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Mini-Review

A glance through the effects of CD4$^+$ T cells, CD8$^+$ T cells, and cytokines on Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia. Unfortunately, despite numerous studies, an effective treatment for AD has not yet been established. There is remarkable evidence indicating that the innate immune mechanism and adaptive immune response play significant roles in the pathogenesis of AD. Several studies have reported changes in CD8$^+$ and CD4$^+$ T cells in AD patients.

This mini-review article discusses the potential contribution of CD4$^+$ and CD8$^+$ T cells reactivity to amyloid β (Aβ) protein in individuals with AD. Moreover, this mini-review examines the potential associations between T cells, heme oxygenase (HO), and impaired mitochondria in the context of AD. While current mathematical models of AD have not extensively addressed the inclusion of CD4$^+$ and CD8$^+$ T cells, there exist models that can be extended to consider AD as an autoimmune disease involving these T cell types. Additionally, the mini-review covers recent research that has investigated the utilization of machine learning models, considering the impact of CD4$^+$ and CD8$^+$ T cells.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia that normally starts in late life [1]. Despite decades of intensive research on AD, there is still a lack of effective strategies to prevent and treat AD [2]. A study by Jia et al. [3] investigated the socioeconomic costs of AD in China, collecting data from 3,098 AD patients and estimating the worldwide costs associated with AD. According to their findings, the annual cost for an individual was estimated to be US $19,144.36 and the total cost was US $167.74 billion in 2015. Based on their prediction, the annual total cost will rise US $507.49 billion in 2030 and US $1.89 trillion in 2050. Therefore, it is vital to develop effective strategies aimed at reducing the prevalence of AD and improving its medical treatment.

T cells, one element of the adaptive immune system, mature in the thymus. When pathogens are present, they become activated [4,5]. Naïve T cells can be activated by antigens, leading to their proliferation and differentiation into effector cells [6]. Effector T cells have three main activities when detecting antigens: cytotoxic T cells kill infected cells, helper T cells activate other cells with cytokines, and regulatory T cells (Tregs) suppress lymphocyte activity to limit damage from an immune response [7]. Effector T cells fight the infection and subsequently die off. However, infection also leads to the development of long-lived memory T cells, which can promptly recognize and respond to the pathogen upon subsequent exposure [8,9]. Some B cells and T cells, stimulated by an antigen, differentiate into memory cells. Upon reexposure to their specific antigen, memory cells can easily develop into effector cells [7]. In the supernatants of activated T cells, interleukin-2 (IL-2) was discovered as a T cell growth factor in 1976 [10,11]. Autoimmune disorders are characterized by the immune-mediated attack on healthy tissue, often due to a misdirected immune response to self-antigen [12]. Tregs play an important role in suppressing the activation of immune system and maintaining immune homeostasis and self-antigen tolerance [10]. The blood-brain barrier (BBB) keeps the central nervous system (CNS) immune privileged [13]. As individuals age, the stability of the BBB diminishes, leading to its leakage. AD worsens this failure of BBB integrity, allowing peripheral immune cells to enter the brain [14,15]. Numerous pathological factors can contribute to BBB breakdown, such as oxidative stress, neuroinflammation, immune system cells, and different types of pathogens [16,17]. Oxidative stress plays an important role in the changes in the BBB. Oxidative stress can damage a variety of cells including BMVECs, pericytes,

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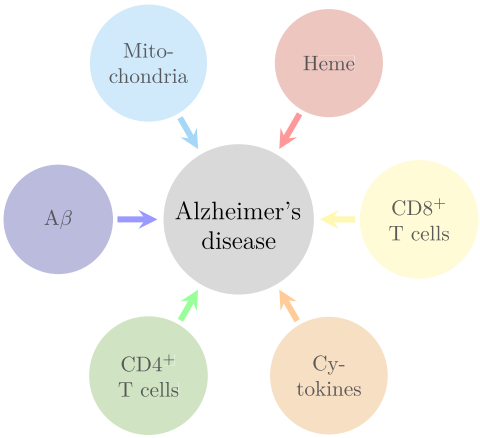

Fig. 1. Figure highlights topics studied in this mini-review paper.

and astrocytes, destroying the BBB [16]. The brain itself has been found to regulate or shape immune responses therein, and immune cells have a part in the progression of AD [18,19]. The innate immune system and the adaptive immune system are both involved in the pathology of AD. Postmortem AD patients' brain parenchyma has revealed the presence of T cells, and T cell abnormalities have been detected in the blood and cerebral spinal fluid of AD patients [20–23]. In comparison to the non-AD control group, the majority of AD patients exhibit a higher occurrence of T cells in the brain parenchyma [22]. Numerous studies have provided evidence to suggest the involvement of $CD4^+$ T cells, $CD8^+$ T cells, and cytokines in AD pathogenesis [24–29].

Many mathematical models have been proposed to study the progression of AD without considering T cells activity [30–35]. This highlights the importance of gaining a better understanding of the role of T cells in the pathogenesis of AD. Exploring potential mathematical models [4,5,36] may provide valuable insights into the complex mechanisms of the disease, with a particular emphasis on the contributions of T cells and cytokines. This mini-review provides a comprehensive summary of the various changes observed in $CD4^+$ and $CD8^+$ T cells, cytokines, as well as the involvement of innate and adaptive immune responses in AD. By investigating the connections between heme oxygenase (HO), $CD4^+$ and $CD8^+$ T cells, and dysfunctional mitochondria, this study aims to provide insights into the interplay of these factors and their contribution to AD pathogenesis. It summarizes mathematical models that can be extended to AD as an autoimmune disease, providing a framework for studying immune dysregulation. Additionally, the mini-review highlights the relevance of machine learning models in AD research, with a specific focus on the involvement of $CD4^+$ and $CD8^+$ T cells. Fig. 1 illustrates the explored topics in the mini-review article.

2. Amyloid β in AD and its relation to the immune response

AD is characterized by the accumulation of Aβ deposition, tau pathology and neuroinflammation [37]. Therefore, the main objective of Aβ immunotherapy is to decrease the formation, spread, and deposition of Aβ aggregates in the human brain [38]. Numerous studies have demonstrated that antibodies against Aβ can robustly clear amyloid plaques and slow cognitive decline in AD [39–42]. Currently, several targets are under investigation for active vaccine therapy in AD. Immunization procedures against Aβ deposition account for about 85% of reported cases, while 15% are against tau. However, no AD vaccine has received the Food and Drug Administration (FDA) approval as of yet [43,44]. Aβ immunotherapy is useful in the reduction of Aβ deposition in relatively young mice, while it is less useful in older mice [45]. While Aβ42 immunization resulted in clearance of amyloid plaques, it did not stop progressive neurodegeneration [46]. The FDA provided full approval for lecanemab (Leqembi), an Aβ–directed antibody, in July 2023 for the treatment of AD [47]. Lecanemab decreased markers of amyloid in early AD and led to moderately less decline in cognitive and functional measures compared to a placebo at 18-months. However, it was linked to adverse events. Extended trials are needed to determine the effectiveness and safety of lecanemab in early AD [48]. Aducanumab, the anti-Aβ antibody that FDA has approved, appears more effective than certain other candidate anti-Aβ antibodies that do not bind to newly formed plaques to inhibit the seeding of Aβ oligomers in a mouse model [42,49,50]. However, up to 40% of AD patients who received a high dose of aducanumab (10 $mgkg^{-1}$) exhibited amyloid-related imaging abnormalities (ARIA), including brain edema and hemorrhage. It has been proposed that antibody therapy can trigger non-specific immune cell activation and Fc receptor (FcR)-mediated pro-inflammatory responses [41,51,52]. Although Aβ immunization has some advantages, such as reducing cognitive malfunction, according to Janus [53], it can also cause cerebral bleeding and a massive Th1 response [54]. Active immunotherapy produces high-concentration antibodies with fewer injections and lower costs compared to passive immunotherapy, but passive immunotherapy is considered more effective for elderly patients with reduced vaccine responsiveness [55]. However, passive immunization needs costly production of humanized monoclonal antibodies and monthly injections, making it less practical for long-term treatment of a large population compared to active immunization [56]. Early active immunization with Aβ3–10-KLH vaccine decreases tau phosphorylation in the hippocampus and protects cognition of mice [57]. Despite promising preclinical results in animal models, several immunotherapeutic approaches have failed in clinical trials as they did not demonstrate beneficial effects in treating or slowing down the progression of the disease [38]. It cannot be denied that immunotherapy may represent the most advanced disease-modifying strategy for AD treatment, but its issues still need to be addressed [55].

