

REVIEW

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Neuroinflammation in Alzheimer's disease: insights from peripheral immune cells

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Abstract

Alzheimer's disease (AD) is a serious brain disorder characterized by the presence of beta-amyloid plaques, tau pathology, inflammation, neurodegeneration, and cerebrovascular dysfunction. The presence of chronic neuroinflammation, breaches in the blood-brain barrier (BBB), and increased levels of inflammatory mediators are central to the pathogenesis of AD. These factors promote the penetration of immune cells into the brain, potentially exacerbating clinical symptoms and neuronal death in AD patients. While microglia, the resident immune cells of the central nervous system (CNS), play a crucial role in AD, recent evidence suggests the infiltration of cerebral vessels and parenchyma by peripheral immune cells, including neutrophils, T lymphocytes, B lymphocytes, NK cells, and monocytes in AD. These cells participate in the regulation of immunity and inflammation, which is expected to play a huge role in future immunotherapy. Given the crucial role of peripheral immune cells in AD, this article seeks to offer a comprehensive overview of their contributions to neuroinflammation in the disease. Understanding the role of these cells in the neuroinflammatory response is vital for developing new diagnostic markers and therapeutic targets to enhance the diagnosis and treatment of AD patients.

Keywords Alzheimer's disease, Neuroinflammation, Neutrophils, T lymphocytes, B lymphocytes, NK cells

Introduction

According to the most recent report from Alzheimer's Disease (AD) International, the number of individuals with dementia worldwide is projected to increase from 50 million in 2019 to 152 million by 2050. Furthermore, the annual cost of dementia is estimated to increase from \$1 trillion in 2019 to \$2 trillion in 2030, and it will further increase to \$9.12 trillion by 2050 [1]. According to the report "Global status report on the public health response to dementia" from WHO in 2021, AD is the most common form of dementia, accounting for approximately 60–70% of all cases. This neurodegenerative disorder progresses over time, resulting in memory and cognitive issues [2]. AD is strongly associated with aging, with 10% of people aged 65 and over and 32% of those aged 85 and over having been diagnosed with the condition [3]. Apart from age, genetic factors are major risk

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factors for AD [4], particularly the APOE ϵ 4 gene, which contributes to the development and progression of AD by influencing lipid metabolism [5], reducing amyloid-beta (A β) clearance [6], exacerbating neuroinflammation [7], and affecting synaptic function and neuroplasticity [8]. In addition, traumatic brain injury [9], stroke [10], various tumors [11], viral infections [12], diabetes [13], hypertension [14], cardiovascular disease [13], obstructive sleep apnea [15], and obesity can also contribute to the onset of AD.

AD is characterized primarily by the formation of A β plaques and the tangling of neurofibrils. Enzymatic digestion of the amyloid precursor protein (APP) produces various lengths of A β , with A β _{1–42} being more prone to aggregation compared to the more soluble A β _{1–40}, resulting in cytotoxic effects [16–18]. The Arctic mutation (E693G) and mutations in genes coding for PS (Presenilin) 1 and PS2 proteins (PSEN1 and PSEN2) are linked to abnormal APP metabolism and early-onset familial AD [19–21], while the APOE ϵ 4 allele is identified as a risk factor associated with increased A β accumulation [22, 23]. When clearance mechanisms fail or APP metabolism is disrupted, higher A β production results in plaque formation, impeding neuronal communication and causing functional decline and cell death [24]. Additionally, in healthy conditions, the tau protein maintains neuronal structure and function [25]. However, excessive phosphorylation of tau leads to the formation of neurofibrillary tangles, which disrupt neuronal metabolism and signal transmission, ultimately causing neuronal death and cognitive impairment [26]. Subsequent pathological changes include cerebral amyloid angiopathy, neuronal loss, and synaptic dysfunction [27–29]. Research has indicated that neuroinflammatory reactions are a key factor in the progression of AD [30]. It is widely recognized that in specific hippocampal regions of the brain, microglia and astrocytes are the primary cells involved in the neuroinflammatory response [31]. Furthermore, the interaction between complement and these two types of cells [32], as well as the formation of inflammasomes, particularly the NLRP3 inflammasome [33], contributes to exacerbating neuroinflammation in the brain by promoting A β and tau pathology [34], and inducing the release of IL (Interleukin) -1 β and IL-18 [35]. This ultimately leads to the disruption of the BBB, a key pathological feature of AD [36]. Besides, a previous study has shown that elevated levels of pro-inflammatory cytokines and chemokines in the peripheral system contribute to the advancement of AD [37]. The pro-inflammatory environment can trigger the innate and adaptive immune systems, resulting in the recruitment of peripheral immune cells into brain tissue through the weakened BBB. This may be involved in the pathological progression of AD. AD has the potential to induce a systemic inflammatory

reaction, leading to the activation of peripheral immune cells such as neutrophils, T lymphocytes, B lymphocytes, and NK cells [38–42]. This can result in the formation of a cytokine storm, damaging neurons. Figure 1 summarizes the pathological features and mechanisms of AD, methods for clinical diagnosis, and risk factors for the development of AD. In this review, we aim to offer a comprehensive overview of the contributions of neutrophils, T lymphocytes, B lymphocytes, NK cells, and monocytes to neuroinflammation in AD. Furthermore, it delves into the pathogenesis of AD to enhance the diagnosis and management of the disease in the future.

Peripheral immune cells and neuroinflammation in AD

The pathology of AD is significantly influenced by peripheral immune cells including neutrophils, T lymphocytes, B lymphocytes, and NK cells. Activated neutrophils can accumulate and adhere to vascular walls, potentially obstructing blood flow. They can also enter brain tissue through a compromised BBB, where they worsen the disease by releasing inflammatory cytokines and neutrophil extracellular traps (NETs) [42]. T lymphocytes indirectly contribute to disease progression by affecting glial cell function [43]. B lymphocytes impact the progression of the disease by secreting inflammatory cytokines and antibodies, which then regulate behavior [44–46]. NK cells also contribute to the disease's progression through interactions with microglia and the release of inflammatory mediators [47, 48]. These complex cellular activities drive the pathogenesis of AD and suggest potential targets for therapeutic intervention. Figure 2 provides a summary of the progress and potential mechanisms of peripheral immune cells and neuroinflammation in AD.

Neutrophils in AD

Activation and migration of neutrophils in AD

The bone marrow constitutes the primary reservoir of neutrophils, which are also present in the bloodstream and the marrow adjacent to the cranial bones within the CNS [49]. Generally, neutrophils circulate within blood vessels and face difficulty traversing the BBB to enter the brain. Consequently, circulating neutrophils lack robust cell adhesion molecules, which prevents their infiltration into the brain parenchyma. In patients with AD, a systemic inflammatory response coupled with a compromised BBB potentially activates neutrophils, facilitating their infiltration into the brain parenchyma [36, 50]. Numerous studies indicate heightened neutrophil activation in the bloodstream of AD patients, evidenced by increased reactive oxygen species (ROS) and NETs detected in their vasculature [51]. This activation mechanism is in stark contrast to that of healthy individuals, where plasma levels of IL-6 and IL-8 are typically lower

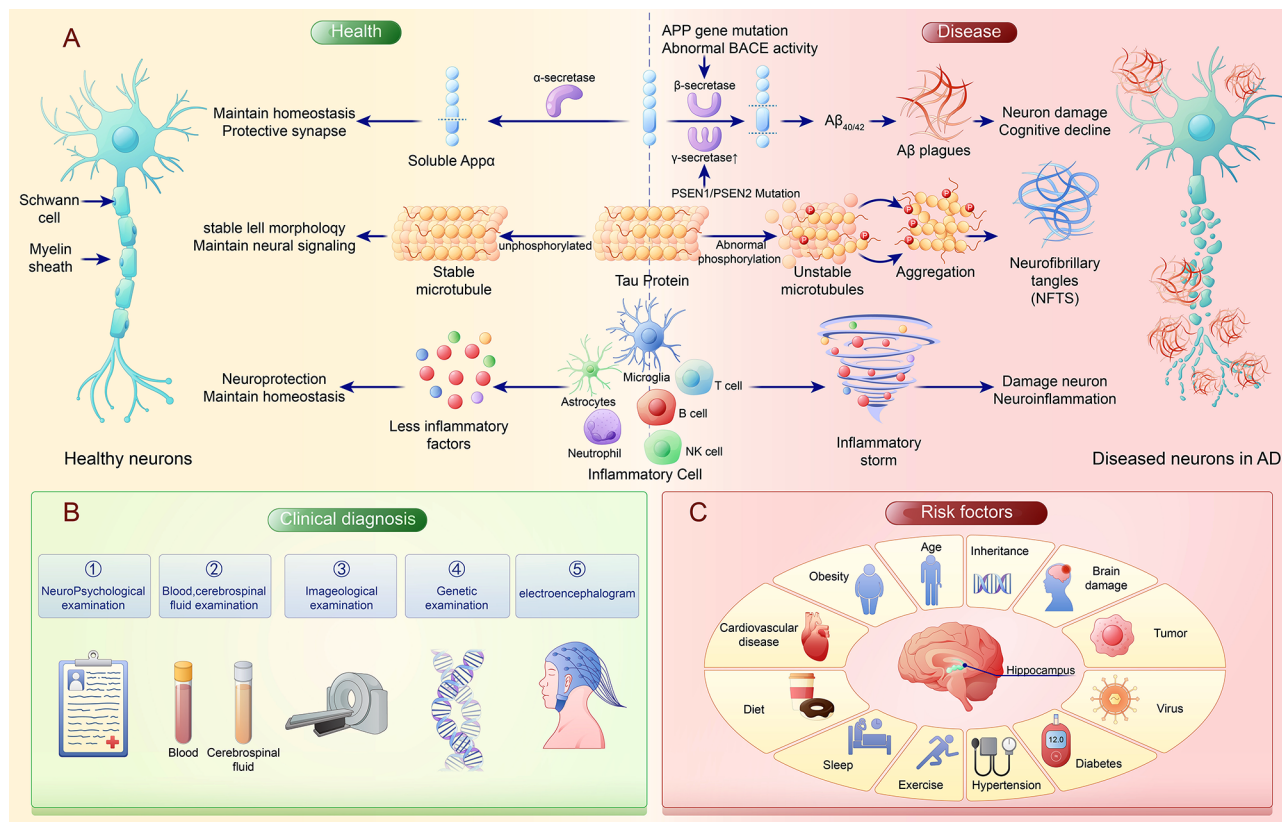


Fig. 1 The pathological mechanism, clinical diagnosis, and potential risk factors of Alzheimer's disease. **(A)** Alzheimer's Disease (AD) is characterized by the accumulation of A β plaques and hyperphosphorylated tau protein in the brain, leading to neuronal damage and the formation of neurofibrillary tangles. In addition, neuroinflammation caused by cytokine storm triggered by the joint action of microglia, astrocytes, and peripheral immune cells such as neutrophils, lymphocytes, and NK cells plays an important role in the disease progression of AD. **(B)** The diagnosis of AD typically involves a combination of neuropsychological assessments, biomarker analysis, neuroimaging studies, and electroencephalography. **(C)** The risk of developing AD is influenced by various factors, including age, genetic predisposition, weight management, sleep quality, mental health, and physical activity. The interaction of these factors determines an individual's likelihood of developing AD

