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OBM Neurobiology

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Review

The Role of Adaptive Immune Response in Alzheimer's Disease: Focus on Amyloid Beta-Reactive T Cells and Amyloid Beta-Specific Antibodies

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Academic Editor: Fabrizio Stasolla

OBM Neurobiology
2026, volume 10, issue 3
doi:10.21926/obm.neurobiol.2603346

Received: January 03, 2026
Accepted: August 13, 2026
Published: August 21, 2026

Abstract

Alzheimer's disease is one of the most prevalent neurodegenerative diseases among older people. Generally, there are two main pathologies of Alzheimer's disease, including the accumulation of amyloid beta and the hyperphosphorylation of the microtubule-associated Tau protein in the brain. Recently, more studies have discovered that changes in the immune system can be one of the causes of amyloid-beta deposits. Amyloid-beta is a product of the breakdown of the glycoprotein amyloid precursor protein, a transmembrane protein that is cleaved by β-secretase and γ-secretase. In the brain, amyloid-beta deposits can trigger microglia activation, which helps eliminate the deposits. However, microglia activation may induce neuroinflammation by releasing pro-inflammatory cytokines and damage the blood-brain barrier, which can cause an influx of peripheral immune cells, including the adaptive

immune system, into the brain. The role of the adaptive immune system in Alzheimer's disease pathology is quite complicated and may alter due to aging. Aging can directly alter the immune system by reducing protective immunity through reduced production of naïve T cells and increased memory T cells. The increase in memory T cells, which have already recognized specific antigens, such as amyloid beta, may act as amyloid beta-reactive T cells and induce activation and release of amyloid beta-specific antibodies from B cells. This condition increases neuroinflammatory processes. Several drugs that directly target the immune system showed promising results as Alzheimer's disease progressed. However, due to limited data, inconsistent results, and late adverse outcome effects, these drugs still require further research.

Keywords
Alzheimer's disease; amyloid beta reactive T cells; amyloid beta specific antibodies; thymic involution; neuroinflammation

1. Introduction

Alzheimer's disease (AD) is one of the neurodegenerative diseases that occur in old age, with an estimated duration of 10 years for the preclinical stage, 4 years for the prodromal stage, and 6 years for the dementia stage of AD, resulting in a total disease span of approximately 20 years in individuals aged 70 years [1].

The two primary pathogenic mechanisms in AD are the accumulation of the amyloid beta (Aβ) peptide and the hyperphosphorylation of the microtubule-associated Tau protein in the brain [2]. Aβ is formed by the cleavage of the glycoprotein amyloid precursor protein (APP), which is normally present in the brain as a part of the signal transduction process [3]. APP is a transmembrane protein that, after being cleaved by β-secretase and γ-secretase, generates various lengths of Aβ peptides composed of Aβ42 and Aβ40, with Aβ42 being the one that gets converted into Aβ plaques in AD [4]. Imbalances between Aβ biosynthesis and catabolism can lead to accumulation and contribute to cognitive decline in patients with AD [5].

Tau, a microtubule-associated protein, preserves the stability and integrity of the neuronal microtubules [6]. The hyperphosphorylation of Tau results in Aβ accumulation, which is the main cause of Tau protein to oligomerize, dissociate, and create large tau filaments that eventually aggregate into neurofibrillary tangles (NFTs) [7]. Besides Aβ accumulation, NFTs form a barrier to nutrient transport in brain cells, leading to neurodegeneration, and are considered one of the golden hallmarks of AD [8].

However, AD pathogenesis is not only related to the accumulation of Aβ and NFTs. A study by Yamakawa et al. performed an RNA sequencing analysis on elderly patients with AD, mild cognitive impairment (MCI), and normal cognition, which showed that AD might be associated with gene expression, changes in the immune system, cell cycle, and protein processing [9].

Changes in the immune system in elderly people commonly occur during aging. Aging may lower the protective immune system, leading to increased inflammation [10]. This condition is known as immunosenescence, including thymic involution and inflammaging. Thymic involution is a condition

characterized by the decline of naïve T cells that leads to increased memory T cells [11]. This condition could be associated with the role of Aβ-reactive T cells in the brain of AD [12] and could change Treg function [13], while inflammaging is a condition characterized by chronic inflammation caused by cell damage from free radicals, an imbalance in inflammatory cytokines, and cellular senescence [14]. Both thymic involution and inflammaging could be associated with neuroinflammation processes, which exacerbate the AD pathology.

