME, Coccia R, Cini C, *et al.* Redox proteomics in aging rat brain: involvement of mitochondrial reduced glutathione status and mitochondrial protein oxidation in the aging process. *Journal of Neuroscience Research*. 2010; 88: 3498–3507. <https://doi.org/10.1002/jnr.22500>.
- [117] Zhao Y, Wu X, Li X, Jiang LL, Gui X, Liu Y, *et al.* TREM2 Is a Receptor for  $\beta$ -Amyloid that Mediates Microglial Function. *Neuron*. 2018; 97: 1023–1031.e7. <https://doi.org/10.1016/j.neuron.2018.01.031>.
- [118] Walter J. The Triggering Receptor Expressed on Myeloid Cells 2: A Molecular Link of Neuroinflammation and Neurodegenerative Diseases. *The Journal of Biological Chemistry*. 2016; 291: 4334–4341. <https://doi.org/10.1074/jbc.R115.704981>.
- [119] Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, *et al.* Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal  $\beta$ -catenin pathway function in an Alzheimer's disease model. *Journal of Immunology* (Baltimore, Md.: 1950). 2011; 187: 6539–6549. <https://doi.org/10.4049/jimmunol.1100620>.
- [120] Chen Y, Yu Y. Tau and neuroinflammation in Alzheimer's disease: interplay mechanisms and clinical translation. *Journal of Neuroinflammation*. 2023; 20: 165. <https://doi.org/10.1186/s12974-023-02853-3>.
- [121] Almalki WH, Almuji SS. Therapeutic approaches to microglial dysfunction in Alzheimer's disease: Enhancing phagocytosis and metabolic regulation. *Pathology, Research and Practice*. 2024; 263: 155614. <https://doi.org/10.1016/j.prp.2024.155614>.
- [122] Xu Y, Propson NE, Du S, Xiong W, Zheng H. Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2023418118. <https://doi.org/10.1073/pnas.2023418118>.
- [123] Ebrahimi T, Rust M, Kaiser SN, Slowik A, Beyer C, Koczulla AR, *et al.*  $\alpha$ 1-antitrypsin mitigates NLRP3-inflammasome activation in amyloid  $\beta$ <sub>1–42</sub>-stimulated murine astrocytes. *Journal of Neuroinflammation*. 2018; 15: 282. <https://doi.org/10.1186/s12974-018-1319-x>.
- [124] Zou C, Shi Y, Ohli J, Schüller U, Dorostkar MM, Herms J. Neuroinflammation impairs adaptive structural plasticity of dendritic spines in a preclinical model of Alzheimer's disease. *Acta Neuropathologica*. 2016; 131: 235–246. <https://doi.org/10.1007/s00401-015-1527-8>.
- [125] Zysk M, Beretta C, Naia L, Dakhel A, Pávénis L, Brismar H, *et al.* Amyloid- $\beta$  accumulation in human astrocytes induces mitochondrial disruption and changed energy metabolism. *Journal of Neuroinflammation*. 2023; 20: 43. <https://doi.org/10.1186/>



s12974-023-02722-z.

- [126] Verkhatsky A, Parpura V, Rodriguez-Arellano JJ, Zorec R. Astroglia in Alzheimer's Disease. *Advances in Experimental Medicine and Biology*. 2019; 1175: 273–324. [https://doi.org/10.1007/978-981-13-9913-8\\_11](https://doi.org/10.1007/978-981-13-9913-8_11).
- [127] Kumar A, Fontana IC, Nordberg A. Reactive astrogliosis: A friend or foe in the pathogenesis of Alzheimer's disease. *Journal of Neurochemistry*. 2023; 164: 309–324. <https://doi.org/10.1111/jnc.15565>.
- [128] Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Translational Neurodegeneration*. 2020; 9: 42. <https://doi.org/10.1186/s40035-020-00221-2>.
- [129] Pal A, Rani I, Pawar A, Picozza M, Rongioletti M, Squitti R. Microglia and Astrocytes in Alzheimer's Disease in the Context of the Aberrant Copper Homeostasis Hypothesis. *Biomolecules*. 2021; 11: 1598. <https://doi.org/10.3390/biom11111598>.