and not linked to such neutrophil activation. In patients, this activation is orchestrated by cellular factors including C5a, leukotriene B4, platelet-activating factor, and N-Formylmethionyl-leucyl-phenylalanine [51, 52]. Such activation triggers the release of lipid mediators and proteases, amplifying inflammation and attracting additional white blood cells, ultimately worsening tissue damage. Studies using animal models have revealed that mice with cognitive deficits display elevated levels of CD45⁺ and CD18⁺ cells compared to their wild-type counterparts. Furthermore, the detection of Gr-1-positive cells and CAP37 in the cerebral vessels and parenchyma suggests a predominant presence of neutrophils within these regions in AD [42, 53]. Concurrently, a different study employing two-photon microscopy on a mouse AD model observed neutrophil infiltration in the brain parenchyma, with a propensity to migrate towards A β plaques [41]. Simultaneously, mature neutrophils express CD177 and LFA-1, enhancing their interaction with CD31 (PECAM-1) and ICAM-1 on endothelial cells and facilitating their infiltration into brain tissue [42,

54]. Nonetheless, this infiltration is typically mild, characterized chiefly by adhesion to endothelial cells. While migrated neutrophils show a preference for A β plaques, it is posited that A β proteins may not directly attract neutrophils, which necessitates further study [41]. Excessive accumulation of activated neutrophils can disrupt cerebral blood flow and amplify oxidative stress and inflammation, potentially compromising the integrity of the BBB and provoking vascular inflammation [55].

Adhesion of neutrophils to vascular endothelium

Neutrophil aggregation has been extensively documented in cerebral blood vessels, particularly adhering to and clustering around areas with A β deposition [42]. These activated neutrophils can induce vascular inflammation by disrupting the BBB [50, 55]. A study indicated that neutrophil adhesion to blood vessels could lead to the breakdown of the BBB [55]. It is also implicated in the production of reactive ROS, inflammatory molecules, tissue proteases, and arachidonic acid derivatives that may damage the vascular wall [56]. Upon binding with

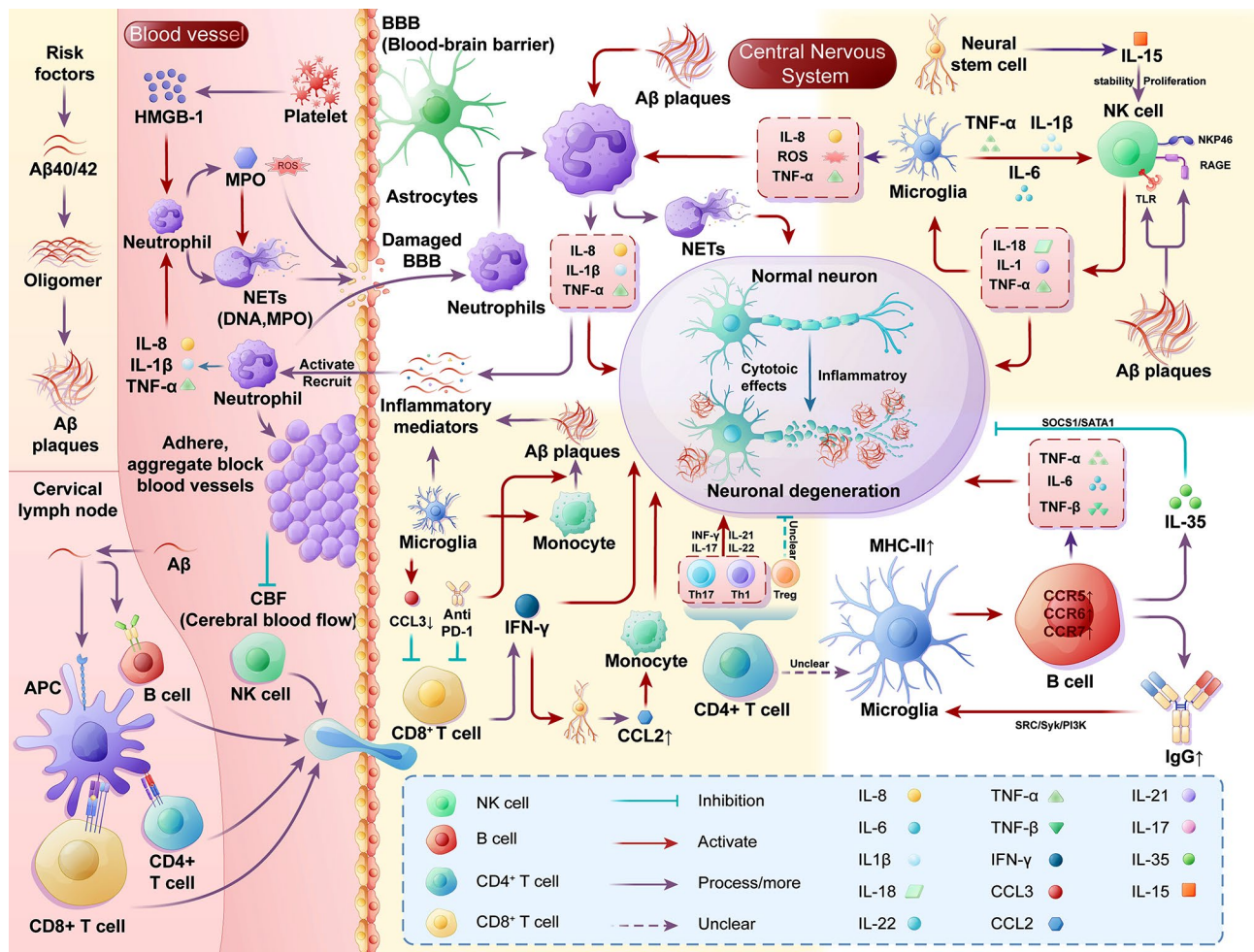


Fig. 2 Mechanism of action of neutrophils, T lymphocytes, B lymphocytes and NK cells in Alzheimer’s disease. Neutrophils, T lymphocytes, B lymphocytes, NK cells, and monocytes play crucial roles in the pathological progression of AD. **(A)** β -amyloid ($A\beta$) reaches the cervical lymph nodes via the bloodstream or lymphatic system, where it is processed and presented by antigen-presenting cells, subsequently activating lymphocytes. These activated lymphocytes then enter the bloodstream and infiltrate brain tissue. **(B)** Neutrophils in the vasculature interact with MPO, HMGB-1, and pro-inflammatory factors, leading to their activation and overexpression of adhesion molecules. This causes them to aggregate and adhere to the vasculature, obstructing blood vessels. Activated neutrophils release neutrophil extracellular traps (NETs) and reactive oxygen species (ROS), which disrupt the blood-brain barrier (BBB). Neutrophils within the brain, influenced by $A\beta$ and microglia, release NETs and pro-inflammatory factors, accelerating the pathological progression of AD. **(C)** After entering the brain, T lymphocytes interact with microglia and $A\beta$ plaques. $CD8^+$ T lymphocytes can directly promote AD pathology, while various $CD4^+$ T lymphocytes modulate neuroinflammation by releasing cytokines, either promoting or inhibiting the process. **(D)** B lymphocytes enhance the phagocytic ability of microglia toward $A\beta$ through the release of IgG and directly delay AD pathology via IL-35. However, they also exacerbate neuroinflammation by releasing pro-inflammatory factors. **(E)** NK cells can be directly activated by $A\beta$, leading to the release of pro-inflammatory factors. These factors interact with those released by microglia, exacerbating neuroinflammation through a feedback-like mechanism

endothelial cells, the $\alpha M\beta 2$ integrin Mac-1 can trigger the release of NETs [57].

Research has shown that neutrophils from 5x*FAD* mice, which lack the $\alpha L\beta 2$ variant of $\beta 2$ integrin, are unable to enter brain tissue by adhering to endothelial cells [42]. It has been observed that in AD patients, the interaction between LFA-1 and endothelial cell ICAM-1 can cause changes in the cell cytoskeleton and increased permeability of blood vessels [58–60]. In laboratory experiments, it has been found that $A\beta$ proteins can stimulate the expression of endothelial adhesion molecules, including ICAM-1 [61]. As a result, brain vascular endothelial

cells in AD patients or AD mouse models show higher levels of ICAM-1 expression, which promotes the adhesion and movement of neutrophils. In mice with early-stage AD who were treated with anti-LFA-1 therapy, there was a decrease in the presence of neutrophils in brain blood vessels and a reduction in their movement out of the vessels, leading to improved cognitive function [42]. Additionally, this study discovered that the treatment also decreased the activation of microglia, a finding that had not been previously reported. This suggests that the interaction between exosmotic neutrophils and microglia can enhance and prolong their activation in

the brain. The high activation of neutrophils in AD and their accumulation in blood vessels may be linked to the decreased presence of the endothelial glycocalyx-protein complex [62]. Recent research has identified a new process of neutrophil adhesion in vascular inflammation called Neutrophil DREAM, which enhances neutrophil stickiness during vascular inflammation through both NF- κ B-dependent and NF- κ B-independent pathways [63]. However, this mechanism has not yet been linked to AD.