Thus, the review will discuss aging-related changes in the immune system, neuroinflammation, adaptive immune systems, therapeutic implications, and translational challenges. The review aims to improve the understanding of immune mechanisms, especially the adaptive immune system in AD pathology, which hopefully opens the doors of opportunity for researchers to develop the treatments.

2. Aging-Related Thymic Involution (Aging T Cell)

Aging is a part of pathophysiological change characterized by the loss of physiological integrity [15]. Aging is associated with a declining protective immune system combined with an increasing incidence of inflammatory disease, such as cardiovascular disease and neurodegenerative disease, including AD [10]. Age-related reduced immune system function is known as immunosenescence, which includes thymic involution and inflammaging. Thymic involution is characterized by decreased production of naïve T cells caused by a reduction in thymocyte proliferation and increased apoptosis processes in the thymic cortex [11].

A study by Reis et al. showed that aging is linked to a reduction of forkhead box N1 (FOXN1), crucial to the production of naïve T cells [16]. FOXN1 plays an important role as a master regulator of thymic epithelial cells (TECs) in T cell development. The reduction of FOXN1 is associated with the reduction of TEC, leading to reduced thymopoeisis [15]. On the other hand, a study by Wu et al. showed that reduced or impaired thymopoeisis in the thymus of aged mice caused by senescence-associated secretory phenotype (SASP) was responsible for inflammatory processes [17].

Additionally, thymic involution directly impaired negative selection [13]. During T cell development in the Thymus, negative selection is aimed to ensure that T cell entering the periphery can be tolerant to and do not react with “self” antigens [18]. Impaired negative selection due to thymic involution leads to an increased generation of self-reactive T cells [19]. In these cases, there was an increasing number of Aβ-reactive T cells in both AD patients and the elderly. A study by Monsonego et al. exhibited that Aβ-reactive T cell response in the elderly and AD patients was higher than that in middle age. The study by Monsonego et al. assumed that immunodominant Aβ epitopes in humans residing in amino acids 16-33 are identifiable by T cell receptors and have been associated with T cell differentiation in aged people [12].

However, the increased Aβ-reactive T cells in both AD patients and the elderly remain unattainable. This is allegedly caused by a reduction in thymic output, especially naïve T cells, which subsequently decreases peripheral T cell diversity, resulting in elevated memory T cells [20]. A study by Gericke et al. showed an increase of CD45RA-reactivated T effector memory T cells in the blood of AD patients, which indicated an association with the early accumulation of Aβ [21].

3. Aging-Related Inflammaging

Inflammaging is a condition characterized by chronic inflammation occurring in aging and associated with elevated pro-inflammatory cytokines in circulation, such as IL-6, TNFα, and CRP [22]. This aging-related inflammaging is caused by cell damage from free radicals, an imbalance in inflammatory cytokines, and cellular senescence [14].

It is assumed that aging alters the gut microbiota, resulting in elevated lipopolysaccharide (LPS), which can directly stimulate the inflammation process through NF-κB activation [11]. The condition directly alters the composition of gut microbiota. In the intestines of APP/PS1 mice, a change in gut microbiota, or known as dysbiosis, was connected to Aβ deposits in the central nervous system [23].

The possible mechanism of how dysbiosis causes Aβ deposits is related to the release of certain bacterial metabolites, such as the microbially derived metabolite trimethylamine N-oxide (TMAO) by gut microbiota. TMAO can increase β-secretase activity, which aggravates Aβ accumulation [24].

LPS-induced activation of the NF-κB signaling pathway can increase levels of the pro-inflammatory miRNAs, miRNA-146a and miRNA-155, resulting in downregulation of complement factor H expression [25]. To validate the hypothesis, a study by Hasantari et al. confirmed that complement inhibitor factor H, injected into the brain of APP/PS1 AD mice at the early or late stage of AD, showed the reduction of pro-inflammatory IL-6, TNF-α, IL-1β, MAC, and Aβ levels [26].

In addition, activation of the NF-κB signaling pathway can involve inflammasome activation, which activates caspase-1, leading to proteolytic processing and secretion of IL-1β and IL-18, thereby contributing to neuroinflammation [27]. Hence, Aβ deposits in AD are hypothesized to correlate with gut dysbiosis; however, there is still a lack of data, and further research is still required.