- [130] Fakhoury M. Microglia and Astrocytes in Alzheimer's Disease: Implications for Therapy. *Current Neuropharmacology*. 2018; 16: 508–518. <https://doi.org/10.2174/1570159X15666170720095240>.
- [131] Johnstone M, Gearing AJ, Miller KM. A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. *Journal of Neuroimmunology*. 1999; 93: 182–193. [https://doi.org/10.1016/s0165-5728\(98\)00226-4](https://doi.org/10.1016/s0165-5728(98)00226-4).
- [132] Chen Y, Fu AKY, Ip NY. Synaptic dysfunction in Alzheimer's disease: Mechanisms and therapeutic strategies. *Pharmacology & Therapeutics*. 2019; 195: 186–198. <https://doi.org/10.1016/j.pharmthera.2018.11.006>.
- [133] Khan S, Barve KH, Kumar MS. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. *Current Neuropharmacology*. 2020; 18: 1106–1125. <https://doi.org/10.2174/1570159X18666200528142429>.
- [134] Wischik CM, Bentham P, Gauthier S, Miller S, Kook K, Schelker BO. Oral Tau Aggregation Inhibitor for Alzheimer's Disease: Design, Progress and Basis for Selection of the 16 mg/day Dose in a Phase 3, Randomized, Placebo-Controlled Trial of Hydromethylthionine Mesylate. *The Journal of Prevention of Alzheimer's Disease*. 2022; 9: 780–790. <https://doi.org/10.14283/jpad.2022.63>.
- [135] Santos RX, Lee SH, Lofthouse R, Melis V, Robinson L, Leith M, *et al.* Hydromethylthionine sustains truncated tau-dependent inflammation-lowering effects in mouse brain. *The FEBS Journal*. 2025; 292: 2602–2623. <https://doi.org/10.1111/febs.70021>.
- [136] Prins S, de Kam ML, Teunissen CE, Groeneveld GJ. Inflammatory plasma biomarkers in subjects with preclinical Alzheimer's disease. *Alzheimer's Research & Therapy*. 2022; 14: 106. <https://doi.org/10.1186/s13195-022-01051-2>.
- [137] Novak P, Kovacech B, Katina S, Schmidt R, Scheltens P, Kontseva E, *et al.* ADAMANT: a placebo-controlled randomized phase 2 study of AADvac1, an active immunotherapy against pathological tau in Alzheimer's disease. *Nature Aging*. 2021; 1: 521–534. <https://doi.org/10.1038/s43587-021-00070-2>.
- [138] Shulman M, Kong J, O'Gorman J, Ratti E, Rajagovindan R, Viollet L, *et al.* TANGO: a placebo-controlled randomized phase 2 study of efficacy and safety of the anti-tau monoclonal antibody gosuranemab in early Alzheimer's disease. *Nature Aging*. 2023; 3: 1591–1601. <https://doi.org/10.1038/s43587-023-00523-w>.
- [139] Schauer SP, Toth B, Lee J, Honigberg LA, Ramakrishnan V, Jiang J, *et al.* Pharmacodynamic effects of semorinamab on plasma and CSF biomarkers of Alzheimer's disease pathophysiology. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2024; 20: 8855–8866. <https://doi.org/10.1002/alz.14346>.
- [140] Ramakrishnan V, Bender B, Langenhorst J, Magnusson MO, Dolton M, Shim J, *et al.* Semorinamab Pharmacokinetics and The Effect on Plasma Total Tau Pharmacodynamics in Clinical Studies. *The Journal of Prevention of Alzheimer's Disease*. 2024; 11: 1241–1250. <https://doi.org/10.14283/jpad.2024.146>.
- [141] Monteiro C, Toth B, Brunstein F, Bobbala A, Datta S, Cenicerios R, *et al.* Randomized Phase II Study of the Safety and Efficacy of Semorinamab in Participants With Mild-to-Moderate Alzheimer Disease: Lauriet. *Neurology*. 2023; 101: e1391–e1401. <https://doi.org/10.1212/WNL.00000000000207663>.