Neutrophils obstruct cerebral blood flow (CBF)

At the early stages of AD, decreased cerebral blood flow (CBF) has been identified as a prominent sign of onset [64]. Studies conducted using wild-type mice have shown that sustained reduction in CBF to 35% can cause significant cognitive impairments and amplify brain inflammation [65]. Decreased CBF can also disrupt the balance of the CNS by disrupting energy metabolism in the brain [66]. People with AD show increased expression of ICAM-1 in cerebral endothelial cells [42, 67]. This molecule binds to β 2 integrins (Mac-1, LFA-1) on neutrophils, enabling them to adhere, crawl, and aggregate in blood vessels, resulting in a reduction in CBF. At the same time, activated platelets also express HMGB1, which has the ability to activate neutrophils, induce cytokine secretion, and increase the expression of VCAM-1 and endothelial cell selectin [68]. After one month of treatment in AD mouse models (3xTg and 5xFAD) with antibodies targeting neutrophils (α -GR-1, α -LFA-1, and α -Ly6G), the study found a significant increase in CBF and continued improvement in cognitive function [42]. It is evident that the decline in CBF observed in AD is not only caused by the accumulation of neutrophils and vasoconstriction, but may also be linked to vascular inflammation and the adhesion of other types of leukocytes. Further research is needed to gain a comprehensive understanding of the issue and its potential treatments. Nevertheless, it is possible that inhibiting neutrophil adhesion to blood vessels could be a viable therapeutic option for AD in the future.

The infection-fighting ability of neutrophils in patients with AD

It is generally accepted that AD is a systemic disorder. Neutrophils, which are the first line of defense in the human innate immune system, may be less responsive to external infections in the inflammatory state of AD, thus increasing the risk of infection [69]. Studies have suggested that, although there is a decrease in the peripheral and cerebral anti-infective capabilities of neutrophils in patients with mild cognitive impairment (MCI) and AD in the early stages, they still have the ability to express Toll-like receptor (TLR) receptors [51, 70, 71]. However, there is still debate and conflicting reports regarding this

matter. Some studies have indicated that neutrophils in individuals with AD maintain normal phagocytic and degranulation functions [72]. On the other hand, other reports have suggested a decrease in phagocytic function and an increase in degranulation activity among AD patients. Further research is needed to gain a better understanding of these mechanisms and their effects on AD.

Neutrophil-associated biomarkers in AD

As key players in inflammation, neutrophils contribute to the synthesis and secretion of biomarkers that are critical for evaluating immune status and diagnosing related diseases. Studies have shown a significant increase in the number and activity of neutrophils in the blood and brain of patients with AD [73]. This increase was positively correlated with disease severity and the rate of progression of mental decline [74]. Therefore, further investigations could potentially unearth new biomarkers for AD, including NETs, myeloperoxidase (MPO), neutrophil gelatinase-associated lipocalin (NGAL), and the neutrophil-to-lymphocyte ratio (NLR). Table 1 lists the relevant studies of MPO, NGAL and NLR in AD in recent years. The changes in these substances in the blood and cerebrospinal fluid are promising markers to reflect the pathological course of AD.

Neutrophil extracellular traps (NETs) Neutrophils are known to release NETs, which are intricate structures made up of DNA, histones, and a variety of enzymes [88]. Generally, they are known to be a way to trap and stop the movement of bacteria and viruses, thus hindering the transmission of sickness [88]. Excessive NETs or their poor clearance can lead to tissue damage and contribute to various diseases, including viral infections, autoimmune conditions, thrombosis, and cancer progression and angiogenesis [89–92]. When pathogens or inflammatory mediators become activated, neutrophils create ROS, such as superoxide anions. The unraveling of nuclear DNA results in the splitting of the nuclear membrane. The linear DNA combines with histones, basic proteins, and NE in the cytoplasm, forming a fibrous mesh-like structure that is then released into the extracellular space [93, 94]. In animal models of AD, such as 5xFAD and 3xTg-AD mice, neutrophils have been observed infiltrating regions with A β deposits and releasing NETs and IL-17. Neutrophils produce IL-17, which can recruit additional neutrophils and directly damage neurons and the BBB [95]. A 2015 study found that autopsies of brains from AD victims showed the presence of neutrophils and NETs in the brain and microvasculature [42]. Previous experiments have indicated that activated endothelial cells release pro-inflammatory cytokines, including tumor necrosis factor (TNF)- α , IL-1 β , and IL-8. These cytokines can

Table 1 Overview of neutrophil biomarkers in Alzheimer's disease Studies

Biomarkers	Sample types	Groups	Numbers	Age (year)	Female/Male	Study types	Methods	Findings (Mean ± SD)	References
NGAL	Plasma (ng/ml)/CSF (pg/ml)	AD	26	79±6	13/13	Retrospective cohort study	ELISA	1494±172, (AD vs. HC, $P=0.036$); 169±19	[75]
		MCI	28	79±4	14/14			1340±119, (MCI vs. HC, $P=0.0027$); 152±17	
	Brain tissue (Entorhinal cortex)	HC	26	78±5	13/13	Western Blot	Significant increase in entorhinal cortex* and hippocampus** (AD vs. HC, * $P<0.05$; ** $P<0.005$)	2079±172; 132±13	[76]
		AD	10	78±6	5/5				
		HC	10	82±6	5/5				
	Plasma (ng/ml)	AD	62	72.16±6.35	46/16	Retrospective cohort study	ELISA	191 (AD vs. MCI, $P=0.009$)	[76]
		MCI	41	69.02±7.77	23/18			296 (MCI vs. HC, $P=0.005$)	
	Plasma (ng/ml)	HC	38	64.92±5.57	23/15	Retrospective cohort study	ELISA	163	[77]
		AD	19	69.7±6.0	8/11			65.1±21.0; AUC=0.766 (AD vs. HC, $P=0.002$)	
		MCI	27	67.7±9.0	12/15			80.5±21.8; AUC=0.612 (MCI vs. HC, $P=0.155$)	
HC		28	72.1±6.9	19/9	97.6±49.0				
MPO	Serum(ng/ml)	AD	17	78.1±6.4	16/1	Retrospective cohort study	ELISA	(63.8±31.8)/(42.1±22.7), (AD vs. HC, $P=0.018$)	[78]
		HC	37	71.8±8.1	25/12				
	Plasma (ng/ml)	AD	38	72.8±8.0	18/20	Cross-sectional study	ELISA	(82.0±23.7)/(71.5±20), (AD vs. HC, $P=0.007$)	[79]
		HC	118	67.4±7.7	73/45				
	Plasma (ng/ml)	AD	28	72.9±9.0	16/12	Prospective cohort study	ELISA	(132.8±114.8)/(55.0±42.6), (AD vs. HC, $P=0.002$); AUC=0.745	[80]
		HC	27	67.6±9.7	11/16				
Brain tissue (Frontal cortex)	AD	25	76.4±11.9	12/13	Descriptive Study	Immunohistochemistry	(8.46±0.81)/(5.08±0.62), (AD vs. HC, $P=0.003$)	[81]	
	HC	20	76.3±11.8	9/11			(MPO ⁺ cells/mm ²)		

Table 1 (continued)

Biomarkers	Sample types	Groups	Numbers	Age (year)	Female/Male	Study types	Methods	Findings (Mean ± SD)	References
NLR	Peripheral blood (ratio)	PVFFMC	9760	70.2 (Median)	5750/4010	Retro-spective cohort study	Cox regression Restricted cubic spline	AD: when NLR > 5.44, HR = 1.50, [95% CI: 1.17–1.93]	[82]
		AD	132	70.83 ± 9.35	69/63	Retro-spective cohort study	-	(2.96 ± 2.46)/(1.9 ± 0.66), (AD vs. HC, P = 0.005); Cut-point = 1.91, AUC = 0.649, SEN = 65.2%, SPE = 47.4%	[83]
		HC	38	71.09 ± 5.77	13/25				
		AD	56	69.04 ± 9.05	30/23	Retro-spective cohort study	Multivariable logistic regression	(2.61 ± 1.04)/(1.88 ± 0.44), (AD vs. HC, P < 0.001); OR = 6.27 [95% CI: 3.98–9.82], (P = 0.003); Cut-point = 2.35, SEN = 83.05%, SPE = 53.57%; AUC = 0.721, (P < 0.001); (2.25 ± 1.01)/(1.88 ± 0.44), (MCI vs. HC, P = 0.011); OR = 1.93 [95% CI: 1.07–3.47], (P = 0.028); Cut-point = 2.34, SEN = 84.38%, SPE = 40.24%; AUC = 0.60, (P < 0.03)	[84]
		MCI	57	70.67 ± 9.26	27/30				
		HC	59	68.12 ± 5.81	25/24				
		AD	241	76.53 ± 6.00	165/76	Cross-sectional study	-	(3.21 ± 1.35)/(2.74 ± 4.21), (AD vs. HC, P < 0.001); Cut-point = 2.48, SEN = 69.29%, SPE = 79.43%, PPV = 82.3%, NPV = 65.3%; OR = 4.774 [95% CI: 2.821–8.076], (P < 0.001)	[85]
		HC	175	71.95 ± 5.40	78/97				
		AD	94	74.2 ± 9.6	54/40	Retro-spective cohort study	-	(2.2 ± 1.2)/(1.9 ± 0.7) (AD vs. HC, P = 0.09)	[86]
		HC	61	65.7 ± 4.6	30/31				
		MCI	186	73.10 ± 3.29	108/78	Retro-spective cohort study	Multivariable logistic regression	(2.39 ± 0.55)/(1.94 ± 0.51) (MCI vs. HC, P < 0.001); When NLR ≥ 2.07, OR = 5.993 [95% CI: 3.467–10.155, P < 0.001], SEN = 73.67%, SPE = 69.3%, PPV = 74.48%, NPV = 68.4%	[87]
		HC	153	71.19 ± 3.32	81/72				

Abbreviation AD, Alzheimer's Disease; AUC, Area Under the Curve; CI, Confidence Interval; HR, Hazard Ratio; HC, Healthy Controls; MCI, Mild Cognitive Impairment; NPV, Negative Predictive Value; OR, Odds Ratio; PPV, Positive Predictive Value; PVFFMC, Patients Visiting for Family Medicine Consultation; SEN, Sensitivity; SPE, Specificity

attract neutrophils and stimulate the release of NETs [96, 97]. Exposing brain endothelial cells to A β peptides in a laboratory setting leads to an increase in the expression of cytokine genes, particularly IL-1 β . Elevated levels of IL-1 β have been observed to activate NETs [98]. The resulting NETs may play a role in AD progression by damaging the BBB and neuronal cells [99, 100].