4. Neuroinflammation Mechanism in Alzheimer's Disease

APP is an integral transmembrane protein that maintains normal neuronal functions [28]. At a young age, APP is processed mainly through the non-amyloidogenic pathway to produce sAPPα, which promotes cell survival, neurite outgrowth, and synaptogenesis. However, in old age, APP processing shifts toward the amyloidogenic pathway, generating insoluble Aβ [29].

Aβ is a soluble monomer that, in AD pathogenesis, can aggregate into amyloid fibrils, protofibrils, and oligomers. Amyloid beta oligomer (AβO) is considered the primary neurotoxic species in AD development [30]. In the brain, Aβ can make pores that invade the blood-brain barrier, preventing the brain from infection, but it also can form pores in brain cells, leading to cellular damage [31]. Aβ can activate the NLR family pyrin domain-containing 3 (NLRP3) inflammasome in microglial cells through nuclear factor kappa beta (NF-κB). This inflammasome activation promotes the production and release of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and IL-18, both of which induce pyroptosis, a programmed cell death [32].

Microglial exposure to Aβ increases IL-1β. Elevated IL-1β is associated with elevated caspase-1, and Caspase-1 is a part of the family of intracellular proteases and regulated by signal-dependent autoactivation of the inflammasome [33]. Caspase-1 acts as a cleavage of the precursor pro-IL-1β into IL-1β. In the brains from AD patients and APP/PS1 mice, a high level of active caspase-1 was found. Deficiency of caspase-1 in APP/PS1 mice appeared as a protective effect by skewing microglial cells from a pro-inflammatory M1-like phenotype to an M2-like phenotype [34]. Furthermore, the inflammatory cytokine IL-1β significantly reduces the expression of low-density

lipoprotein-related protein 1 (LRP1), which reduces Aβ clearance in the brain. Such a condition is associated with Aβ deposition, which can trigger a neuroinflammation process [35].

Neuroinflammation is defined as acute or chronic inflammation in the central nervous system (CNS) due to the increased inflammatory cytokine levels caused by infection, trauma, or neurodegenerative diseases. The neuroinflammation mechanism in AD is mediated by various peripheral white blood cells, including innate (NK cells and neutrophils) and adaptive immune systems (T cells and B cells) [36].

In vitro, using two transgenic models of AD (5xFAD and 3xTg-AD mice), neutrophils were found to extravasate into the brain and to be present in areas with Aβ deposits, where they released neutrophil extracellular traps that damaged the blood-brain barrier (BBB) and induced inflammation [37]. On the other hand, natural killer (NK) cells can release cytotoxic molecules and inflammatory cytokines, including granzymes, cathepsins, perforins, IFN-γ, and TNF-α [38]. In the brains of 3xTg-AD mice, NK cells were shown to contribute to the inflammation profiles, while depletion of NK cells by anti-NK1.1 antibodies showed drastically reduced inflammation and improved cognitive function of 3xTg-AD mice [39].

5. Adaptive Immune Mechanisms (Aβ-Reactive T Cells, Aβ-Specific Antibodies, and Complements) in Alzheimer's Disease

Aβ in the brain can be recognized by microglia through specific receptors, such as the class A1 scavenger receptor (SCARA1), cell-surface cluster of differentiation (CD) markers (CD36, CD14, CD47), α6β1 integrin, and Toll-like receptors [40]. Microglia, as one of the cerebral innate immune cells, can act as antigen-presenting cells (APC). As APCs, microglia, which already express Aβ on the surface, can be recognized by T cells [41].

In normal conditions, T cells cannot enter the brain because they are blocked by the BBB. However, due to the neuroinflammation process, the BBB can be damaged, resulting in an influx of peripheral immune cells, such as T cells [36]. Peripheral T cells migrate to the brain by binding α4β1-integrin on the surface of peripheral $CD4^+$ T lymphocytes to vascular cell adhesion protein 1 (VCAM-1) in the BBB [42]. Moreover, epithelial cells of the BBB express MHC-I, which can promote migration of cytotoxic T lymphocytes (CTLs) into the brain [43]. In the brain, CTLs can release cytotoxic granules, such as perforin and granzymes, which contribute to further BBB damage [44].