- [142] Mummery CJ, Börjesson-Hanson A, Blackburn DJ, Vijverberg EGB, De Deyn PP, Ducharme S, *et al.* Tau-targeting antisense oligonucleotide MAPT<sub>rx</sub> in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nature Medicine*. 2023; 29: 1437–1447. <https://doi.org/10.1038/s41591-023-02326-3>.
- [143] Florian H, Wang D, Arnold SE, Boada M, Guo Q, Jin Z, *et al.* Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. *Brain: a Journal of Neurology*. 2023; 146: 2275–2284. <https://doi.org/10.1093/brain/awad024>.
- [144] Michelson D, Grundman M, Magnuson K, Fisher R, Levenson JM, Aisen P, *et al.* Randomized, Placebo Controlled Trial of NPT088, A Phage-Derived, Amyloid-Targeted Treatment for Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*. 2019; 6: 228–231. <https://doi.org/10.14283/jpad.2019.37>.
- [145] Prins ND, Harrison JE, Chu HM, Blackburn K, Alam JJ, Scheltens P, *et al.* A phase 2 double-blind placebo-controlled 24-week treatment clinical study of the p38 alpha kinase inhibitor neflamapimod in mild Alzheimer's disease. *Alzheimer's Research & Therapy*. 2021; 13: 106. <https://doi.org/10.1186/s13195-021-00843-2>.
- [146] Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, *et al.* A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-A $\beta$  protofibril antibody. *Alzheimer's Research & Therapy*. 2021; 13: 80. <https://doi.org/10.1186/s13195-021-00813-8>.
- [147] van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, *et al.* Lecanemab in Early Alzheimer's Disease. *The New England Journal of Medicine*. 2023; 388: 9–21. <https://doi.org/10.1056/NEJMoa2212948>.
- [148] Cohen S, van Dyck CH, Gee M, Doherty T, Kanekiyo M, Dhadda S, *et al.* Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*. 2023; 10: 771–777. <https://doi.org/10.14283/jpad.2023.123>.
- [149] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, *et al.* Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023; 330: 512–527. <https://doi.org/10.1001/jama.2023.13239>.
- [150] Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S, *et al.* Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. *The New England Journal of Medicine*. 2023; 389: 1862–1876. <https://doi.org/10.1056/NEJMoa2304430>.
- [151] Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, *et al.* Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*. 2022; 9: 197–210. <https://doi.org/10.14283/jpad.2022.30>.
- [152] Toda Y, Iwatsubo T, Nakamura Y, Matsuda N, Miyata M, Jin M, *et al.* Japanese Subgroup Analyses from EMERGE and ENGAGE, Phase 3 Clinical Trials of Aducanumab in Patients

- with Early Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*. 2024; 11: 1260–1269. <https://doi.org/10.14283/jpad.2024.106>.
- [153] Lizama BN, North HA, Pandey K, Williams C, Duong D, Cho E, *et al.* An interim exploratory proteomics biomarker analysis of a phase 2 clinical trial to assess the impact of CT1812 in Alzheimer's disease. *Neurobiology of Disease*. 2024; 199: 106575. <https://doi.org/10.1016/j.nbd.2024.106575>.
- [154] LaBarbera KM, Sheline YI, Izzo NJ, Yuede CM, Waybright L, Yurko R, *et al.* A phase 1b randomized clinical trial of CT1812 to measure A $\beta$  oligomer displacement in Alzheimer's disease using an indwelling CSF catheter. *Translational Neurodegeneration*. 2023; 12: 24. <https://doi.org/10.1186/s40035-023-00358-w>.
- [155] Novak G, Streffer JR, Timmers M, Henley D, Brashear HR, Bogert J, *et al.* Long-term safety and tolerability of atabecestat (JNJ-54861911), an oral BACE1 inhibitor, in early Alzheimer's disease spectrum patients: a randomized, double-blind, placebo-controlled study and a two-period extension study. *Alzheimer's Research & Therapy*. 2020; 12: 58. <https://doi.org/10.1186/s13195-020-00614-5>.