Studies indicate that platelets significantly contribute to the formation of vascular NETs [68, 101, 102]. Research conducted on mouse models and AD patients has illustrated that when platelets become activated and interact with A β deposited in the blood vessels, it can lead to an increase in vascular inflammation [103]. The formation of vascular NETs is likely caused by the interaction between TLR4 and LFA-1 integrin, according to two studies [42, 104]. Activated platelets can release HMGB1, a damage-associated molecular pattern [105]. Neutrophils have receptors for HMGB1, including advanced glycation end products RAGE receptors and TLR4 [104, 106, 107]. HMGB1 activates the production of NETs by neutrophils through interactions with these receptors [102]. Additionally, HMGB1 stimulates neutrophils to produce pro-inflammatory cytokines, which act on endothelial cells and increase the expression of VCAM-1 (Vascular Cell Adhesion Molecule-1) and selectins [42, 108, 109]. Studies have shown that blocking the interaction between RAGE and A β can effectively decrease inflammation and neuronal damage. This can be achieved with RAGE antagonists, antibodies, or drugs [102]. Such interventions could prevent A β -induced inflammation, minimize neuronal damage, and offer potential therapeutic benefits. However, more research is necessary to assess the efficacy and safety of treatments targeting RAGE.

Neutrophil gelatinase-associated lipocalin (NGAL) The protein known as NGAL, also referred to as lipocalin-2 or siderocalin, is recognized as a potential factor in the progression of AD and depression [77, 110]. In general, NGAL is not highly expressed in peripheral blood and cerebrospinal fluid (CSF) under normal circumstances. However, during AD-associated inflammation, neutrophils release more NGAL, leading to elevated levels of this protein in the bloodstream [111]. Clinical data indicates that individuals with AD and MCI have elevated plasma NGAL levels [73, 76]. Conversely, studies have found no significant difference in NGAL concentrations in the CSF of patients with AD or MCI compared to healthy individuals [112]. An autopsy examination of brain tissue from AD patients showed a marked rise in NGAL levels specifically in the hippocampus [75]. Consequently, while NGAL shows potential as an early biomarker for AD, the variations in its levels in different body fluids imply limitations in its use. The reason for lower NGAL levels in the CSF of AD patients, as one hypothesis

suggests, could be due to reduced expression of megalin in the choroid plexus [113].

Myeloperoxidase (MPO) MPO is a protein that is abundantly present in the azurophilic granules of neutrophils. Its essential function includes producing hypochlorous acid and reactive oxygen species, contributing to inflammatory processes [114]. Studies have shown that elevated levels of MPO in the brains of AD patients are linked to increased numbers of neutrophils in the brain vasculature [115]. In the brains of AD patients and the APP/PS1 AD mouse model, MPO co-localizes with neutrophil markers such as CD66B and S100A8 [116]. There is a positive correlation between the increase in peripheral blood MPO levels and A β ₁₋₄₂ concentration in AD patients [80, 81, 117]. Neutrophil-derived MPO may disrupt the BBB and damage endothelial cells during inflammation [115]. MPO disrupts vascular relaxation by oxidizing endothelium-produced nitric oxide [118]. Neutrophils are known to play a role in the initiation and progression of vascular inflammation, and high levels of MPO produced by these cells can lead to an increase in ROS. This has been linked to the development of AD through oxidative stress. Studies involving APP23 mice that were crossbred with the human MPO gene have shown exacerbated cognitive impairments [119]. However, further research is essential to elucidate the role of neutrophil-derived MPO in the pathogenesis of AD.

Neutrophil-to-lymphocyte ratio (NLR) Recent studies have explored the use of the NLR ratio as a simple and convenient marker of inflammation. Multiple studies have shown that the peripheral blood NLR in patients with AD and MCI is significantly higher than in healthy controls [82, 83, 86, 120, 121]. Multivariate regression analysis indicates NLR as an independent predictor with robust prognostic value for AD [85]. Dong et al. determined that the NLR exhibits high sensitivity and specificity for the diagnosis of AD [84, 85]. The NLR is a composite biomarker that assesses inflammation by analyzing the counts or proportions of neutrophils and lymphocytes. This method is superior to relying solely on the absolute numbers of specific white blood cells because it provides a more nuanced view of the body's inflammatory status. This method is also superior to relying solely on the absolute numbers of specific white blood cells because it gives a more nuanced view of the body's inflammatory status.

Recent studies suggest that NETs, NGAL, and MPO could act as potential biomarkers for tracking disease progression and prognosis in AD. Further research is necessary to elucidate the clinical diagnostic and prognostic significance of these biomarkers and to assess their viability as therapeutic targets. Moreover, more investigation is needed to determine the correlations between

neutrophil biomarkers, AD-specific biomarkers, and other concurrent pathologies in AD.

Lymphocytes in AD **T lymphocytes in AD**

Under normal conditions, lymphocytes cannot cross the BBB into the brain. However, in AD, the permeability of the BBB increases due to elevated levels of adhesion molecules such as VCAM-1 and ICAM-1 [42]. This enhanced permeability facilitates the interaction between the peripheral immune system and the CNS, allowing lymphocyte infiltration into brain tissue. Studies have also discovered that A β proteins in the brain can migrate to the cervical lymph nodes through the lymphatic system [122]. Here, antigen-presenting cells capture and present them to T lymphocytes, thus activating the adaptive immune response [123].

Prior studies have shown that AD is characterized by heightened migration of CD4⁺ and CD8⁺ T lymphocytes to the affected regions [124]. Compared to healthy control groups, AD patients show an increased CD4/CD8 ratio and a decreased percentage of CD8⁺ T lymphocytes in peripheral blood. Increased levels of CD4⁺ and CD8⁺ effector T lymphocytes have been detected in the brain parenchyma of those with AD and MCI [38, 125–127]. However, the precise mechanisms by which T lymphocytes penetrate the BBB and enter the CNS remain elusive. Research has identified distinct subsets of CD4⁺ and CD8⁺ T lymphocytes, including Th1, Th17, and Treg, that are implicated in either promoting or mitigating chronic neuroinflammation in AD [127–131].

CD8⁺ T lymphocytes in AD Research on CD8⁺ T lymphocytes in the peripheral blood of AD patients has yielded inconsistent results. Earlier studies have indicated lower levels of CD8⁺ T lymphocytes in AD patients, possibly linked to the systemic inflammation characteristic of the disease [121, 132, 133]. However, a recent cohort study found a correlation between clonally amplified CD8⁺ T lymphocytes levels in the CSF and cognitive decline in patients with AD [38]. Moreover, infiltration of CD8⁺ T lymphocytes has been detected in the brains of both AD patients and mouse models of the disease [38, 134, 135]. To enhance our understanding of the role of CD8⁺ T lymphocytes in AD, Unger et al. conducted a study to investigate the effects of depleting CD8⁺ T lymphocytes using an anti-CD8a antibody in the APP/PS1 mouse model. Their research suggests that brain CD8⁺ T lymphocytes may directly lead to dysfunction in neurons that regulate synaptic plasticity [136].

A recent study investigating peripheral blood T lymphocytes in AD patients found no significant differences in PD-1 expression compared to a healthy control group. However, the same study observed increased PD-L1

expression in CD8⁺ T lymphocytes, which inversely correlated with cognitive function [137]. While the link between PD-1/PD-L1 expression and cognitive decline requires further investigation, inhibiting PD-1 or PD-L1 has shown promise in enhancing the clearance of brain A β plaques by monocyte-derived phagocytic cells and in improving cognition in mouse models [138, 139]. More research is necessary to elucidate the effects of T cell PD-1/PD-L1 expression discrepancies on the pathology of AD. Furthermore, research into the purine receptor P2 \times 7R in AD found that mice lacking P2 \times 7R (APP/PS1xP2 \times 7Rko) exhibited reduced A β plaque formation and diminished T cell infiltration in the brain, mediated by lower glial cell CCL3 expression [140]. This effect corresponded with reduced recruitment of CD8⁺ T lymphocytes into the choroid plexus and hippocampus, offering new insights into the interplay between glial cells and T lymphocytes affecting AD pathology [140]. Although blocking P2 \times 7R as a means to alleviate A β burden in AD has been reported [141–143] it is the inaugural inclusion of first study to include T lymphocytes in such research.

CD4⁺ T lymphocytes in AD CD4⁺ T lymphocytes have garnered significant interest in AD pathology and therapeutic research. Initial comparisons between age-related AD patients and healthy controls indicated a modest elevation in CD4⁺ T lymphocytes [133]. Th17 cells are a subtype of helper T lymphocytes known for secreting cytokines such as IL-17 [144]. Research has identified molecules such as IL-6, TGF- β , and IL-23, along with transcription factors ROR γ t and NFATc1, as key players in the differentiation of Th17 lymphocytes in patients with AD [127, 145, 146]. Furthermore, AD patients exhibit higher levels of Th17 cell cytokines, including IL-17 and IL-21, compared to individuals with MCI or healthy controls. Although the differences between MCI patients and healthy subjects are marginal, studies show that both MCI and AD patients have significantly increased counts of peripheral blood CD3⁺ CD8⁻ IL-17 A⁺⁺ Th17 cells than the healthy cohort [126].

Studies have shown that in 3xTg mouse models, IL-17 is able to exacerbate cognitive and synaptic dysfunction in the early stages of Alzheimer's disease [147]. Preconditioning with an IL-17 antibody through intraventricular injection, or administration via intranasal injection post-induction, can mitigate A β ₁₋₄₂-induced neurodegeneration and lead to cognitive improvement [148]. Moreover, administration of IL-17 antibody restored acetylcholine-mediated vasodilation, improved hemostasis, and reduced thrombosis [149]. The transfer of A β -specific TH17 effector T lymphocytes (Teffs) into the AD mouse model resulted in a significant reduction in postsynaptic protein expression, exacerbating cognitive deficits [131, 150]. Research has shown that A β directly modulates

the expression of Th17 cytokines, resulting in compromise of the BBB and subsequent infiltration of Th17 cells into the brain parenchyma. This is evidenced by elevated levels of IL-17 and IL-22 within the brain parenchyma [130]. Moreover, IL-17 has been implicated in the induction of cognitive deficits in AD murine models. Cognitive deficits in APP/PS1 mice can be ameliorated by targeting Th17 cell differentiation pathways, such as the IL-12/IL-23 signaling [151]. Intriguingly, patients with AD exhibit elevated levels of IL-23, a cytokine critical for Th17 cell differentiation and activation [152]. However, IL-17 levels do not show a corresponding increase. Nonetheless, heightened expression of ROR γ t in these patients suggests active involvement of Th17 cells. Furthermore, these cells can produce a considerable amount of IL-21, indicating that there is a subset of Th17 cells whose main function is to secrete IL-21 and promote the development of AD pathology [127]. The precise function of Th17 cells in AD progression is currently unclear. Research has yielded inconsistent outcomes regarding Th17 cell-related cytokine levels and their quantities across various stages of AD. This may be due to the interaction of Th17 cells with other T cell subpopulations. For example, research on A β -specific Th1 and Th17 effector cells has demonstrated that their combined presence exacerbates memory deficits and amyloid accumulation in APP/PS1 mice [150]. This contrasts with prior findings indicating that memory could be adversely affected by interferon (IFN)- γ produced by A β -specific Th1 cells [131]. Therefore, the researchers suggested that the joint pathological effects of Th1/Th17 effector cells may be activated in culture conditions that contain IFN- γ and IL-12 [150].