The immune system plays a vital role in defending the organism against both external and internal challenges [58]. The Aβ-reactive T cells have been described in AD [59–64]. While Aβ deposition occurs in elderly individuals without AD signs, patients with AD consistently exhibit increased T cell reactivity to Aβ, unlike the elderly individuals without AD [59]. The reactivity of T cells to Aβ is believed to have either positive or negative effects [60]. Aβ-reactive T cells can directly facilitate the clearance of Aβ. Immune infiltrates in the brain, along with activated microglia and macrophages, can clear Aβ, with greater efficiency for Aβ1–40 than Aβ1–42 [61]. Aβ-reactive effector T cells contributed to the progression of AD pathology by downregulating anti-inflammatory and immunosuppressive Tregs in the periphery and within the central nervous system [62]. Aβ-reactive T cells can enhance the phagocytic activity of neighboring microglia through the expression of triggering receptor expressed on myeloid cells 2 (TREM2) and signal regulatory protein beta-1 (SIRPb1), which are induced by IFN-γ [60,61,63,64]. Activated innate immune cells may cause programmed cell death. The cell death often results in the release of proinflammatory cytokines that increase the innate immune response and can eliminate Aβ plaques and aggregated tau proteins. However, chronic neuroinflammation, often brought on by cell death, can worsen AD [65]. Aβ deposition in the brain activates innate immunity [66,67], making microglia autotoxic and resulting in the destruction of neighboring neurons, causing cognition problems in AD [67]. Microglia play a role in the clearance of Aβ, which is advantageous in preventing Aβ buildup but becomes harmful when Aβ levels are increased, leading to prolonged inflammation [37]. In the human brains, the classically, inflammatory activated microglia (M1) and an alternative, anti-inflammatory phenotype (M2) are present and are hybrids of these two phenotypes [68,69]. In AD, M1 microglia are thought to promote inflammatory damage while M2 microglia possess neuroprotective properties. The development of AD is significantly accelerated by imbalanced microglial polarization, which is in the form of excessive M1 microglia activation and M2 microglia dysfunction [70,71]. Balancing M1 and M2 microglia

or promoting the shift from M1 to M2 might have therapeutic potential for AD treatment [72]. For the first time, Kim et al. [73] showed that low-dose ionizing radiation (LDIR) regulates LPS- and Aβ-induced neuroinflammation triggered by enhancing M2 polarization through TREM2 expression, with positive effects on AD-related factors such as Aβ accumulation and memory loss.

B cells are another important type of lymphocyte within vertebrate immune system. They express a different type of antigen receptor compared to T cells and play distinct roles in the immune system [7]. Until now, the majority of research has concentrated on the innate immune responses of microglia. However, emerging evidence implicates adaptive immune responses by T cells and B cells in the progression of AD [74]. The activation and expansion of T cells in response to Aβ have been found in AD patients and the elderly control group. This may occur because local antigen-presenting cells (APCs) can capture Aβ [59]. Antigens are presented to T cells by mature APCs expressing high major histocompatibility complex (MHC) class I and class II molecule expression levels in order to prime and activate T cells [60]. B cells recognize antigens through unique rearranged B cell receptors (BCR) [74]. According to Kim et al. [75], AD is associated with the accumulation of activated B cells in circulation, and their infiltration into the brain parenchyma, leading to the deposition of immunoglobulins around Aβ plaques. A crosstalk has been suggested between the adaptive immune system and microglial cells. The ablation of functional T and B cells reduces brain Aβ pathology and Aβ levels while increasing microgliosis and the removal of Aβ aggregates [76]. The use of murine transgenic models has revealed that AD progression requires B cells. The elimination of B cells alone decreases Aβ plaque burden and disease-associated microglia. It also reverses behavioral and memory deficits and restores TGF-β^+ microglia [75].

3. Certain populations of T cells and cytokines in AD

Both CD4$^+$ T cells and CD8$^+$ T cells respond to an antigen in association with MHC class II or class I molecules, respectively [77]. Some studies have suggested the presence of two distinct types of CD4$^+$ T cell: T helper (Th1) type 1 and T helper type 2 (Th2) [78–80]. Harrington [81] later described a subset of interleukin (IL)-17-producing T (Th17) cells distinct from Th1 or Th2 cells. In addition to Th1, Th2, and Th17 cells, several other subsets of CD4$^+$ T cells have been identified, including Tregs, Th9 cells, and Th22 cells [82]. The immune system has two distinct subsets of Tregs, namely natural Tregs (nTregs) and induced Tregs (iTregs). These subsets differ in their developmental origin, with nTregs originating as a distinct lineage in the thymus, iTregs emerging from peripheral naïve conventional T (Tconv) cells [83,84]. Three types of iTregs have been described based on the cytokines that induce their development: iTr-TGF-β, iTr-IL-10, and iTr-IL-35 (iTr35) [85,86]. Memory T cells are diverse, and both CD4$^+$ and CD8$^+$ T cells can be classified into four main subsets: Central memory T cells (TCM), effector memory T cells (TEM), tissue-resident memory T cells (TRM), and terminal effector (TEMRA) [7,87]. A reciprocal increase in late-differentiated memory cells is also significantly higher in AD patients than in age-matched controls [25].

Several T cell population are involved in AD pathology (see Table 1). Some studies have highlighted the significance of CD4$^+$ T cells, CD8$^+$ T cells, and cytokines as key contributors to the pathogenesis of AD [24,88–90]. Patients with late-onset AD (LOAD) have been found to have higher levels of CD4$^+$ and CD8$^+$ T cells [88]. High levels of activated CD4$^+$ and CD8$^+$ T cells in the peripheral blood are strongly associated with cognitive impairment and abnormalities on magnetic resonance imaging (MRI) of specific brain regions in AD patients [24,89]. CD4$^+$ T cells produce nerve growth factor (NGF) [91]. NGF reduces the pro-inflammatory responses of microglia, which may help regulate microglia-mediated neuroinflammation [92]. The effects of CD4$^+$ T cells on neurodegeneration vary depending largely on their subsets [90].