In the brain, T cells, especially T helper (Th) cell subsets including Th1 and Th17, which recognize Aβ, are called Aβ-reactive Th1 and Aβ-reactive Th17 (Figure 1). A study by Browne et al. demonstrated that the brain of APP/PS1 mice exhibited accumulation of Aβ-reactive Th1 and Aβ-reactive Th17, but, of the two cells, only Aβ-reactive Th1 showed a significant correlation with cognitive function deficit [45].

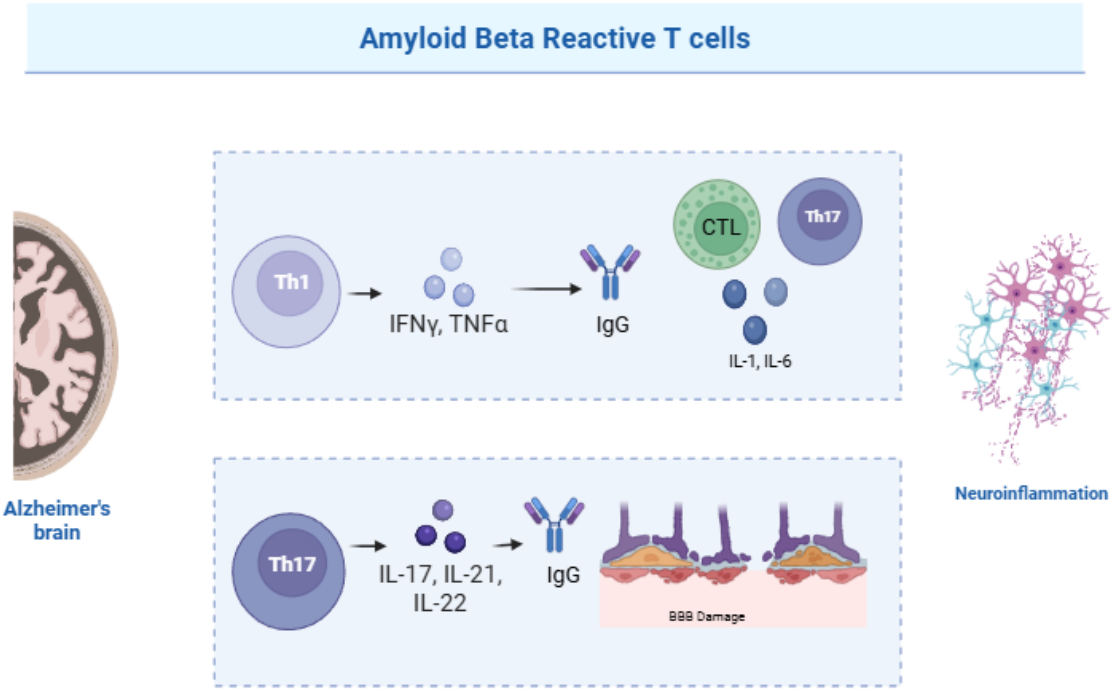

Figure 1 Role of Aβ-reactive T cells in AD. Differentiation of Aβ-reactive Th1 cells releases TNF-α and IFN-γ, which promote neuroinflammation through IgG production, CTL and Th17 differentiation, and release of IL-1 and IL-6. Differentiation of Aβ-reactive Th17 cells led to the release of IL-17, IL-21, and IL-22, which increased BBB damage and IgG production. Created by BioRender.

These Aβ-reactive Th1 cells release pro-inflammatory cytokines, such as IFN-γ and TNF-α [46]. Interferon-γ (IFN-γ) can modulate IgG antibody production by using myelin oligodendrocyte glycoprotein (MOG)-specific B cells, induce $CD8^+$ T cells [47], regulate $CD4^+$ T cell differentiation toward Th17 [26], and enhance microglial phagocytosis and activation [48]. Administration of neutralizing IFN-γ antibody reverses the outcome of Aβ-reactive Th1 cells and Aβ deposits [41].

Tumor necrosis factor-α (TNF-α) plays fundamental roles in modulating excitotoxicity, BBB permeability, oligodendrocyte survival, myelin formation, and repair [49]. However, dysregulated TNF-α production can promote neurodegenerative disease [50]. The role of TNF-α in AD remains incompletely understood, but it may contribute to chronic brain inflammation [49]. A study by Llano et al. showed that cerebrospinal fluid (CSF) pro-inflammatory cytokines, such as IL-1β, IFN-γ, and TNF-α in patients with AD have been confirmed to be highly elevated compared to age-matched control subjects [51]. Such confirmation reveals that when TNF-α binds TNFR2, the binding can induce PI3K/NF-κB pathway activation, which leads to the production of other pro-inflammatory cytokines, such as IL-1 and IL-6 [49].