- [156] Egan MF, Mukai Y, Voss T, Kost J, Stone J, Furtek C, *et al.* Further analyses of the safety of verubecestat in the phase 3 EPOCH trial of mild-to-moderate Alzheimer's disease. *Alzheimer's Research & Therapy*. 2019; 11: 68. <https://doi.org/10.1186/s13195-019-0520-1>.
- [157] Mirzaei M, Ahmadi N, Bagheri Fahraji B, Ardekani AM, Rahimdel A, Soltani MH, *et al.* A randomized clinical trial evaluating Hydralazine's efficacy in early-stage Alzheimer's disease: The EHSAN Study. *Scientific Reports*. 2024; 14: 28837. <https://doi.org/10.1038/s41598-024-79616-4>.
- [158] Sosa S, Bringas G, Urrutia N, Peñalver AI, López D, González E, *et al.* NeuroEPO plus (NeuralCIM®) in mild-to-moderate Alzheimer's clinical syndrome: the ATHENEA randomized clinical trial. *Alzheimer's Research & Therapy*. 2023; 15: 215. <https://doi.org/10.1186/s13195-023-01356-w>.
- [159] Hannestad J, Duclos T, Chao W, Koborsi K, Klutzaritz V, Beck B, *et al.* Safety and Tolerability of GRF6019 Infusions in Severe Alzheimer's Disease: A Phase II Double-Blind Placebo-Controlled Trial. *Journal of Alzheimer's Disease: JAD*. 2021; 81: 1649–1662. <https://doi.org/10.3233/JAD-210011>.
- [160] Cummings JL, Atri A, Feldman HH, Hansson O, Sano M, Knop FK, *et al.* evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. *Alzheimer's Research & Therapy*. 2025; 17: 14. <https://doi.org/10.1186/s13195-024-01666-7>.
- [161] Dubois B, López-Arrieta J, Lipschitz S, Doskas T, Spiri L, Moroz S, *et al.* Masitinib for mild-to-moderate Alzheimer's disease: results from a randomized, placebo-controlled, phase 3, clinical trial. *Alzheimer's Research & Therapy*. 2023; 15: 39. <https://doi.org/10.1186/s13195-023-01169-x>.
- [162] Wang S, Mustafa M, Yuede CM, Salazar SV, Kong P, Long H, *et al.* Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. *The Journal of Experimental Medicine*. 2020; 217: e20200785. <https://doi.org/10.1084/jem.20200785>.
- [163] Long H, Simmons A, Mayorga A, Burgess B, Nguyen T, Budda B, *et al.* Preclinical and first-in-human evaluation of AL002, a novel TREM2 agonistic antibody for Alzheimer's disease. *Alzheimer's Research & Therapy*. 2024; 16: 235. <https://doi.org/10.1186/s13195-024-01599-1>.
- [164] Fang C, Hernandez P, Liow K, Damiano E, Zetterberg H, Blennow K, *et al.* Buntanetap, a Novel Translational Inhibitor of Multiple Neurotoxic Proteins, Proves to Be Safe and Promising in Both Alzheimer's and Parkinson's Patients. *The Journal of Prevention of Alzheimer's Disease*. 2023; 10: 25–33. <https://doi.org/10.14283/jpad.2022.84>.
- [165] Humpel C. Identifying and validating biomarkers for Alzheimer's disease. *Trends in Biotechnology*. 2011; 29: 26–32. <https://doi.org/10.1016/j.tibtech.2010.09.007>.
- [166] Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, *et al.* CSF biomarkers of Alzheimer's disease concord with amyloid- $\beta$  PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2018; 14: 1470–1481. <https://doi.org/10.1016/j.jalz.2018.01.010>.
- [167] Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, *et al.* CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet. Neurology*. 2016; 15: 673–684. [https://doi.org/10.1016/S1474-4422\(16\)00070-3](https://doi.org/10.1016/S1474-4422(16)00070-3).
- [168] Taylor J, Jaros M, Chen C, Harrison J, Hilt D. Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11 $\beta$ -HSD1 Inhibitor Xanemem® for Mild Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*. 2024; 100: 139–150. <https://doi.org/10.3233/JAD-231456>.