3.1. The role CD4$^+$ T cells in AD

Naïve CD4$^+$ T cells differentiate into distinct subsets of Th cells in response to various stimuli. These Th cells secrete several cytokines that can have both protective and harmful effects on the CNS [104]. Aβ-specific CD4$^+$ Th1 cells have the ability to stimulate a MHC II$^+$ population of microglia, which can abrogate AD-like pathology in a mouse model, possibly through the signaling of interferon γ (IFN-γ) cytokine [90,105]. When injected into the ventricles of APP/PS1 animals, Aβ-specific Th1 cells increased microglial clearance of amyloid plaque and decreased pathology [105,106]. In contrast, injecting Aβ-specific CD4$^+$ Th1 and Th17 cells into the brains of APP/PS1 mice exacerbates the levels of Aβ, microgliosis, neuroinflammation, and cognitive impairment [62,90]. Aβ-specific Th1 or Th17 cells increased the production of inflammatory cytokines and MHC class II and co-stimulatory molecule expression on Aβ-treated microglia. Additionally, Th2 cells reduced cytokine production by Th1 and Th17 cells and diminished the activation of microglia by these T cells [93]. Through interaction and cytokine secretion, T cells can control the activity of their APCs and neighboring cells. When Th1 and Th17 cell types generate pro-inflammatory cytokines, it might negatively influence neighboring neurons or glial cells via the bystander effect, amplifying the inflammatory environment in AD. Moreover, the transfer of Aβ-specific Th2 cells is beneficial, reducing cognitive problems and amyloid buildup in blood vessels in a mouse model [94,95].

Various research studies have illustrated the impacts of Tregs in AD [102,103,107–110]. Tregs have an influence on cognitive function, reducing Aβ deposition and inflammatory cytokines. In contrast, when Tregs are depleted, it accelerates the onset of cognitive deficit, increases the Aβ burden, enhances the responses of microglia/macrophages, and decreases glucose metabolism in 3xTg-AD mice [102]. The frequency of Tregs (CD4$^+$Foxp3$^+$) rises with age and is accompanied by elevated suppressive action for Tregs in patients, as observed in an analysis of Tregs from both AD patients and unaffected individuals. Higher Tregs activity or numbers may suppress any favorable immune effector mechanisms and affect AD [103]. Treg-mediated systemic immune suppression worsens AD pathology. Transient reduction of Tregs or pharmacological inhibition of their activity leads to the clearance of Aβ plaques, reduction of neuroinflammation, and the reversal of cognitive decline [107]. Shalit et al. [27] reported a doubled IL-2 secretion in moderately severe AD group compared to mild-stage patients and control, which is mainly due to the fact that CD4$^+$ T cells secrete IL-2. Numerous studies have explored the effects of IL-2 in AD pathology [108–110]. Reduced IL-2 levels have been observed in hippocampus biopsies of AD patients. IL-2 and Tregs levels are elevated in mice following peripheral IL-2 delivery. IL-2 treatment rescues memory impairment, restores impaired synaptic plasticity, and alleviates hippocampal amyloid pathology in mice [108,110]. In APPPS1 mice, amplification of Tregs by low dose IL-2 therapy boosts the number of plaque-associated microglia and improves cognitive abilities [109,110]. Moderately severe AD showed a notable rise in IL-2 and IFN-γ secretion. In the mild stage of the disease, there was a significant decrease in IL-3 and tumor necrosis factor (TNF) levels. The production of interleukin-1 (IL-1β) did not show significant variations [26]. IL-3 prevents neuronal death induced by fibrillar by amyloid peptide [111]. In primary cortical neuronal cells, IL-3 provides cellular protection against Aβ neurotoxicity by modulating microtubular dynamics and prevention of tau cleavage and hyperphosphorylation [112]. The beneficial effects of Tregs can have an impact on the pathophysiology not only in the early disease stages but also in animals with more established pathology [110]. Tregs can be induced in the periphery from Foxp3-Th cells when IL-2 and TGF-β are present [113]. The immunosuppressive IL-35 cytokine induces the conversion of Tconv cells into IL-35-producing Tregs [86]. It has been reported that IL-35 is an anti-inflammatory cytokine [114]. Moreover, iTregs can be further broken down into TGF-β-producing iTr-TGF-β, and IL-10-producing iTr-IL-10 [113]. IL-10 can suppress neuroinflammation and enhance neu-

Table 1
The effects of certain populations of T cells on AD pathology.

Cell types	Pros	Cons	References
Th1 cells		produce inflammatory cytokines exacerbates the levels of Aβ cognitive impairment	McQuillan et al. 2010, [93]. Jorfi et al. 2023, [90]. Machhi et al. 2021, [62].
Th2 cells	lower cognitive problems lower amyloid buildup		McManus et al. 2010, [94]. Cao et al. 2009, [95].
Th17 cells		produce inflammatory cytokines exacerbates the levels of Aβ cognitive impairment bone loss	McQuillan et al. 2010, [93]. Jorfi et al. 2023, [90]. Machhi et al. 2021, [62]. Gu et al. 2020, [96].
Th9 cells	anti-apoptotic properties inflammatory mediator	no effect on microglia proliferation	Kumari et al. 2023, [97]. Ding et al. 2015, [98]. Liu et al. 2022, [99]. Wharton et al. 2019, [100].
T22 cells	protective role of IL-22BP against neuronal damage	pro-inflammatory cytokine production via activation of glial cells	Lee et al. 2022, [101]. Chen et al. 2022, [89].
Tregs	reduce Aβ deposition decrease inflammatory cytokine levels affect cognitive function	higher Tregs suppress a useful immune response depleted Tregs: • hasten the onset of cognitive deficits, • increase the burden of Aβ, • boost the responses of microglia/macrophages, • decreased glucose metabolism.	Rosenkranz et al. 2007, [103]. Baek et al. 2016, [102].

rogenesis in AD. IL-10 improves spatial cognitive dysfunction in mice [115]. Conversely, the anti-infammatory cytokine IL-10 prevents Aβ clearance by microglia, worsening cognitive decline in mouse models in AD [116,117]. Neuronal expression of the anti-inflammatory cytokine IL-4 recovers the spatial learning function through its distinct effect on Aβ reduction, glial activation, NR2B expression, and neurogenesis [118]. Comparing the AD group to the control group, the level of serum TGF-β was noticeably lower in the AD group [119]. TGF-β can suppress both proinflammatory cytokine production and their action, subsequently protecting the brain [120]. Astrocytes prevent synapse loss induced by Aβ oligomers, through production of TGF-β1. Moreover, astrocyte-derived TGF-β1 prevents memory deficits induced by Aβ oligomers [121]. TGF-β, however, may also promote astrocyte aggregation around brain microvessels and Aβ buildup on vascular basement membranes [122]. The pathogenesis of AD may be influenced by impaired TGF-β signaling [123]. TGF-β1 signaling plays a crucial role in the formation of tau pathology, as a decrease in TGF-β1 transcription has been found to coincide with an increment in NFTs in AD [124].