Aβ-reactive Th17 in the brain can produce and release IL-17, IL-22, and IL-21 [52]. IL-17, especially IL-17A, increases neutrophil infiltration and microglial activation [53]. A study by Cao et al. demonstrated that in APP/PS1 mice, IL-17A through the TLR4/NF-κB signaling pathway can increase TNF-α levels in the brain and exacerbate neuroinflammation, inhibiting microglia phagocytosis and promoting the deposition of Aβ 42 [54].

Interactions between IL-17 and IL-22 can reduce occludin and zonula occludens-1 (ZO-1), tight junction proteins involved in endothelial cell defence, thereby causing damage to the BBB [55]. The

release of IL-21 stimulates B lymphocytes to produce antibodies and switch classes from IgM to IgG [56]. In addition, Aβ-reactive Th17 activation leads to the extrinsic apoptotic pathway by binding the ligands to the receptors, which can cause more neuronal death [57].

B cells can be activated and mediated by the $CD4^+$ T cell subset of T follicular helper cells (Tfh cells). These B cell activation Aβ-specific antibodies included IgM and IgG (Figure 2) [58]. A study by Agrawal et al. showed that the plasma patients with AD exhibit Aβ-specific IgM and IgG compared to aged subjects. However, the level of Aβ-specific IgM has been observed to be lower than Aβ-specific IgG. This occurrence is caused by IL-21, the major cytokine in class switching [59].

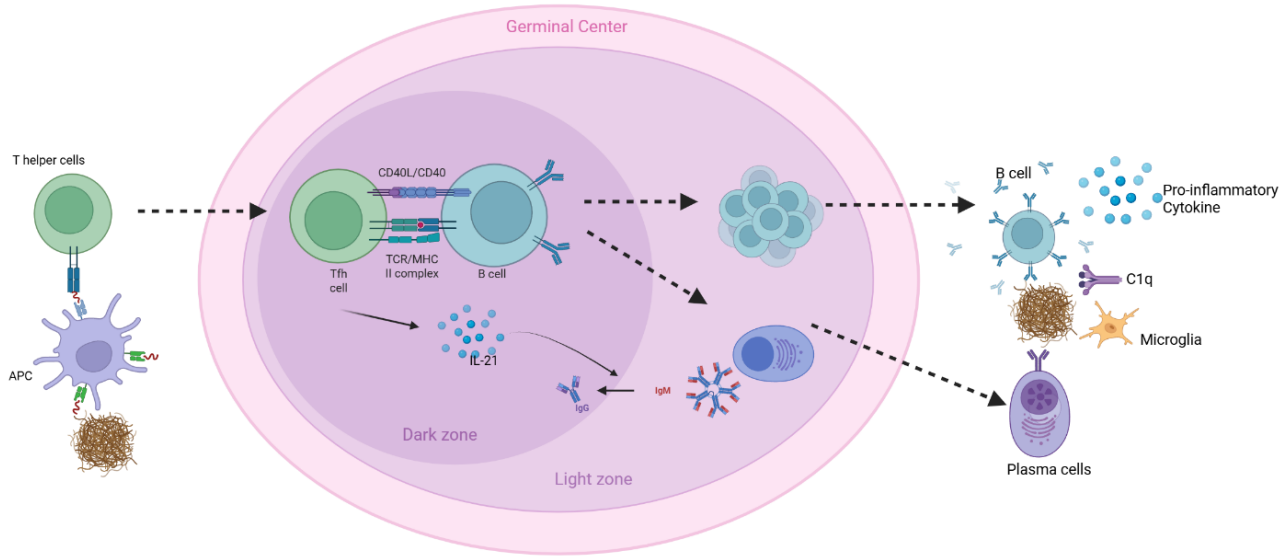

Figure 2 Role of B Cells in AD. Activation of B cells by Tfh promotes B cell proliferation, the production of pro-inflammatory cytokines, the activation of the complement system, and the production of Aβ-specific antibodies by plasma cells. Created by BioRender.