Regulatory T lymphocytes in AD Regulatory T lymphocytes (Tregs) are an important part of the immune system because they possess the transcription factors FoxP3, CD25, and CTLA-4, which are responsible for regulating the immune response and promoting immune tolerance [153]. Tregs are known to maintain immune tolerance during disease, but this tolerance may be altered in the context of AD [154]. In AD, effector T lymphocytes respond to misfolded A β deposits, undergo clone amplification, and then influence neuroinflammation and AD neuropathology [155]. Regarding the development of Tregs in AD pathology and clinical studies in mouse models, there is a range of reported results, with some studies indicating an increase [156] and others a decrease [157]. Depletion experiments of Foxp3⁺Tregs [128, 158] and animal research [43] have confirmed the potential neuroprotective effect of Tregs. By constructing A β -specific Tregs, some scholars have found that A β -specific Tregs can reduce reactive microglia and amyloid deposition through antigen-mediated immunosuppression, thereby

improving memory and generating neuroprotective responses [159]. However, D69⁺Treg cells in the healthy brain can rapidly expand during neuroinflammation, inhibiting astrocyte proliferation through amphiregulin and converting microglia to a pro-inflammatory phenotype through IL-10 secretion [160, 161]. In vitro expansion of clonal Tregs has also been shown to inhibit microglia [162, 163]. The role of Tregs in the progression of AD remains to be further studied. However, due to the powerful anti-inflammatory and immunosuppressive activity of Tregs, adoptive transfer of Treg inducers or polyclonal Tregs can protect against multiple neurodegenerative diseases. Therefore, this immunotherapy targeting Tregs provides a specific immune profile that can improve disease outcomes. The key to developing antigen-specific Treg therapy for AD will be to target A β -specific cells that accumulate amyloid-containing parts of the brain. Additionally, Tregs may be able to block immune cells from entering the CNS, reducing the recruitment of immune cells [128, 164].

Therapy of AD based on T lymphocytes

Immunotherapy for AD has been a popular field of research, whether through increasing the levels of various cytokines in AD patients [165]. However, the AN1792 A β vaccine trial was discontinued due to severe T-lymphocyte meningoencephalitis in 6% of participants. Still, 12 of 59 patients treated with AN1792 developed antibody responses [166, 167]. Subsequent immunotherapies, including the phase 2 bapineuzumab [141] and the phase 3 solanezumab [168, 169], have not improved cognitive impairment in Alzheimer's patients. Studies have shown that CD4⁺T lymphocytes expressing A β -specific receptors are present in humans [170], and the immune response to A β varies according to the MHC genotype [171, 172]. Furthermore, A β ₃₃₋₄₁NP has shown efficacy in eliciting specific CD8⁺T lymphocytes in C57BL/6 and APP/PS1 mice without side effects [173]. Thus, although targeted immunotherapy for AD amyloid shows promise, its safety and effectiveness warrant further investigation. Exploring individual variation, MHC genes, and immune response correlations, along with enhancing treatment safety and efficacy through anchor optimization, is essential.

Studies have aimed at augmenting cytokine levels in Alzheimer's patients by administering low-dose IL-2 in APP/PS1 mice. This intervention not only boosted the quantity and activity of Tregs but also enhanced amyloid plaque-associated microglia and cognitive performance in mice [128]. Notably, humans have shown good tolerance to low doses of IL-2 [174], indicating its prospective application in clinical settings. Another investigation demonstrated that IL-2 can initiate astrocyte activation and recruitment in the hippocampus, decrease A β _{42/40}

ratios, lower amyloid plaque load, and enhance synaptic plasticity [175]. Scientists are investigating the use of neurotrophins and T lymphocytes for AD treatment by employing retroviruses to insert brain derived neurotrophic factor (BDNF) into A β -specific Th1 cells. This approach successfully prompted the cells to emit BDNF, which decelerates cognitive deterioration in AD sufferers [176]. In a five-year study, mice were observed to investigate the effects of transplantation on amyloid plaques [177]. The results showed that the cells had the capacity to migrate to the plaques, resulting in an increase in synaptic molecules and a decrease in amyloid load. Moreover, increased levels of TrkB and VAMP2 were noted, implying a role for BDNF in synaptic and neural repair. These findings offer fresh perspectives on potential therapy options for AD. Additionally, BACE1 was found to be increased in the plasma of those with AD [178]. In 5x*FAD* mice treated with Th1-BDNF, there was a noted decrease in BACE1 levels [177]. As a result, BACE1 inhibitors have undergone testing and have been shown to curtail the formation of amyloid plaques [178].

Th1 cells have been found to be effective in cell therapy, and Hyejin Yang et al. further used A β peptides to induce the production of A β antigen-specific Tregs both in vitro and in vivo, and then conducted adoptive therapy [163]. Following treatment, 3xTg-AD mice exhibited a significant reduction in hippocampal amyloid plaques and lower levels of tau protein phosphorylation [163]. This impact was most notable in the early stages of AD, at 3 months in 3xTg-AD mice. Moreover, the A β -specific Treg cells that were transferred survived for more than a week, contributing to the improvement. Research has shown that modulating biological therapy can benefit APP/PS1 and 3XTG-AD mice by activating the STAT4/JAK2/STAT5 pathways, which increases the expression of IFN- γ /IL-10 in CD4⁺T lymphocytes. This approach has the potential to enhance the brain's milieu, fostering neurogenesis and cognitive enhancement [178]. These pathways play a crucial role in mediating immune responses, where STAT4 activation promotes the differentiation of Th1 cells, leading to increased production of IFN- γ [179]. JAK2 and STAT5 are involved in signaling that enhances the anti-inflammatory response through the upregulation of IL-10 in CD4⁺T lymphocytes [180]. The interaction of immune pathways in AD can balance the immune response, reducing neuroinflammation, amyloid plaques, and tau phosphorylation. This may promote neurogenesis and cognitive enhancement. In early AD, boosting Th1 activity is beneficial, while in later stages, enhancing regulatory T cell responses can minimize inflammation and neuronal damage. Immunotherapies offer promise for AD patients by potentially alleviating symptoms and decelerating disease progression. Enhancing the efficacy of T cell therapy requires further research to ascertain

optimal cell phenotypes, administration sites, dosages, and delivery methods.

B lymphocytes in AD

B lymphocytes and neuroinflammation B lymphocytes, as dedicated APCs, are vital to the functioning of adaptive immunity. Upon stimulation by antigens, B lymphocytes differentiate into plasma cells that secrete antibodies, while concurrently processing antigens for presentation to T lymphocytes. For instance, in AD caused by bacterial infection, B lymphocytes expressing TLR4 on their surface can be stimulated by lipopolysaccharide and induce various neurodegenerative diseases, including AD [181]. This suggests that the immune reaction mediated by B lymphocytes may be involved in the pathological process of AD. The spleen is widely recognized as the primary source of B lymphocytes. However, discrepancies exist in the alterations of B lymphocytes in the spleen and meninges, as observed in the 5x*FAD* mouse model of AD [182, 183]. One possible explanation is that the meningeal B lymphocytes, which are the main source of B lymphocytes in the brain, originate from the calvaria and undergo negative selection against self-antigens locally [184]. Non-AD transgenic mice expressing APOE ϵ 3 and ApoE ϵ 4 also display elevated B lymphocyte counts in peripheral blood and pervasive IgG distribution throughout the brain, with the most pronounced effects seen in female APOE ϵ 4 transgenic mice [185, 186]. Interestingly, in regions heavily affected by AD, such as the hippocampus, only minimal levels of IgG are detected alongside significant A β deposition [187].

Studies using flow cytometry and single-cell RNA sequencing have shown reductions in both absolute counts and relative percentages of B lymphocyte subsets in the blood of AD patients [44, 133]. Furthermore, there is an increase in IgG synthesis and upregulation of the CCR (Chemokine receptor) 5 chemokine receptor, suggesting activation of B lymphocytes in AD [188]. Comparative analyses of healthy elders and AD patients show an elevated level of double-negative (IgD⁻CD27⁻) B lymphocytes [189, 190]. A link has been suggested between early-onset AD (EOAD) and increased circulating double-negative CCR6⁺B lymphocytes [191]. Additionally, a notable decrease in naive IgD⁺CD27⁻ B lymphocytes has been observed [192]. RNA sequencing data indicate upregulation of KIR3DL2, PPP2R2B, and QPCT and downregulation of FRAT2 and WWC3 in B lymphocytes, hinting at their possible roles in AD [193–195]. The impact of Ras protein signaling in B lymphocytes in relation to AD remains to be fully elucidated.