There is a type of T cell that exclusively generates IL-22, without co-expressing IL-17 or IFN-γ. These cells are known as Th22 cells [89,125]. IL-22 can activate glial cells, leading to the production of pro-inflammatory cytokines and the promotion of lymphocyte infiltration in the brain [89]. IL-22Rα is naturally present in brain cells, particularly in microglia and hippocampal neurons. The interaction of IL-22 with IL-22Ra induces production of pro-inflammatory cytokine in BV2 and HT22 Cells. Given the established role of microglia in neuronal protection, it seems that IL-22 binding protein (IL-22BP) may have a protective role in IL-22-induced neuronal damage [101].

The effector cytokine IL-9, produced by Th9 lymphocytes, is significantly elevated in AD patients, indicating an upregulation of Aβ-specific Th-9 lymphocytes in AD [126]. Th17 cells produce IL-9, impacting both Th17 and Tregs. In combination with TGF-β, IL-9 induces the differentiation of naïve $CD4^+$ T cells into Th17 cells, while paradoxically enhancing the suppressive functions of $FoxP3^+$ $CD4^+$ Tregs in vitro. In vivo, a lack of IL-9 signaling weakens nTregs suppressive activity, resulting in increased effector cells [127]. The observed effects of IL-9 on neurons further validate its anti-apoptotic properties in AD [97]. Additionally, Ding et al. [98] showed that IL-9 has no effect on microglia proliferation. The activity of Th9 cells in AD is influenced by the inflammatory mediator IL-9, which is upregulated after Aβ stimulation [99,100]. The involvement of Th17 cells and Th17-derived proinflammatory cytokines such as IL-17 has been reported in the pathogenesis of AD [28,128–131]. In a mouse model of AD, IL-17 promotes the infiltration of $CD8^+$ T cells into the brain [28]. Aβ peptides increase the stimulation of Th17 cells, and IL-17 production [128,129]. Cristiano et al. [130] demonstrated that IL-17 neutralization causes a significant functional recovery of Aβ-induced neuroinflammation and memory impairment. Neutralizing IL-17 could potentially modulate systemic inflammation, peripheral vascular dysfunction, and related prothrombotic state in AD, as suggested by Vellecco et al. [131]. Neutrophils contribute to the development of AD and cognitive impairment. Migrating neutrophils in the cortex and hippocampus produce IL-17, and depleting neutrophils has been shown to improve memory [132]. Regardless of the type, severity, and duration of the disease, individuals with dementia experienced a decrease in hip bone mineral density (BMD), an increase in the occurrence of osteoporosis, and a low bone mass (LBM) compared to those without cognitive impairments [133]. BMD has been found to be a highly accurate identifier of participants with AD, and it can also distinguish those with cognitive impairment from those without. This suggests that low BMD may be useful in identifying individuals with AD or cognitive decline [134]. The regulation of bone turnover depends on various essential factors, including the receptor activator of NF-κB (RANK), its ligand (RANKL), and osteoprotegerin (OPG), the receptor that binds to RANKL. Among these factors, RANKL and OPG play a crucial role in preserving bone density [135]. AlCl3-induced AD caused a significant increase in the RANKL/OPG ratio, indicating bone resorption. This is confirmed by a significant increase in serum RANKL levels and a marked decrease in OPG levels compared to the control group [136]. IL-6 and IL-17 are recognized as significant pro-inflammatory cytokines for triggering inflammatory bone loss [96]. IL-17A is produced by Th17 cells, and it is detected in the vicinity of aggregated Aβ proteins [137,138]. IL-17A is a PTH-induced upstream cytokine that stimulates osteocytic production of RANKL. Therefore both osteocytes and Th17 cells play a crucial role in the bone catabolism caused by continuous PTH (cPTH) [139]. IL-6 is necessary for the development of Th17 cells [140,141]. IL-17 enhances the IL-6/sIL-6R (IL-6/R) signaling cascade and positive-feedback loop of IL-6 expression in astrocytes [140,142,143]. Post-mortem examination of AD brains re-

Table 2
The effects of IL-2, IL-3, IL-4, IL-10, and IL-6 on AD pathology.

Cell types	Pros	Cons	References
IL-2	IL-2 treatment: • rescues memory impairment, • rescues impaired synaptic plasticity, • alleviates hippocampal amyloid pathology, • boosts the number of plaque-associated microglia, • enhances cognitive abilities.		Alves et al. 2017, [108]. Dansokho et al. 2016, [109]. Dansokho et al. 2017, [110].
IL-3	• prevents neuronal death • cellular protection against Aβ neurotoxicity • prevention of tau cleavage and hyperphosphorylation		Zambrano et al. 2007, [111]. Zambrano et al. 2010, [112].
IL-4	• anti-inflammatory cytokine • recovers spatial learning function • Aβ reduction • neurogenesis		Kiyota et al. 2010, [118].
IL-10	• suppress neuroinflammation • enhance neurogenesis • improves spatial cognitive dysfunction	• prevents Aβ clearance by microglia • worsens cognitive decline	Kiyota et al. 2012, [115]. Michaud et al. 2015, [116]. Porro et al. 2020, [117].
IL-6	• suppress Aβ deposition via induction of gliosis • IL-6 receptors support neuronal cell survival	• pro-inflammatory cytokine • trigger bone loss • exacerbates neuronal damage via Aβ • global cognitive decline • rises tau phosphorylation • enhances the accumulation of Aβ • memory/cognitive impairment • metabolic dysregulation	Dhapola et al. 2021, [152]. Chakrabarty et al. 2010, [151]. Gu et al. 2020, [96]. Erta et al. 2012, [143]. Kummer et al. 2021, [145]. Bradburn et al. 2018, [146]. Weston et al. 2021, [29]. Griseta et al. 2023, [148]. Garner et al. 2018, [149]. Elcioğlu et al. 2016, [150]. Lyra et al. 2021, [144].

vealed elevated levels of IL-6 and suppressor of cytokine signaling 3 (SOCS3) [144]. SOCS3 acts as a negative-feedback regulator, indicating that SOCS3 in astrocytes functions as an attenuator of inflammatory responses [142]. Aβ peptide-induced neuronal damage is exacerbated by IL-6 in cultured rat cortical neurons [143]. Individuals with high IL-6 levels in their blood are more likely to experience global cognitive decline than those with low IL-6 levels [145,146]. In response to acute systemic inflammation, loss of IL-10 activates microglia, boosts IL-6, and leads to hyperphosphorylation of tau on AD-relevant epitopes [29]. Accumulation of Aβ activates microglia, promoting TNF-α and IL-6 production, exacerbating the deterioration of the brain environment, and disrupting synaptic plasticity [147]. IL-6 causes the activation of microglial cells and enhances the accumulation of Aβ peptides [148–150]. In an experimental rat model of AD, the administration of tocilizumab, an anti-IL-6 receptor antibody, was found to improve learning and spatial memory functions [148,150]. Memory/cognitive impairment and metabolic dysregulation in AD are linked by dysregulated IL-6 signaling, a major mechanism [144].