According to a study by Lekhraj et al., Aβ-specific IgGs, typically found in the sera of AD patients and the elderly, were predominantly Aβ-specific IgG1 and Aβ-specific IgG3 in the early stage, while, in the late stage, they were predominantly Aβ-specific IgG2 and Aβ-specific IgG4. Aβ-specific IgG1 and Aβ-specific IgG3 have been suggested to exert pro-inflammatory effects that benefit amyloid pathology and neurotoxicity. Elevated Aβ-specific IgG2 may be related to Aβ-specific IgG4 [60]. Higher Aβ-specific IgG4 levels in related diseases, such as AD, are similar to those observed with IgG4 antibodies targeting antigens, especially Aβ. The targeted effect induced blocking interactions with the target antigen, leading to increased disease progressivity [61].

Elevated levels of Aβ-specific IgG antibodies can activate the complement system (Figure 2) [62]. Complement is part of the innate immune system and consists of the classical, alternative, and lectin pathways. Aβ-specific IgG antibodies can activate the classical pathway mediated by C1q [63]. In the aging human brain, C1q levels are substantially found to be higher near hippocampal synapses. This finding is also found in the human AD brain [64]. Evidence from animal models has supported this hypothesis as well. A study by Hong et al. observed elevated C1q levels in the brains of J20 AD model mice, a finding also observed in 3xTg AD models. Elevated C1q levels increase amyloid plaque deposits and synapse loss [65].

Complement activation acts as a "double-edged sword" that has both neuroprotective and neuroinflammatory functions in AD [66]. The neuroprotection function involving C1q is mediated by inducing a signaling pathway to repair neurons through the phosphorylation of CREB [67]. Phosphorylated CREB stimulated the synthesis of brain-derived neurotrophic factor (BDNF), which is one of the main modulators for synaptic plasticity, preserving long-term memory, and promoting neurogenesis [68].

In contrast, activation of C1q is followed by the release of other classical complement components, such as C3a. Interaction between C3a and C3a receptors (C3aR) on neurons and microglia leads to defective synaptic function through intraneuronal calcium dysregulation and impaired microglial phagocytic function, resulting in Aβ deposits and synapse loss [66]. In addition, C1q can induce an A1 phenotype in astrocytes, which contributes to secondary inflammatory processes and neuronal or oligodendrocyte death by secreting neurotoxins and losing neurotrophic functions, such as promoting neuronal growth, synapse formation, and phagocytosis [69].

6. Treg Production and Function in Alzheimer's Disease

Regulatory T cells (Tregs) are a subset of T cells that suppress the immune system, maintaining homeostasis and self-tolerance, especially peripheral tolerance. In the brain, Treg cells can directly inhibit the neuroinflammation process and ameliorate Aβ deposits [70]. A study by Yang et al. showed that Aβ-specific regulatory T cells that were transferred into 3xTg-AD mice may represent an inhibitory effect on microglial pro-inflammatory activity, which can effectively inhibit neuroinflammation and Aβ deposits during AD pathology [71].

Treg cells are assumed to modulate microglia, promoting a switch from M1 to M2 phenotypes, thereby making microglia more anti-inflammatory [72]. Additionally, Treg cells maintain peripheral immune tolerance by secreting inhibitory cytokines (IL-4 and IL-10), modulating the IL-2 signaling pathway, and disrupting T cell activation [73]. Interleukin-4 (IL-4) can inhibit Th1 cells and promote Aβ clearance via the scavenger receptor CD36 and the Aβ-degrading enzyme neprilysin [74]. The interleukin-2 (IL-2) signaling pathway is one of the pathways to promote and regulate Foxp3 and CD25, which can create a positive feedback loop for transcriptional and Treg production [75].

IL-10 is one of the inhibitory cytokines that can downregulate the inflammation response, including microglial activities in the brain [76]. In the brain, IL-10 can stimulate the shift in differentiation of microglia to the M2 phenotype, which has a more anti-inflammatory effect, resulting in the inhibition of the neuroinflammation process [77]. However, the proper function of IL-10 in AD has not been fully understood. A study by Kiyota et al. demonstrated that IL-10 overexpression in the hippocampus of APP+PS1 mice can increase neurogenesis and cognition, which provides evidence for a possible neuroprotective role [78]. Conversely, Guillot-Sestier et al. reported an opposite effect of IL-10. APP/PS1 mice deficient in IL-10 have been found to reduce IL-10/STAT3 signaling, enhancing microglia phagocytic activity toward Aβ, which may be effective for AD treatment [79]. Therefore, the current work requires further research toward IL-10 role in AD, a constant reminder that research subjects are typically of diverse conditions.