CD4⁺T lymphocytes are critical for B cell activation. Recent research has shown that CD4⁺T lymphocytes promote MHC-II expression on microglia, enhancing

their antigen presentation capabilities [196]. Non-A β -specific IgG molecules primarily attach to microglia via the Fc region, activating the Src/Syk/PI3K signaling pathway and boosting microglial phagocytosis of A β fibrils [197]. Brain IgG could induce chronic stress-related conditions by activating microglial Fc receptors and causing synaptic disruption and neuroinflammation through the CR3 and Fc γ R pathways [45, 46]. Changes in TGF- β ⁺ microglia can affect B cell function and the secretion of IgG [198]. Depleting B lymphocytes has been shown to lower TGF- β ⁺ microglia levels and reduce Trem2, Clec7a, and Itgax expression in the hippocampus, indicating that B lymphocytes may drive chronic microglial dysfunction and amyloid plaque buildup in disease conditions [199]. Tfh cells significantly promote the isotype conversion and antibody secretion of B lymphocytes [96]. The cytokine IL-21, characteristic of Tfh cells, shows a marked elevation in AD patients [200] and has a positive correlation with IgG levels [201]. IL-21 is primarily secreted by Tfh cells in lymph node germinal centers [202] and plays a role in sustaining immunoglobulin class switching and antibody synthesis [203]. This aligns with the elevated Tfh cell populations observed in the spleens of AD mice [201]. Additionally, IL-21 influences Tfh cells to induce Th17 cell differentiation [204], correlating with the rise in Th17 cells seen in AD mice [127]. The activity and differentiation of B lymphocytes are affected by the inflammatory environment. In both aging and AD, B cell subsets and functions have been found to be highly diverse [189, 190]. This implies that B lymphocytes may be involved in the development of AD. The study suggests that B lymphocytes may have a dual role in the neuroinflammation of AD. For example, in APP/PS1 transgenic mice, depletion of B lymphocytes via anti-CD19/B220 antibodies led to heightened hippocampal A β deposition and worsened cognition [44]. Additionally, increased B cell numbers, including an IL-35-secreting subset, were observed in the frontal cortex and meninges of 5 \times FAD mice. It was discovered that IL-35 interacts with neuronal IL-35 receptors, enhancing cognitive function by inhibiting BACE1 transcription through the SOCS1/STAT1 pathway. These results suggest that B lymphocytes could serve as a neuron-specific protective agent and offer a potential avenue for future B cell-focused therapies [197].

In various neurodegenerative diseases, B lymphocytes emit substantial amounts of TNF- α , TNF- β , IL-6, and GM-CSF [205]. Pro-inflammatory factors such as A β in AD patients can activate B lymphocytes and transform them into pro-inflammatory B lymphocytes, which then release pro-inflammatory cytokines to promote neuroinflammation and aggravate AD symptoms. Higher expression levels of the pro-inflammatory chemokine receptors CCR5, CCR6, and CCR7 were observed on B lymphocytes of moderate to severe AD [40, 206]. In autoimmune

conditions like autoimmune encephalomyelitis and multiple sclerosis, CCR6 influences T cell migration into the cerebrospinal fluid along with selectins and integrins, but this is not observed in AD models [207]. Additionally, CCR7 has proven to be a pro-inflammatory receptor in various chronic inflammatory disease models in both human and mouse studies [208, 209]. These results indicate that the expression of CCR5, CCR6, and CCR7 may be influenced by the pro-inflammatory milieu in AD patients. These cells are similar to DN B lymphocytes associated with AD and the elderly. An elevated presence of DN B lymphocytes is considered contributory to AD development [191].

Antibodies in AD Antibody production is a principal mechanism through which B lymphocytes contribute to adaptive immunity. B lymphocytes also produce autoantibodies that may be implicated in autoimmune diseases or contribute to immune equilibrium. While rare, B lymphocytes can infiltrate the brain via the cerebrospinal fluid and choroid plexus [210]. B lymphocytes can differentiate into plasma cells within cervical lymph nodes in response to stimuli, including A β , APOE/A β complexes, α -synuclein, and tau proteins [211–213]. In Alzheimer's patients, the serum contains higher levels of non-specific and A β -specific antibodies, which are thought to have neuroprotective properties [214]. These antibodies engage with a range of neurotransmitters and receptors, including N-methyl-D-aspartate (NMDAR), oxidized low-density lipoprotein (oxLDL), and RAGE. Only a fraction of the circulating antibodies can traverse the BBB in healthy mice [215]. In AD, a compromised BBB potentially permits increased antibody ingress into the brain, contributing to pathogenesis through antigen binding. Moreover, heightened IgG levels in the choroid plexus of wild-type mice imply that choroid plexus dysfunction in AD may facilitate brain access for circulating IgG [216].

Both healthy individuals and AD patients can exhibit antibodies against A β . In AD patients, these antibodies are thought to interfere with the aggregation and toxicity of A β [217]. Studies have discovered that naturally occurring immunity targets several A β epitopes, such as the N-terminal A₄-A₁₀ segment, triggering antibody production [218]. Although these antibodies can reduce amyloid plaques, they have not significantly reversed cognitive impairments [219]. Furthermore, antibodies specific to the mid-to C-terminal region of A β , beginning at amino acid 28, have been detected (NAbs-A β). In healthy individuals, these antibodies can bind to A β dimers and trimers, potentially preventing plaque formation and ameliorating cognitive deficits in transgenic mice [217]. Research has produced mixed findings on the presence of anti-A β antibodies in both AD patients and healthy subjects. Table 2 (End of manuscript) outlines the

Table 2 Heterogeneity of A β antibody levels in body fluids of Alzheimer's disease patients

Basic information	Type of samples	Research type	Methods	Findings	Country	References
AD patients ($n=39$), (73.2 \pm 8.2) years HC ($n=39$), (77.7 \pm 10.8) years	Serum	Prospective cohort study	ELISA	Ig anti-A β_{42} (Titer): 50 (30 \pm 80)/117 (70 \pm 200), (AD vs. HC, $P=0.02$) IgG anti-A β_{42} (Titer): 295 (180 \pm 490)/724 (440 \pm 1200), (AD vs. HC, $P=0.01$)	United States	[220]
AD patients ($n=99$), (70 \pm 8) years, Male/Female(33/63), MMSE (21 \pm 5) HC ($n=30$), (55 \pm 9) years, Male/Female (16/14), MMSE (29 \pm 1)	Serum	Case-control study	Immunoprecipitation	Anti-A β_{1-42} antibody(U): (3.1 \pm 3.28)/(5.88 \pm 4.54), (AD vs. HC, $P=0.001$)	Germany	[221]
AD patients ($n=49$); HC ($n=46$)	CSF	Case-control study	ELISA	Anti-A β antibody (Titer) (210.7 \pm 23.5)/(303.4 \pm 32.78), (AD vs. HC, $P=0.02$)	United States Germany	[222]
AD patients ($n=59$), (77 \pm 8) years, Male/Female (0.49) HC ($n=59$), (70 \pm 10) years, Male/Female (0.44)	Plasma	Case-control study	ELISA	Reduced anti-CAPS antibodies (AD vs. HC, $P=0.018$)	United States	[223]
AD patients ($n=53$), (72.3 \pm 7.5) years, Male/Female (20/33), MMSE (19.8 \pm 6.3) HC ($n=60$), (67.6 \pm 5.8) years, Male/Female (39/21), MMSE (28.9 \pm 2.6)	Serum	Case-control study	ELISA; Dot blot assay	Anti- A β_{42} , A β_{1-15} , and A β_{16-30} antibodies (Average concentration, μ g/ml): (0.59 \pm 0.05)/(0.82 \pm 0.08), (AD vs. HC, $P=0.02$)	United States	[224]
AD patients (Mild, $n=8$; Moderate, $n=9$; Severe, $n=3$), (67.6 \pm 6.8) years, MMSE (Mild = 20 ~ 26, Moderate = 14 ~ 19, Severe < 14), Average duration (4.1 \pm 2.8) years; HC ($n=20$), (68.0 \pm 7.2) years	Serum	Case-control study	ELISA	Affinity of A β antibodies: 0.92 (0.86 ~ 1.09)/1.32 (1.02 ~ 1.41), (AD vs. HC, $P=0.03$)	China	[225]
AD patients($n=153$), (74.89 \pm 5.96) years, Male/Female (44/109), MMSE (20.46 \pm 6.20) HC ($n=193$), (72.31 \pm 5.86) years, Male/Female (81/112), MMSE (27.0 \pm 3.08)	Serum	Case-control study	ELISA	Anti-A β IgG (Titer): 23.3/45.8, (AD vs. HC, $P<0.05$)	Korea	[226]
AD patients($n=136$), (70.0 \pm 10.0) years, Male/Female (100/36), MMSE (17.3 \pm 6.9) HC ($n=210$), (70.0 \pm 9.8) years, Male/Female (128/82)	Serum	Case-control study	ELISA	Reduced anti-A β autoantibody levels (AD vs. HC, $P<0.0001$)	Korea	[227]
AD patients($n=33$), (75.09 \pm 8.61) years, Male/Female (19/14), MMSE (14.09 \pm 9.23) HC ($n=42$), (65.67 \pm 9.52) years, Male/Female (15/24), MMSE (29.13 \pm 1.49)	Plasma	Case-control study	ELISA	Nearly fourfold (AD vs. HC, $P=0.001$)	United States	[215]
AD patients ($n=16$), (76.9 \pm 6.0) years, Male/Female (4/12), MMSE (17.3 \pm 3.8) HC ($n=31$), (72.5 \pm 6.4) years, Male/Female (13/18), MMSE (29 \pm 1.4)	Serum	Case-control study	ELISA	Aggregated β -amyloid IgG (AD vs. HC, $P<0.005$); Soluble antibody (AD vs. HC, $P<0.05$)	United States	[228]
AD patients ($n=17$); HC ($n=15$)	Serum	Case-control Study	ELISA	Anti-A β_{25-35} antibody (Relative units): (161.4 \pm 48.8)/(5.6 \pm 0.7), (AD vs. HC, $P<0.01$)	Russia	[229]
AD patients (n1 = 22, n2 = 26), (77.0 \pm 7.0)/(79.0 \pm 5.0) years, Duration (n1 < 5 years, n2 > 10 years) HC ($n=28$), (75.0 \pm 4.0) years, MMSE (27)	Serum	Case-control study	ELISA Dot blot hybridization	Elevated anti-A β_{25-35} oligomer (AD vs. HC, $P<0.05$)	Russia	[230]

Table 2 (continued)