However, IL-6 induces extensive gliosis, which can suppress Aβ deposition [143,145,151]. In vivo, this is accompanied by an increase in glial phagocytic markers, leading to increased microglia-mediated phagocytosis of Aβ aggregates in vitro in the early stages of the disease process [151]. Normal levels of IL-6 receptors aid in the survival of neuronal cells, while elevated IL-6 activation levels may cause neurodegeneration [152]. During the early preclinical phases of the disease, IL-6 has no effect on endogenous levels of amyloid precursor protein (APP) or Aβ [151]. Memory impairment and metabolic changes in AD may be reduced by targeting pro-inflammatory IL-6 signaling [144]. Additionally, inhibiting IL-6 trans-signaling reduces the amyloid plaque burden in the cortex and hippocampus, along with the levels of Aβ40 and Aβ42 in the cortex of female mice [153]. A summary of the effects of IL-2, IL-3, IL-4, IL-6, and IL-10 can be seen in Table 2.

3.2. *Cytotoxic CD8$^+$ T cells in AD*

Simultaneous staining with CD45RA and CD27 mAbs were used to distinguish functionally distinct subpopulations of human CD8$^+$ T cells. The findings revealed distinct phenotypic and functional characteristics of naïve, memory, and effector CD8$^+$ T cells within the human CD8$^+$ compartment [154]. The post-mortem human AD hippocampus showed increased numbers of parenchymal CD8$^+$ T cells [155,156]. Clonally expanded CD8$^+$ T effector memory CD45RA$^+$ (TEMRA) cells were observed in the cerebrospinal fluid of patients with AD. CD8$^+$ TEMRA cells were negatively associated with cognition [23,157]. TEMRA cells release inflammatory and cytotoxic molecules, indirectly contributing to neuronal damage, and they directly interact with and sever neuronal processes, forming spheroids linked to AD [18]. Through MHC I/II molecules, primed microglia process and present self-antigens like Aβ and modified tau to the infiltrating T cells [158]. While neurons that express only MHC I present antigens to CD8$^+$ T cells, microglia express both MHC class I and II and are able to present antigens to both CD8$^+$ and CD4$^+$ T cells, respectively [106]. Remarkably, the prevention of spatial memory deficits in T-cell-depleted THY-Tau22 mice was linked to a significant decrease in the number of CD8$^+$ cells within the hippocampus [159]. Ablation of CD8$^+$ T cells had no effect on amyloid pathology and failed to restore learning deficits in APP-PS1 mice [155]. According to hippocampus RNAseq analysis, CD8$^+$ T-cell ablation upregulate neuronal- and synapse-related gene expression in

APP-PS1 mice [155]. In the brain of APP-PS1 mice, microglia cells exert partial control over the $CD8^+$ T-cell population. This is evident as the removal of microglia cells for a duration of 4 weeks increased the number of brain infiltrating $CD8^+$ T-cells [160]. Additionally, the increased secretion of IFN-γ by cytotoxic $CD8^+$ T cells resulted in a reduction neurogenesis in the hippocampus [161]. IFN-γ released by $CD8^+$ T cells within the brain can enhance tau pathology and neurodegeneration by promoting inflammatory microglial signaling and antigen-presentation functions [162]. The information about different aspects of $CD8^+$ T cell abnormalities in AD patients is inconsistent and contradictory. Some studies report increased numbers and activity, while others report decreased numbers and activity. Additionally, some studies show no changes compared to controls of similar age and sex [24,163–165].

3.3. Comparison of the effects of $CD4^+$ T cells and $CD8^+$ T cells in AD

In the cerebrospinal fluid (CSF) of healthy individuals, there are 150,000 to 750,000 cells present, with 90% of them being T cells. The ratio of $CD4^+$ T cells to $CD8^+$ T cells is 3.5 to 1 [104]. The CD4:CD8 ratio has been shown to be a marker that predicts mortality in an elderly Swedish population [25]. Individuals were identified as having an inverted $CD4^+/CD8^+$ ratio if their CD4/CD8 ratio was below 1.00. Notably, the prevalence of an inverted ratio increased from about 8% in the age range of 20-59 years to approximately 16% in the age range of 60-94 years [166]. In a study [25] that examined a group of 40 patients with AD, 21 healthy elderly individuals, and 11 young subjects, individual patients within the AD group exhibited the most significant differences. They had the lowest percentage of $CD4^+$ and the lowest $CD4^+/CD8^+$ ratios. However, there was a significantly increased $CD4^+/CD8^+$ ratio and a significantly decreased number of $CD8^+$ T cells in AD patients compared to healthy controls [167]. The increase in the ratio of $CD4^+/CD8^+$ was caused by a decline in $CD8^+$ T cells in AD patients [168]. In AD, the percentage of $CD4^+$ T cells increased, while the percentage of $CD8^+$ T cells decreased. $CD4^+$ T cells were particularly vulnerable to apoptosis in patients with relatively moderate AD. However, $CD8^+$ T lymphocytes had increased apoptosis in patients with severe AD [169]. However, these findings contradict the findings of Richartz-Salzburger et al. [170], who found a minor increase in $CD4^+$ T cells, a decline in $CD8^+$ T cells, and no discernible change in the $CD4^+/CD8^+$ ratio in AD. Shalit et al. [27] reported that there were no differences in the populations of $CD4^+$ and $CD8^+$ T cells in the mild AD group. However, in the moderately severe AD group, they observed a huge rise in $CD4^+$ T cells and a slight reduction in $CD8^+$ T cells. These discrepancies may be attributed to the heterogeneity of the studied AD patients. In the blood of patients with AD, there was an increased presence of $CD4^+$ T helper cells and a decreased presence of $CD8^+$ cytotoxic T cells [163,171]. In mild AD, there are significant changes in subsets of $CD4^+$ T cells. Naïve cell numbers decrease significantly, while memory cells increase. Additionally, there is an increased proportion of $CD4^+$, but not $CD8^+$ T cells [163]. The elevated levels of apoptosis in peripheral lymphocytes of AD patients are mostly caused by $CD4^+$ cells, with no alterations in $CD8^+$ T cells' apoptosis susceptibility found [172]. Another study observed a notable decrease in $CD4^+$ and $CD8^+$ T cells among individuals with AD [173]. $CD8^+$ T cells had higher proportions in control samples than in AD samples, while $CD4^+$ T cells had a higher proportion in the AD samples [174]. Table 3 summarizes findings from studies of human subjects regarding the effects of $CD4^+$ and $CD8^+$ T cells in AD.

4. Possible links between heme oxygenase, T cells, and dysfunctional mitochondria in AD

There are three isoforms of HO in mammals: HO-1, HO-2, and HO-3 [175]. The least researched of them is HO-3 [176]. HO-1 expression has been found to be increased in brain tissue from individuals with AD, while HO-2 decreased [177–179]. Bilirubin, produced by activation of HO-2, protects neurons against oxidative stress injury [180]. Heme metabolism appears to be altered in AD patients. Aβ decreases the level of HO-2 and heme degradation, which may occur at the beginning of AD [2]. HO-2, by lowering the level of its own protein in response to cellular heme deficiency, aids in the restoration of heme homeostasis [181]. HO-2 has shown neuroprotective properties both in vivo and in vitro [182]. Furthermore, HO-2 can suppress inflammatory pathways by reducing pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 in macrophages [182,183].