Treg can increase expression of co-stimulatory CTLA4 on the cell surface, which can suppress T cell activation by binding to the CD80 and CD86 ligands [80]. However, this immunosuppressive effect of Treg cells has yielded inconsistent results in AD [81]. A study by Rosenkranz et al. reported that Treg isolation from AD patients showed enhanced suppressive activity [82]. In contrast, a study

by Faridar et al. showed that Treg isolated from moderate to severe AD patients exhibit impaired suppressive activity associated with reduced CD25 expression [73]. These discrepancies suggest Treg function may differ depending on disease stage and methodological approach [81].

One factor that can lead to differences in Treg functions is aging. Aging can directly change Treg ability [13]. First, it occurs during thymic involution [83]. This condition increases IL-6 production, a pro-inflammatory cytokine [84], which transmits suppressive signals to TECs, reducing thymopoiesis and cellularity [85]. Second, the overall endocrine changes in the aged, such as an increased level of glucocorticoids, positively affect the increase in Treg frequency and accumulation [86] but change Treg function to be less suppressive and more Th1-like cells (Figure 3) [87]. This change is associated with an inhibitory effect on the differentiation of new Treg cells [88] and on Treg function, which can only suppress certain T cells while leaving others unaffected [86].

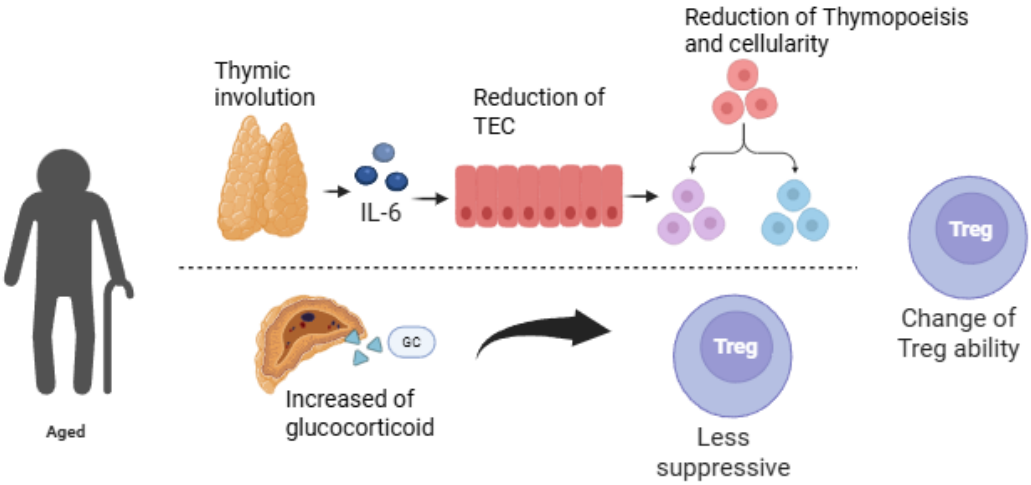

Figure 3 Change of Treg ability caused by aging is mediated by the thymic involution process and increased production of glucocorticoids.

7. Therapeutic Implications and Translational Challenges

Generally, there are four main drugs for AD: donepezil, rivastigmine, galantamine, and memantine. These drugs only improve cognitive abilities but cannot prevent the progression of AD [89]. These limitations highlight the need for alternative therapeutic strategies by targeting neuroinflammation or immune dysregulation processes.

Administration of an anti-IL-17A antibody to block IL-17A in an AD mouse model can decrease the neuroinflammation induced by Aβ-42 injection. These results are followed by reduced neurodegeneration processes and improved cognitive impairment [90]. Blocking IL-17A may prevent the expression of TNFα, IL-6, or other pro-inflammatory cytokines [91]. However, other studies have shown the opposite, indicating that administering or overexpressing IL-17A in an animal model of AD can play a protective role by reducing cerebral amyloid angiopathy, improving glucose metabolism, alleviating learning deficits, and decreasing soluble Aβ levels in the hippocampus and CSF [92].