Basic information	Type of samples	Research type	Methods	Findings	Country	References
AD patients ($n=54$), (52–91) years HC ($n=49$), (64–90) years	Serum	Comparative study	ELISA	Significantly higher optical density of A β antibodies (AD vs. HC, $P < 0.001$)	United States	[231]
AD patients ($n=82$), (76.0 \pm 7.11) years, Male/Female (22/64) HC ($n=271$), (75.8 \pm 5.9) years, Male/Female (87/184)	Plasma	Prospective cohort study	ELISA	Anti-a β antibody (Average titer): (16.07 \pm 17.5)/(16.96 \pm 41.5), (AD vs. HC, $P < 0.05$)	United States	[232]
AD patients ($n=36$), (76.5) years, Male/Female (13/23), Average MMSE (17) HC ($n=34$), (72.0) years, Male/Female (7/27), Average MMSE (29)	Serum	Case-control study	ELISA	Log10 IgG to Ab40: (2.83 \pm 0.29)/(2.78 \pm 0.19), (AD vs. HC, $P=0.19$) Log10 IgG to A β 42: (2.95 \pm 0.39)/(2.83 \pm 0.19), (AD vs. HC, $P=0.056$)	France	[233]
AD patients ($n=113$), (75) years, Male/Female (32/81), MMSE (14.9 \pm 6.7) HC ($n=155$), (76) years, Male/Female (59/96), MMSE (29.7 \pm 0.4)	Plasma	Case-control study	Tissue amyloid plaque immunoreactivity (TAPIR)	High incidence of TAPIR: 45.1%/41.3%, (AD vs. HC, $P=0.77$)	Japan	[234]

Abbreviation AD, Alzheimer's Disease; CAPS, Cross-linked beta-amyloid protein species; CSF, Cerebrospinal fluid; ELISA, Enzyme-linked immunosorbent assay; HC, Healthy controls; MMSE, Mini-Mental State Examination; TAPIR, Tissue amyloid plaque immunoreactivity

diverse outcomes of these experiments. Challenges with enzyme-linked immunosorbent assay -based detection of A β antibodies - including immune complex formation and the potential for misinterpretation caused by A β monomer adsorption - may result in inconsistent results. Acid treatment to dissociate complexes, ELISpot for measuring soluble A β , and specific strategies for addressing antibody complex concerns are possible solutions to these challenges [188].

Damage to neurons and synapses in AD results in the release of tau proteins, neurofilaments, and microtubule-associated proteins, which can stimulate B lymphocytes to produce specific antibodies [235]. Research indicates that immunoglobulins can bind to tau and cytoskeletal proteins, potentially modifying their structure and activity, and contributing to the pathology of neurodegenerative diseases [236]. In TAU58/2 mice, a deficiency of B lymphocytes has been linked to the exacerbation of cognitive deficits. Conversely, long-term B cell depletion via anti-CD20 antibodies did not lead to worsening of cognitive deficits [237].

B lymphocytes dependent therapy in AD Although the A β -IgG complex in cerebrospinal fluid has been linked to cognitive performance in patients with AD, this does not necessarily mean that it has a positive effect on improving cognitive impairment [238]. Indeed, less than 0.0017% of administered immunoglobulin reaches the brain post-intravenous injection, contributing to its limited effectiveness in treating AD [239, 240]. Consequently, this therapeutic approach may be suboptimal. NMDARs, a class of ionotropic glutamate receptors, play crucial roles in synaptic activity, memory development, and controlling neu-

ronal damage due to overstimulation [241]. Dysfunctional NMDARs in AD hinder neuronal communication, which is a reason why memantine, an NMDAR antagonist, is used to treat moderate to severe AD [242]. Agents like memantine, non-competitive NMDAR antagonists, can suppress B cell response to BCR and TLR4 signals, leading to reduced calcium entry and signaling, decreased levels of IgM and IgG, and lower B cell mobility and viability. Conversely, ifenprodil, another NMDAR antagonist employed in depression therapy, can instigate the BCR/cd40 pathway, stimulating the production of the anti-inflammatory cytokine IL-10 by B lymphocytes. The divergent effects likely result from differences in drug timing and dosage, necessitating additional research to uncover the underlying molecular processes [243].

NK cells in AD

Natural killer (NK) cells play a crucial role in innate immunity and are divided into two subsets: CD56bright and CD56dim. The CD56bright subset produces cytokines and chemokines to regulate inflammation and the immune response, while the CD56dim subset releases cytotoxic molecules to destroy tumor and infected cells [244]. The risk of AD increases with age, and studies have shown an increase in NKp46⁺ cells in the dentate gyrus of elderly individuals and aging mice [39]. Aging neural progenitor cells release factors that attract NK cells to aging areas and upregulate genes associated with immune regulation, cellular senescence, and DNA damage response. In both human AD patients and 3xTG-AD mice [47, 245–248]. NK cells have been observed to enter the brain's circulatory system, primarily located in the

choroid plexus, pial meninges, and surrounding vasculature with limited penetration into the brain parenchyma [47].

NK cells can be categorized into different subgroups, such as NK1AD cells (Thy1-CD7-/low) that have high levels of cytotoxic molecules (Ctsc, Ctsd), pro-inflammatory chemokines (CCL3, 4), adhesion molecules (ICAM-1), and lymphocyte activation molecules (Nfatc1, Tbx21, Nfkbia, Il12rb, and Klra9). Studies have shown that both NK1a cells, which have low levels of cytotoxic molecules, and NK1b cells, which have high levels of cytotoxic molecules, exhibit increased activity [47]. In mice, treatment with anti-NK_{1.1} improved cognitive function and reduced the expression of genes related to microglial proliferation (Mki67, Cdc42) and pro-inflammatory cytokines (TNF, IL-1, IL-18), while maintaining the microglia's ability to clear A β [249]. In AD, inflammatory molecules such as A β and IL-18 activate NK cells through receptors like RAGE and TLR [250, 251]. This activation leads to increased secretion of cytokines, including IL-1, IL-18, and TNF, creating a feedback loop that worsens neuroinflammation and cognitive decline. In comparison to healthy individuals, NK cells in AD patients show heightened responsiveness to IL-2 and IFN- β , with IL-2 stimulating the production of IFN- γ and TNF- α [245]. Analysis of NK cell transcriptomes in AD patients reveals decreased levels of cytotoxic (NK0) and adaptive (NK2) subgroups in the blood, but an increased presence in the brain [252]. Bioinformatics analysis identified 17 transcription factors shared between NK cells in the blood and AD brain tissue, with 13 showing increased expression [48].

Research has shown a connection between the activation of STAT3 and the infiltration of immune cells in tumors. Inhibiting STAT3 has been linked to a decrease in NK cell infiltration and IFN- γ levels. These findings suggest that STAT3 may play a role in NK cell activation and brain infiltration in AD, but further research is needed to confirm this [253]. Analysis of NK cells in the brains of 3XTg-AD mice revealed more activated clusters, indicating active NK cell infiltration in the Alzheimer's brain [48]. Treating 3XTg-AD mice with anti-NK_{1.1} resulted in fewer EdU⁺NeuN⁺ cells in certain brain regions, suggesting enhanced neurogenesis [47]. Serotonin, a neurotransmitter that plays a role in emotions, sleep, learning, and memory, has been shown to moderately improve cognitive function in Alzheimer's patients. AD patients have been found to have increased expression of the 5-HT_{2C} receptor on NK cells, which may be related to the decreased serotonin levels often seen in these patients, who commonly experience depression and anxiety [254, 255]. Despite evidence showing serotonin's dose-dependent inhibition of NK cell cytotoxicity, more

research is necessary to investigate the impact of this cytotoxicity on AD progression.

Recent studies have shown that neural stem cells play a significant role in regulating the activity of NK cells in the brain during neuroinflammation [256]. NSCs release high levels of IL-15, which is crucial for the proliferation and function of NK cells. This interaction between IL-15 and IL-15R α is essential for the survival of NK cells [257]. However, more research is needed to fully understand the role of NK cells in AD and their impact on neuroinflammation. Further investigation into their interaction with glial cells and their potential role in nerve regeneration could provide valuable insights and lead to the development of targeted therapies for AD.

Monocytes

Recruitment and migration of monocytes

Monocytes, a crucial component of the peripheral mononuclear phagocyte system, have been found to participate in the clearance of tau protein in AD [258]. However, current studies are limited to the clearance of tau protein in peripheral blood, which can indirectly alleviate tau protein phosphorylation and neuronal damage in the brain [259]. Similar to tau, the diffusion of A β from the brain to the peripheral blood reaches 40-60% [260]. In AD mouse models, this portion of A β is solely cleared by the mononuclear phagocyte system [261]. Therefore, studies suggest that the migration of monocytes to the brain has neuroprotective effects on the CNS [262]. The process of monocyte infiltration into the brain is complex, generally involving the initial penetration of the endothelial monolayer and translocation across the basement membrane. This involves briefly residing on the basement membrane after crossing the endothelial layer and finally relies on the proteolytic activity of matrix metalloproteinases MMP-2 and MMP-9 to traverse the basement membrane and astrocytic end-feet [263]. Under physiological conditions, microglia can self-renew [264]; however, in AD, this regenerative capacity is impaired [265], potentially inducing the recruitment of peripheral monocytes to the brain to compensate for the damaged microglia [266]. These recruited monocytes are predominantly CCR2⁺ monocytes. However, the number of CCR2⁺ monocytes in the peripheral blood and bone marrow of AD patients is decreased [267], suggesting that this spontaneous recruitment is insufficient to sustain such protective functions. Additionally, whether these recruited monocytes can differentiate into microglia within the AD brain remains unclear [268], and these two cell types are difficult to distinguish based on morphology and marker expression. An *in vitro* study induced human peripheral blood monocytes into monocyte-derived induced microglia-like cells (MDMi) via A β oligomers, and observed an increase in phagocytic

index and the upregulation of 20 genes. Interestingly, the gene expression profile of MDMi differed from that of microglia observed in the later stages of AD pathology [269]. Although this finding supports the notion that monocytes may perform functions distinct from resident microglia after migrating to the brain, the artificial nature of the in vitro environment prevents definitive conclusions.

CCL2 (MCP-1) is a chemokine for innate immune cells, and its secretion is increased in the innate immune cells of AD patients [270]. CCL2 plays a crucial role in the infiltration of monocytes through the BBB into the brain [271]. Previous studies have demonstrated that A β ₄₂ can promote the expression of CCL2 in monocytes [272], thereby facilitating their infiltration into the inflamed brain, leading to localized inflammation. Additionally, another study found that MDP (Muramyl dipeptide, a minimal bioactive peptidoglycan motif from most Gram-negative and Gram-positive bacteria) could also enhance CCL2 expression in monocytes. Interestingly, the levels of downstream inflammatory mediator NF- κ B did not show significant changes, suggesting that MDP can increase CCL2 expression and promote monocyte recruitment to brain vasculature independently of pro-inflammatory responses [273]. Additionally, in tau pathology mouse models, targeting the PD-1/PD-L1 pathway has been shown to enhance the recruitment of monocyte-derived macrophages into the brain parenchyma. This recruitment decreases inflammation and reduces cognitive deficits in the brain [139].