IL-10 is a powerful anti-inflammatory and immunosuppressive cytokine produced by various cells of the immune system, including $CD8^+$ T cells, B cells, and Th1, Th2, and Th17 and Tregs [184]. It has been observed that IL-10 can promote the expression of HO-1 [117]. Human $CD4^+$ T cells have been shown to express HO-1 [185,186]. HO-1 deficient mice develop abnormal $CD4^+/CD8^+$ ratios [187]. Dendritic cells expressing HO-1 encourage the differentiation of $Foxp3^+$ Tregs cells [188]. Tregs activity is also modulated by HO-1. Tregs display constitutive expression of HO-1, and its inhibition decreases in vitro Tregs function [189]. In vitro, the HO-1 inhibitor tin mesoporphyrin (SnMP) causes naïve $CD4^+$ and $CD8^+$ T cells to become activated, proliferate, and mature when interacting with $CD14^+$ monocytes [187]. In animal models of AD, HO-1 has been shown to protect neurons against oxidative damage [190,191]. The metabolic products of HO-1 contribute to anti-inflammatory, antioxidant and anti-apoptotic properties [190,192]. However, long-term overexpression of HO-1 causes mitochondrial damage and oxidative stress in the brain via causing iron deposition [193]. Overexpression of HO-1 induces the aggregation of Aβ and tau oligomers, impairing cognitive ability. Additionally, HO-1 induces synapse aberrations in hippocampal neurons [194,195]. Functional heme deficit is brought on by Aβ's binding to heme. Additionally, the Aβ-heme complex acts as a peroxidase and produces reactive oxygen species (ROS), which can generate an array of neurotoxic products [2,196,197]. HO-1 induction, however, prevents tau aggregation [198].

The main source of endogenous carbon monoxide (CO) is HO-1. CO generated by HO-1 reportedly protects against Aβ toxicity in vitro [199–201]. CO reduces the NF-κB-mediated BACE1 transcription, which subsequently leads to a decrease in Aβ production. Moreover,CORM3 treatment reduced the expression of the pro-inflammatory cytokines, TNF-α, IL-6, and IL-1β, in 3xTg mouse brain [201]. In addition, CO generated by HO-1 inhibits T Cells proliferation by inhibiting IL-2 production [185]. Both HO-1 and CO play crucial roles in mediating the anti-inflammatory effects of IL-10 in vivo and in vitro [117]. Pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 are downregulated as a result of CO-derived MAPK pathway activation [202]. CO triggers the release of IL-10, an anti-inflammatory cytokine that prevents the production of pro-inflammatory cytokines, such as IFN-γ, IL-2, IL-3, TNF-α [203,204]. Mitochondria are a major target of CO, and the generation of low levels of mitochondrial ROS is crucial for CO-induced cytoprotection against apoptosis, and inflammation, by modulating mitochondrial dynamic and autophagy [204]. CO controls mitochondrial functioning and oxidative metabolism, enhancing cellular energy state by modulating COX activity, oxygen consumption, mitochondrial biogenesis, and ROS production [205]. Carbon monoxide-releasing molecule-2 (CORM-2) can activate Nrf2 [206]. Carbon monoxide releasing molecule-3 (CORM-3) induces HO-1 expression in rat brain astrocytes via Nox, mitochondria/ROS-dependent PI3K/Akt/mTOR cascade, activating FoxO1 and ROS, leading to Nrf2 activity [207]. There is growing evidence indicating the relationship between nuclear factor erythroid 2 related factor 2 (NRF2) and AD [208–212]. A reduction in the expression of the transcription factor Nrf2, as well as changes in Nrf2-related pathways, have been observed in AD brains [208]. Nrf2 activation decreases tau pathology, prevents neurodegeneration, and mitochondrial failure in AD [209]. The absence of NRF2 caused an earlier onset of the disease, with more severe amyloidopathy and tauopathy, as well as worsened cognitive deficits [211]. Nrf2 is re-

Table 3
Findings from studies of human subjects regarding the effects of $CD4^+$ T cells and $CD8^+$ T cells in AD.

Study subjects	Results	References
people of different ages	inverted $CD4^+/CD8^+$ ratio: 8% of people aged 20 to 59 inverted $CD4^+/CD8^+$ ratio: 16% of people aged 60 to 94	Wikby et al. 2008, [166].
AD patients vs normal group	a slight rise in $CD4^+$ T cells a slight decline in $CD8^+$ T cells no discernible change in the $CD4^+/CD8^+$ ratio in AD group	Richartz-Salzburger et al. 2007, [170].
AD patients vs control group	$CD4^+$ T cell percentage increased $CD8^+$ T cell percentage decreased major changes in subsets of $CD4^+$ T cells but not $CD8^+$ T cells	Schindowski et al. 2006, [169]. Larbi et al. 2009, [163]. Huang et al. 2022, [171].
AD group vs control group	lowest ratio of $CD4^+/CD8^+$ in AD group lowest percentage of $CD4^+$ T cells	Pellicanò et al. 2012, [25].
AD group vs control group	higher $CD8^+$ T cells in control than in AD higher $CD4^+$ T cells in the AD samples than control	Wang et al. 2023, [174].
AD patients vs control group	rised ratio of $CD4^+/CD8^+$ due to reduction of $CD8^+$ T cells in AD	Pirttilä et al. 1992, [168].
AD group vs control group	notable decrease in $CD4^+$ and $CD8^+$ T cells	Sh et al. 2021, [173].
AD patients	mild AD: no differences in $CD4^+$ T cells and $CD8^+$ T cells moderately severe AD: a huge rise of $CD4^+$ T cells, a slight reduction in $CD8^+$ T cells	Shalit et al. 1995, [27].

Table 4
HO-1 and HO-2 effects on AD pathology.

	Effects	References
HO-1	• lack of HO-1 causes abnormal $CD4^+/CD8^+$ ratios • HO-1 modulates Tregs activity • HO-1 induction prevents tau aggregation • HO-1 protects neurons against oxidative damage long-term overexpression of HO-1 causes: • mitochondrial damage, • oxidative stress, • aggregation of Aβ and tau oligomers, • impaired cognitive ability.	Burt et al. 2010, [187]. Funes et al. 2020, [189]. Nitti et al. 2018, [198]. Si et al. 2020, [190]. Jiao et al. 2018, [191]. Wang et al. 2015, [193]. Si et al. 2018, [194]. Li et al. 2015, [195].
HO-2	protects neurons against oxidative stress helps to restore heme homeostasis lowers pro-inflammatory cytokines: IL-1β, TNF-α, and IL-6 suppresses inflammatory pathways	Doré et al. 1999, [180]. Liu et al. 2020, [181]. Intagliata et al. 2019, [182]. Chen et al. 2018, [183].

sponsible for the amelioration of oxidative stress and inflammation [212]. Deleting Nrf2 aggravates neuroinflammation in mice. In the hippocampus, both the levels of IL-1β, IL-6, and TNF-α at the protein and mRNA levels increased with Nrf2 deletion. Conversely, lower levels of IL-4, IL-10, and TGF-β suggest that Nrf2 deficiency worsens microglia and astrocyte activation before the proinflammatory response intensifies in mice [210]. Cytotoxicity of $CD8^+$ T cells towards antigens presented by Nrf2-deficient macrophages was significantly decreased [213,214]. Activated bone marrow-derived macrophages eradicate AD-related Aβ 42 oligomers and protect synapses [215]. The cocaine- and amphetamine-regulated transcript (CART) peptide attenuated oxidative stress damage via the activation of the Nrf2, HO-1, and NQO1 signalings [191]. A summary of the effects of HO-1, and HO-2 can be seen in Table 4.