These findings indicate that the role of IL-17A in AD is complex, suggesting it may have both protective and pathogenic roles depending on the disease stage [53]. In addition, the possible reasons for the role of IL-17A in AD therapy remain inconclusive, caused by a lack of validation of AD-specific animal models, which represents a major barrier to translation, and a poor

understanding of immunological pathway interactions with Aβ, which underlie the therapeutic effect [93].

A study by Yang et al. demonstrated that injecting Aβ-specific human Tregs in 3xTg mouse models of AD and in phase I clinical trials with six AD patients suggests that Aβ-specific human Tregs may modulate AD pathology by suppressing neuroinflammation and that the approach is well tolerated. However, the effectiveness did not reach statistically significant levels across the groups, providing insights into AD treatments and future research [94].

Besides anti-IL-17A and Aβ-specific human Treg, monoclonal antibodies, such as aducanumab and lecanemab, have already been approved by the Food and Drug Administration as one of the drugs for AD [95]. Aducanumab is a human monoclonal antibody that selectively targets aggregated Aβ. In both a transgenic mouse model of AD and human patients with AD, aducanumab can cross the blood-brain barrier, bind to parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose- and time-dependent manner, leading to positive treatment effects. However, during routine brain imaging, an amyloid-related abnormality, considered a safety concern, is observed [96]. Lecanemab is a humanized IgG1 monoclonal antibody that specifically binds to large, soluble Aβ protofibrils. In clinical trial phases I through III, lecanemab showed a positive result with a lack of adverse effects, successfully reducing brain amyloid and improving cognitive decline. However, the side effects of lecanemab therapies will only be evident during routine MRI scans. The side effects of lecanemab were observed among 21% of the patients whose MRI brain imaging resembles ARIA, which may cause brain atrophy characterized by ventricle enlargement [95].

8. Conclusion and Future Directions

AD is one of the neurodegenerative diseases characterized by the accumulation of Aβ in the brain. AD is commonly observed in ages that may be associated with thymic involution. This thymic involution may directly reduce naïve T cells and increase memory T cells, which are recognized as Aβ-specific (Aβ-reactive T cells), leading to a neuroinflammatory process by releasing pro-inflammatory cytokines and activating B cells to produce Aβ-specific antibodies. Generally, the drugs used in AD treatment only improve cognitive abilities but cannot prevent the progression of AD. These limitations underscore the need for alternative therapeutic strategies targeting neuroinflammation or immune dysregulation. Several drugs, such as anti-IL-17A, Aβ-specific human Treg, and monoclonal antibodies, including aducanumab and lecanemab, showed promising results, even though there were still adverse effects and inconsistencies. These clinical limitations could serve as a catalyst for researchers to develop the drug and control its adverse effects.

Abbreviations

Aβ	Amyloid Beta
AβO	Amyloid Beta Oligomer
AD	Alzheimer's Disease
APC	Antigen Presenting Cell
APP	Amyloid Precursor Protein
BBB	Blood Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
C3aR	C3a Receptor

CD	Cluster of Differentiation
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTL	Cytotoxic T Lymphocyte
FOXN1	Forkhead box N1
IFN-γ	Interferon-γ
IL-1β	Interleukin-1β
MCI	Mild Cognitive Impairment
MOG	Myelin Oligodendrocyte Glycoprotein
NFTs	Neurofibrillary Tangles
NF-κB	Nuclear Factor Kappa Beta
NLRP3	NLR Family Pyrin Domain Containing 3
NK	Natural Killer
SCARA1	The class A1 Scavenger Receptor
TCR	T Cell Receptor
TECs	Thymic Epithelial Cells
Tfh cells	T Follicular Helper Cells
Th	T Helper
TMAO	Trimethylamine N-oxide
TNF-α	Tumor Necrosis Factor-α
Treg	Regulatory T cells
VCAM-1	Vascular Cell Adhesion Protein 1
ZO-1	Zonula Occludens-1

Author Contributions

Helen Cyntia Mago was responsible for the conceptualization, writing, review and editing. Valentinus Besin was responsible for review and supervision. Astuti Prodjohardjono was responsible for review and supervision. Amelia Nur Vidyanti was responsible for review and supervision. Waode Fifin Ervina was responsible for project development. Farizky Martriano Humardani was responsible for project development. Lisa Thalia Mulyanata was responsible for graphic design.

Competing Interests

The authors have declared that no competing interests exist

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