The phagocytosis of monocytes decreased

AD predominantly affects elderly individuals. As aging progresses and the disease advances, the energy metabolism status of various immune cells, including monocytes and microglia, becomes impaired. Their glucose metabolism and oxidative phosphorylation levels notably decrease [274], which significantly impacts the functions of these immune cells. The use of an EP2 receptor antagonist (PF-04418948) to inhibit the PGE2-EP2 pathway can restore the energy metabolism of aged monocyte-derived macrophages [275], reverse cellular aging, and enhance their phagocytic functions. This treatment reduces A β burden and tau phosphorylation levels, while simultaneously decreasing IL-1 β and increasing IL-10 levels in the brain, thereby improving cognitive impairments in mice [276]. In elderly and AD populations, significant changes in peripheral blood serum components include elevated levels of inflammatory markers (c-reactive protein, IL-6, TNF- α) [277]. This chronic systemic inflammatory response is not solely derived from brain pathology but it is also closely associated with the involvement of aged peripheral immune cells. Under the dual influence of decreased energy metabolism and a pro-inflammatory

environment, monocytes not only fail to phagocytize A β but also release pro-inflammatory factors that affect the function of other cells [278].

In addition to energy metabolism disorders and pro-inflammatory environments, the pathogenesis is also related to the expression of cell surface membrane proteins. The CD33 gene has been previously identified as a risk factor for AD, and the CD33 protein it encodes is a sialic acid-binding immunoglobulin-like lectin that regulates innate immunity. Previous research indicates that CD33 expression is increased on microglia in the AD brain, and it inhibits microglial uptake of A β [279]. Similarly, another study found that inhibition of CD33 expression in mice leads to enhanced uptake of A β by monocyte-derived macrophages and microglia, thereby reducing A β accumulation [279]. Additionally, studies have shown that TLR2 expression is decreased in AD. This receptor forms a complex with CD14 to recognize and uptake A β [280]. PSK (Polysaccharide Krestin), a cancer treatment drug, can activate anti-tumor immune responses by promoting the maturation of dendritic cells [281]. In AD mouse models, PSK can increase peripheral A β uptake and intracellular metabolism by monocytes through the TLR2-mediated pathway, thereby alleviating cognitive impairments in mice [282]. Moreover, PSK not only targets A β but also inhibits the excessive phosphorylation of tau proteins, thus reducing neuroinflammation and neuronal damage [282]. This indicates that enhancing and activating the TLR2 pathway can improve monocyte function and intervene in the pathogenesis of AD.

Erythropoietin (EPO) has shown immunomodulatory potential and beneficial effects in the treatment of AD. However, its clinical application is hindered by the risk of thrombosis due to erythropoiesis induction. EPO can activate the innate repair receptor (IRR), which comprises the EPOR and β common receptor (β CR), providing neuroprotection in AD mouse models without eliciting erythropoietic effects [283]. ARA290, a peptide derived from EPO, also activates the IRR and regulates immune function without inducing erythropoiesis [284]. Early use of ARA290 in APP/PS1 mice reduces A β pathology in the brain and alleviates cognitive impairments without altering microglial reactivity. ARA290 increases the number of circulating monocytes, and the depletion of these monocytes negates the cognitive benefits provided by ARA290. This suggests that monocytes can potentially delay AD progression by phagocytizing A β . However, this therapeutic effect is limited in late-stage AD models [285].

Monocytes are associated with cerebrovascular amyloidosis

As previously mentioned, anti-amyloid immunotherapy has been tested in multiple late-stage clinical trials. Although patients receiving these antibody treatments

Table 3 The contribution of peripheral immune cells to the pathological development of AD at different stages

Peripheral immune cells	Models	Stages	Effects	Potential mechanism	Reference
Neutrophils	5xFAD and 3xTg-AD mice	Early stage	Promote inflammation.	Neutrophils promote AD-like pathology and cognitive decline via the LFA-1 integrin.	[42]
	APP/PS1 and 5xFAD mice	Not mentioned	Reduces cortical blood flow and impairs memory function.	Antibodies against the neutrophil marker Ly6G reduced the number of stalled capillaries, resulting in an immediate increase in CBF and rapid improvement in spatial and working memory tasks.	[55]
Th17	Rat	Not mentioned	Promote inflammation.	Involvement in neuroinflammation and neurodegeneration through pro-inflammatory cytokines and the Fas/FasL apoptosis pathway.	[130]
CD8 ⁺ T lymphocytes	APP/PS1 transgenic mice	Not mentioned	Infiltrate the brains of individuals with Alzheimer's disease and regulate the expression of genes related to neurons and synapses.	Infiltrate the aged and AD brain, and the brain's CD8 ⁺ T-cells may directly contribute to neuronal dysfunction by modulating synaptic plasticity.	[136]
$\gamma\delta$ T lymphocytes	3xTg-AD mice	Not mentioned	The accumulation of IL-17 in the brain and meninges leads to cognitive and synaptic dysfunction.	This may be related to IL-17 and a finely regulated balance of "inflammatory" cytokines derived from the meningeal immune system.	[147]
Tregs	APP/PS1 mice	Not mentioned	Amyloid- β -specific regulatory T cells attenuate the pathobiology of Alzheimer's disease.	Related to the adoptive transfer of TCR $\alpha\beta$ -Tregs, there was sustained immune suppression, reduced microglial reaction, and decreased amyloid loads.	[159]
			Delay disease progression in Alzheimer-like pathology.	It may be related to slowing disease progression and modulating the microglial response to amyloid- β deposition.	[128]
B lymphocytes	Rag-5xFAD mice	Not mentioned	The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function.	This may be related to IgG inducing A β phagocytosis via a Src/Syk/PI3K signal transduction pathway.	[197]
	3xTg-AD mice	Not mentioned	Increased expression of CCR6 in the brain and peripheral immune organs of both pre-symptomatic and symptomatic 3xTg-AD mice.	Unknown.	[206]
NK cells	3xTg-AD mice	Not mentioned	Promote inflammation.	This may be related to the pro-inflammatory function of NK cells.	[47]
	AD patients	AD	Significant negative correlations were found among the spontaneous release of IFN-gamma and TNF-alpha from NK cells and the decrease in the score of cognitive function (MMSE) in patients with DAT.	This may be related to the control of NK cell cytotoxicity and the release of NK-derived cytokines in AD, which could be involved in the neuroinflammatory mechanism related to disease progression.	[245]
Monocytes	Tg2576 mice	Not mentioned	Promote brain perivascular monocytes initiate the neurovascular dysfunction of Alzheimer's A β peptides.	Through the innate immune receptor CD36, which activates a Nox2-containing NADPH oxidase, leading to cerebrovascular oxidative stress.	[292]

have shown improvements in soluble biomarkers, amyloid pathology, and cognitive function, there have been occurrences of amyloid-related brain edema or microhemorrhage, which pose significant risks for a therapeutic drug [286, 287]. The occurrence of these side effects is not only related to T lymphocytes but may also involve monocytes.

During the normal vascular development of the CNS, perivascular macrophages directly interact with developing blood vessels, influencing various stages of the angiogenesis process [288] and aiding in the clearance of vascular A β deposits in AD mouse models [289]. In Cerebral amyloid angiopathy associated with AD, A β deposits along the drainage pathways around cerebral

blood vessels between the endothelium and the basement membrane. Besides the direct disruption of the vascular wall by A β , which increases BBB permeability [279, 284], it also promotes the expression of pro-inflammatory cytokines, exacerbating vascular inflammation and facilitating monocyte-macrophage infiltration. For instance, the use of Bapineuzumab and mouse monoclonal antibody equivalent 3D6 in anti-A β immunotherapy can reduce total A β levels but also induces significant inflammatory responses, enhances vascular permeability, and compromises vascular integrity [290]. Subsequently, Xavier *et al.* discovered that CD169⁺ perivascular mononuclear macrophages could be activated by the 3D6-A β antibody complexes, which is associated with increased

plasma protein leakage and microhemorrhages in PDAPP mice [291]. Deposited amyloid can stimulate the release of reactive oxygen species by monocytes, leading to increased oxidative stress in cerebral vessels [292]. These findings underscore the critical involvement of perivascular mononuclear macrophages in Cerebral amyloid angiopathy-mediated vascular permeability and microhemorrhages associated with amyloid immunotherapy, potentially through amplification of the local inflammatory milieu and remodeling of the extracellular environment around vascular amyloid deposits [293].

Conclusion

Research on the interactions of immune cells, such as neutrophils, T lymphocytes, B lymphocytes, NK cells, and Monocytes is a growing area of interest in AD. The specific ways in which these cells contribute to the development of AD are not fully understood. We have summarized the known or potential roles of peripheral immune cells in AD in Table 3. Studying how neutrophils migrate could provide new insights into their role in AD. Further research is needed to understand the regulatory effects of T lymphocytes, particularly CD8⁺ cells, and their impact on AD. The mechanisms by which CD4⁺T lymphocytes influence MHC-II expression in microglia and their effects on AD require more investigation. The role of Ras signaling in B lymphocytes in AD progression is not well understood and needs more study. Additionally, the activation and infiltration of NK cells in the AD brain through STAT3 signaling needs to be further explored to clarify their role in the disease. The biggest direction for future monocytes in AD research is to further investigate their recruitment, migration and phagocytosis functions to enhance their ability to clear tau and A β proteins and reduce the side effects of anti-A β immunotherapy. Addressing these knowledge gaps could lead to the discovery of new diagnostic markers, therapeutic targets, and preventive strategies for AD.

Abbreviations

A β	Amyloid-beta
AD	Alzheimer's disease
APCs	Antigen-presenting cells
BBB	Blood-brain barrier
BDNF	Brain derived neurotrophic factor
CBF	Cerebral blood flow
CCR	Chemokine receptor
CNS	Central nervous system
IFN	Interferon
IL	Interleukin
MCI	Mild cognitive impairment
MPO	Myeloperoxidase
NE	Neutrophil elastase
NETs	Neutrophil extracellular traps
NFTs	Neurofibrillary tangles
NLR	Neutrophil-to-lymphocyte ratio
NGAL	Neutrophil gelatinase-associated lipocalin
TNF	Tumor necrosis factor

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

No ethical approval is needed.

Consent for publication

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Competing interests

The authors declare no competing interests.

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