Mitochondrial dysfunction has been linked to the pathogenesis of AD [14,172,216–218]. Oxidative phosphorylation (OXPHOS), which produces both ROS and ATP, is a mitochondrial function frequently affected in neurodegenerative disorders such as AD [216,219,220]. Individuals with AD exhibit increased oxidative stress, elevated apoptosis, and mitochondrial dysfunction in their lymphocytes, making it a potential biomarker for AD [172]. Even in the absence of Aβ plaques and tau tangles, early stage mitochondrial dysfunction in AD may produce other molecular phenomena in AD [217]. The overexpression of aggregated and hyperphosphorylated tau impairs axonal transport, resulting in abnormal mitochondrial distribution. Moreover, tau pathology in AD is promoted by mitochondrial dysfunction [14,218]. Mitochondrial dysfunction, through ROS production, enhances Aβ production, creating a vicious circle not only between mitochondrial dysfunction and ROS but also including the harmful effects of Aβ [14,172].

The activation of $CD4^+$ T cells requires mitochondrial complex III ROS, which is also essential for antigen-specific $CD4^+$ T Cell expansion in vivo [221]. Memory $CD4^+$ T cell survival appears to rely on glucose metabolism [222]. Activated T cells increase glucose uptake [223,224]. In AD brains, there is a significant impairment in glucose metabolism [225,226]. Reduced glucose metabolism is directly correlated with cognitive decline [226]. Mitochondrial dysfunction in the brain can be caused by both defective glucose metabolism and impaired insulin signaling [226,227]. Depletion of Tregs for four months has been shown to decrease glucose metabolism [102]. Overexpression of IL-17A significantly enhances glucose metabolism, reduces levels of soluble Aβ in the hippocampus and cerebrospinal fluid [137]. Overexpressing IL-17A in the central nervous system does not lead to physical or learning impairments or neuroinflammation, suggesting that IL-17A may regulate glucose metabolism via the AKT signaling pathway [138].

Dysfunctional mitochondria in microglial cells inhibit the IL-4-induced alternative response, which is linked to attenuation of inflammation. This suggests that mitochondrial dysfunction in microglia could contribute to the harmful effects of neuroinflammation observed in neurodegenerative diseases [228,229]. Neuroinflammation leads to increased oxidative stress which causes subsequent inflammation [228]. Chronic oxidative stress alters $CD4^+$ T cell differentiation and number, increases Th1 and Th17 responses, and causes poor inflammatory response, contributing to the development of neuroinflammation in AD [228,230]. In the early-stage of AD, $CD4^+$ peripheral lymphocytes exhibit mitochondrial depletion, both at the DNA and protein levels [231]. Additionally, mitochondrial dysfunction has been observed in $CD8^+$ TEMRA [232,233], characterized by decreased mitochondrial mass compared to effector memory T cells and diminished mitochondrial membrane potential [232]. $CD8^+$ TEMRA cells exhibit metabolic instability, as indicated by lower spare respiratory capacity (SRC), reduced mitochondrial mass, increased ROS production, and decreased mitochondrial membrane potential (MMP) compared to other memory subsets [233]. When human and mouse $CD4^+$ T cells are activated, the presence of IL-6 increases their motility. This effect is intrinsic to IL-6 and is linked to an elevation in mitochondrial $Ca2^+$ [234]. Aging is linked to the persistence of dysfunctional mitochondria in $CD4^+$ T cells due to impaired mitochondrial turnover through autophagy. This may trigger chronic inflammation impaire and immune defense [235]. Mitochondrial retrograde signaling plays a crucial role in controlling the fate of immune cells. Activated $CD4^+$ and $CD8^+$ T cells enhance mitochondrial mass, OXPHOS, and levels of ROS. The nuclear factor of activated T cells (NFAT) promotes T-cell activation, while blocking the activity of complex III hinders NFAT nuclear translocation and the expression of target genes, possibly via a ROS-dependent mechanism [221,236,237]. Naïve T cells rely on OXPHOS fueled by glucose and fatty acid oxidation (FAO) to generate ATP due to their lower energy demand. However, upon activation, effector $CD4^+$ and $CD8^+$ T cells shift to glycolysis for rapid ATP production, while utilizing the TCA cycle for the synthesis of protein and lipid intermediates [238]. Impaired mitochondrial OXPHOS limits the self-renewal of T cells exposed to persistent antigen [239]. Heme deficiency alters mitochondrial complex IV, APP, NO synthase (NOS), and zinc and iron homeostasis. These changes also observed in the aging brain and are significantly more prominent in AD [240].

5. Inclusion of $CD4^+$ and $CD8^+$ T cells in AD: insights from machine learning and mathematical models

While genome-wide association studies (GWAS) and transcriptome-wide association studies (TWAS) have been performed in AD, the detailed mechanisms of those significantly AD-related genes cannot be discovered from a sole association study [241–243]. Machine learning has emerged as a potent tool for detecting patterns in complicated datasets, making it applicable for the diagnosis and prognosis determination in AD [174]. Numerous studies have demonstrated the application of machine learning in the discovery of potential biomarkers for AD [173,174,244–247]. Potential biomarkers undergo validations through cross-validations, functional enrichment analyses, and wet-experimental validations, enabling their utilization as clinical diagnostic references upon passing clinical significance tests [244]. Linear and non-linear machine learning models were employed to examine blood biomarkers and study changes in the blood transcriptome in AD. Cell ratios, such as $CD8^+$ naïve T cells/Plasma cells and Th2/$CD8^+$ T cells, decreased gradually, while $CD4^+$ and $CD8^+$ T cells notably declined in AD individuals. The analysis suggests a potential association between natural killer T cell (NKT) homeostasis and AD [173]. Circadian rhythm score (CRscore) was employed to quantify the microenvironment status of circadian disruption in a single-cell RNA sequencing dataset derived from AD. Heterogeneity was observed in B cells, $CD4^+$ T cells, and $CD8^+$ T cells. Bulk sequencing analysis revealed that the CRscore served as a reliable predictive biomarker in AD patients [245]. Four biomarkers (RPL24, RPL5, RPS27A, and RPS4X) were identified having strong diagnostic capabilities in AD. Analysis of immune infiltration showed an elevated presence of $CD4^+$ T cells in AD patients, which was negatively correlated with the identified ribosome-associated core genes. Ribosomal family proteins have the potential to serve as biomarkers for AD diagnosis and treatment and are associated with $CD4^+$ T cell activation [174]. MAFF, ZFP36L1, and ADCYAP1 have all been shown to be diagnostic markers for AD. MAFF positively correlated with activated NK cells, and resting memory $CD4^+$ T cells, while negatively correlated with memory B cells. ADCYAP1 exhibited positive correlations with memory B cells, and activated memory $CD4^+$ T cells, while negatively correlated with $CD8^+$ T cells, and resting memory $CD4^+$ T cells. ZFP36L1 showed positive correlations with resting memory $CD4^+$ T cells and $CD8^+$ T cells. It showed negative correlations with memory B cells and activated memory $CD4^+$ T cells [246]. Differences in the abundance of 22 immune cell subtypes have been found in patients with AD [247,248]. Infiltration levels of $CD8^+$ T cells and Tregs were observed to be higher. Furthermore, correlation analysis results indicated an extraordinary correlation between endoplasmic reticulum (ER) stress-related differentially expressed genes (DEGs) and immune cells such as naïve B cells, memory B cells, and activated memory $CD4^+$ T cells, suggesting that ER stress-mediated immune cells activation might be the major pathological mechanism causing AD progression [247]. AD patients showed elevated infiltration levels of naïve B cells and resting memory $CD4^+$ T cells, while correlation analysis indicated associations between cuproptosis modulators and resting NK cells and $CD8^+$ T cells. This suggests the importance of cuproptosis-related genes (CRGs) in regulating molecular and immune infiltration in AD [248]. In the testing cohort, four core biomarkers (RPL24, RPL5, RPS27A, and RPS4X) showed promising diagnostic power. $CD4^+$ T cells were identified as the predominant cell type in AD samples and displayed a negative correlation with the ribosome-associated core genes. These findings suggest the potential of ribosomal family proteins as biomarkers for AD, linked to $CD4^+$ T cell activation [174].