- [169] Lv X, Zhang M, Cheng Z, Wang Q, Wang P, Xie Q, *et al.* Changes in CSF sPDGFR $\beta$  level and their association with blood-brain barrier breakdown in Alzheimer's disease with or without small cerebrovascular lesions. *Alzheimer's Research & Therapy*. 2023; 15: 51. <https://doi.org/10.1186/s13195-023-01199-5>.
- [170] Zhong X, Wang Q, Yang M, Lin G, Yao K, Wu Z, *et al.* Plasma p-tau217 and p-tau217/A $\beta$ 1-42 are effective biomarkers for identifying CSF- and PET imaging-diagnosed Alzheimer's disease: Insights for research and clinical practice. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2025; 21: e14536. <https://doi.org/10.1002/alz.14536>.
- [171] Yakoub Y, Gonzalez-Ortiz F, Ashton NJ, Déry C, Strikwerda-Brown C, St-Onge F, *et al.* Plasma p-tau217 identifies cognitively normal older adults who will develop cognitive impairment in a 10-year window. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2025; 21: e14537. <https://doi.org/10.1002/alz.14537>.
- [172] Zhuang T, Yang Y, Ren H, Zhang H, Gao C, Chen S, *et al.* Novel plasma protein biomarkers: A time-dependent predictive model for Alzheimer's disease. *Archives of Gerontology and Geriatrics*. 2025; 129: 105650. <https://doi.org/10.1016/j.archger.2024.105650>.
- [173] Fotuhi SN, Khalaj-Kondori M, Hoseinpour Feizi MA, Talebi M. Long Non-coding RNA BACE1-AS May Serve as an Alzheimer's Disease Blood-Based Biomarker. *Journal of Molecular Neuroscience: MN*. 2019; 69: 351–359. <https://doi.org/10.1007/s12031-019-01364-2>.
- [174] Zhuang J, Cai P, Chen Z, Yang Q, Chen X, Wang X, *et al.* Long noncoding RNA MALAT1 and its target microRNA-125b are potential biomarkers for Alzheimer's disease management via interactions with FOXQ1, PTGS2 and CDK5. *American Journal of Translational Research*. 2020; 12: 5940–5954.
- [175] Zhang T, Kong W, Wang S, Mou X. Association Analysis of Peripheral and CSF Biomarkers in Late Mild Cognitive Impairment. *Frontiers in Genetics*. 2020; 11: 834. <https://doi.org/10.3389/fgene.2020.00834>.
- [176] Rosen KM, Moussa CEH, Lee HK, Kumar P, Kitada T, Qin G, *et al.* Parkin reverses intracellular beta-amyloid accumulation and its negative effects on proteasome function. *Journal of Neuroscience Research*. 2010; 88: 167–178. <https://doi.org/10.1002/jnr.22178>.
- [177] Wojdala AL, Bellomo G, Gaetani L, Toja A, Chipi E, Shan D, *et al.* Trajectories of CSF and plasma biomarkers across

- Alzheimer's disease continuum: disease staging by NF-L, p-tau181, and GFAP. *Neurobiology of Disease*. 2023; 189: 106356. <https://doi.org/10.1016/j.nbd.2023.106356>.
- [178] Zhang Y, Zhao Y, Zhang J, Gao Y, Gao X, Li S, *et al*. Proteomics of plasma-derived extracellular vesicles reveals S100A8 as a novel biomarker for Alzheimer's disease: A preliminary study. *Journal of Proteomics*. 2024; 308: 105279. <https://doi.org/10.1016/j.jprot.2024.105279>.
- [179] Myeku N, Clelland CL, Emrani S, Kukushkin NV, Yu WH, Goldberg AL, *et al*. Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. *Nature Medicine*. 2016; 22: 46–53. <https://doi.org/10.1038/nm.4011>.
- [180] Han X, Sun S, Sun Y, Song Q, Zhu J, Song N, *et al*. Small molecule-driven NLRP3 inflammation inhibition via interplay between ubiquitination and autophagy: implications for Parkinson disease. *Autophagy*. 2019; 15: 1860–1881. <https://doi.org/10.1080/15548627.2019.1596481>.