Numerous mathematical models analyzed the progression of AD without taking T cells activation into account [30–35]. The model of AD is represented by a system of partial differential equations involving neurons, astrocytes, microglia, and peripheral macrophages, along with amyloid β aggregation and hyperphosphorylated tau proteins. Simulations indicate that combination therapy using a TNF-α inhibitor and anti-amyloid β treatment could potentially have a substantial impact on slowing down the progression of AD [30]. A set of differential equations describe the dynamic formation of Aβ plaques in AD based on concentrations of Aβ oligomers, PrPC proteins, and the Aβ-PrPC complex. The model proposes that achieving a stable state is challenging in progressive diseases like AD, but collecting experimental data on stabilization can aid in determining model parameters [31]. A stochastic model has been used to predict the progression of AD, particularly utilizing a discrete-time Markov model to explain the movement to describe the movement of individuals through a finite sequence of distinct health and disease states over time [32]. Another model consists of Smoluchowski equations for the amyloid concentration and a kinetic-type transport equation for the distribution function of the degree of neuronal malfunction. The numerical simulations align with clinical images, reflecting disease progression from early to advanced stages [33]. A mathematical model for AD's onset and progression incorporates Smoluchowski equations for Aβ concentration, an evolution equation for tau protein dynamics, and a kinetic-type transport equation for neuronal malfunction. Numerical simulations align qualitatively with clinical observations of brain disease distribution across stages and the impact of tau on disease dynamics [34]. A causal model has been created to simulate biomarker data in AD based on the dynamic biomarker cascade theory. The model used nonlinear ODEs to represent biomarkers associated with AD, including Aβ, tau, neuronal loss, and cognitive impairment. By adjusting parameters, the model's feasibility is tested

and simulated biomarker trajectories are compared with known AD biomarker progression assumptions [35].

Some studies have considered the involvement of autoimmunity in AD, where antibodies attack self-protein in the brains of AD patients [249–251]. The relationship between AD as an autoimmune disease and classical data on Aβ and tau has been discussed by Arshavsky [249]. Further investigation into the autoimmune aspects of AD is crucial to advance the understanding of the pathobiology of this condition [250]. The disruption of BBB may result in an autoimmune reaction against pyramidal neurons. The autoimmune response specifically targets the neurons responsible for memory formation and storage, contributing to the transition of pretangle phosphorylated tau into NFTs. The autoimmune response can be attributed to genetic factors resulting in Aβ deposition or non-genetic factors unrelated to Aβ pathology [249]. Stimulation caused by infection, ischemia, air pollution, and other factors can result in Aβ deposition. As an immunopeptide, Aβ causes an innate immune response and a cytotoxic attack on self neurons [251]. Previous mathematical models did not consider the involvement of T cells in the development of AD. However, there is potential for the creation of mathematical models [4,5,36,252] that take into account AD as an autoimmune disease. In these studies, a set of ordinary differential equations (ODE) was analyzed to model immune responses by $CD4^+$ helper T cells in the presence of Tregs. The equilibria of the respective ODE systems were obtained, as well as formulas for the T cells concentration, Tregs concentration, and antigenic stimulation of T cells. Furthermore, hysteresis occurred between two antigenic stimulation thresholds of T cells, specifying that the cure for autoimmunity may necessitate greater immune suppression. Although immune suppression that diminishes the concentration of $CD4^+$ T cells may result in low levels of Tregs [4]. Afsar et al. [5] fitted time evolutions of a $CD4^+$ T cells immune response ODE model with seven equations to laboratory data reported by Homman et al. [253], which included two time series of $CD4^+$ T cells counts obtained from mice infected with lymphocytic choriomeningitis virus (LCMV) infection for two epitopes: gp61 and NP309. Furthermore, a similar approach was used to fit two ODE systems with five equations [36]. Both approaches can quantify the behavior of $CD4^+$ T cells, Tregs, and IL-2 density. Additionally, these approaches could be used to study the dynamics of autoimmune diseases like AD and estimate parameters and their confidence intervals. It would be worth investigating human data on T cells and Tregs concentration over long periods of time, taking into account memory T cells.

6. Conclusion

AD is a neurological disorder that develops in old age and has no effective treatment. The accumulation of Aβ and tau proteins can stand as markers of AD. The occurrence of T cells has been reported in the brains of AD patients. The immune response in AD involves various subsets of $CD4^+$ T cells, which secrete cytokines that can have both protective and harmful effects on the CNS. Some studies report increased numbers and activity of $CD8^+$ T cells, while others indicate decreased numbers and activity. Additionally, certain studies show no significant changes compared to control groups of similar age and sex. These discrepancies may stem from variations in study design, patient characteristics, and the specific stage of AD under investigation. Furthermore, the interplay between T cells, interleukins, HO isoforms, and mitochondrial dysfunction appears to be involved in the complex mechanisms underlying AD progression. IL-10 can promote the expression of HO-1. $CD4^+$ T cells have been found to express HO-1, and its inhibition affects Tregs function while activating naïve $CD4^+$ and $CD8^+$ T cells. HO-1 deficiency in mice results in abnormal $CD4^+/CD8^+$ ratios. Mitochondrial dysfunction affects lymphocytes, including $CD4^+$ and $CD8^+$ T cells, leading to altered differentiation, mitochondrial depletion, and metabolic instability.

Various studies have employed machine learning algorithms to identify potential biomarkers for AD, such as analyzing blood transcriptome and immune cell ratios. These studies have observed the presence of $CD4^+$ and $CD8^+$ T cells, along with their correlations with specific genes in AD patients. Moreover, differences in immune cell subtypes and their infiltration levels have been identified, suggesting a potential role of T cells in AD progression. Regarding mathematical modeling, previous models have focused on the progression of AD without considering T cell activation. However, there is potential for developing mathematical models that incorporate AD as an autoimmune disease, exploring the interaction between $CD4^+$ T cells, Tregs, and antigenic stimulation. While the involvement of autoimmunity in AD has been suggested in certain studies, it is essential to note that the exact mechanisms and causal relationships between T cells and AD are still being investigated. AD is a complex disease, and comprehensive research that considers all its facets, including the effects of T cells, is crucial for a deeper understanding and potential therapeutic advancements.

Declaration of competing interest

The authors have declared that they do not have any conflicts of interest.

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