



Neuroinflammation and neuroimmunology in Alzheimer's disease: The role of T-lymphocytes in Alzheimer's disease

Chihara, Norio

Tsuji, Asato

Matsumoto, Riki

(Citation)

Clinical and Experimental Neuroimmunology, 14(2):92-99

(Issue Date)

2023-03-21

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

This is the peer reviewed version of the following article: Chihara N, Tsuji A, Matsumoto R. Neuroinflammation and neuroimmunology in Alzheimer's disease: The role of T-lymphocytes in Alzheimer's disease. Clin Exp Neuroimmunol. 2023; 14(2): 92-99, which has been published in final form at <https://doi.org/10.1111/cen3.12747>. This article...

(URL)

<https://hdl.handle.net/20.500.14094/0100491847>



Neuroinflammation and Neuroimmunology in Alzheimer's disease:

The role of T-lymphocytes in Alzheimer's disease

Norio Chihara, Asato Tsuji, Riki Matsumoto

Division of Neurology, Kobe University Graduate School of Medicine, Kobe, Japan

chiharan@med.kobe-u.ac.jp

3613 words

Abbreviations

AD, Alzheimer's disease; A β , amyloid- β ; CNS, central nervous system; NFT, neurofibrillary tangles; TRMs, tissue resident memory T-cells; BBB, blood-brain barrier; BECs, brain endothelial cells; CAA, cerebral amyloid angiopathy; MCI, mild cognitive impairment; APOE, apolipoprotein E; CSF, cerebrospinal fluid; BM, basement membrane; NVU, neurovascular unit; MHC, major histocompatibility complex; Th17, T-helper 17; TEMRA, terminally differentiated, effector, memory re-expressing CD45RA; APP, amyloid-precursor protein; PS1, presenilin 1; PD-1, programmed cell death-1; CTLA-4, cytotoxic T-lymphocyte associated antigen-4; MS, multiple sclerosis; IFN γ , interferon-gamma; Th1, T-helper 1; IL-17, interleukin-17; 5xFAD, mice with three APP and two PS1 gene mutations associated with familial AD; 3xTg, mice with APP, PS1, and tau gene mutations associated with familial AD or tauopathy; Th2, T-helper 2;

Abstract

Alzheimer's disease (AD) is the leading cause of dementia, with the number of patients with AD expected to double in the next quarter-century. Brain deposition of amyloid- β ($A\beta$) and tau proteins is a necessary but insufficient condition for AD pathogenesis. There is also growing evidence to suggest that chronic neuroinflammation due to excessive microglial activation and astrocyte dysfunction exacerbates the pathophysiology of AD, but the factors that disrupt these homeostatic processes remain unclear. Research into AD pathophysiology has shown interest in the changes in adaptive T-cells, which play a pivotal role in immunity.

The immune alterations in the peripheral circulation and increased blood-brain-barrier permeability observed in patients with AD, even in the initial stages of the disease, require investigation of the immune mechanisms resulting from T-cell infiltration into the central nervous system (CNS) during disease initiation and exacerbation. Since T-cells play a two-faceted role in the CNS immune response, including pathogenic and neuroprotective roles, the role of T-cells in AD has been debated. Memory T-cells reside in the brain and communicate with glial cells and neurons. In this review, the role of immune responses in AD is discussed, focusing on the contribution of T-cells.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder of the central nervous system (CNS), accounting for 60-70% of all dementia cases (1). AD is characterized by a slowly progressive cognitive decline. There is a subtle onset of episodic memory loss and amnesia. As the disease progresses, cognitive impairment becomes more severe and widespread, affecting activities of daily living (2, 3).

It is estimated that 55 million people worldwide currently suffer from dementia. As the older adult population increases in many countries, this number is expected to reach 139 million by 2050 (1). In Japan, an advanced super-aged society, one in five people aged 65 or older is expected to suffer from dementia (4).

Pathologically, AD is characterized by neuronal cell loss with two proteinaceous aggregates: intracellular neurofibrillary tangles (NFT) caused by phosphorylated tau, and senile plaques caused by extracellular amyloid group deposition caused by amyloid beta ($A\beta$) (5). $A\beta$ is a degraded protein, composed of about 40 amino acids, produced in the brain. It is divided into $A\beta$ (1-40), which is harmless and easily excreted, and $A\beta$ (1-42), which is highly toxic and tends to accumulate in the brain as proteins attach to each other.

The amyloid cascade hypothesis has been adopted as a major factor in the pathogenesis of AD, in which amyloid β -peptides in senile plaques affect other

pathologies, such as NFT formation, as a result of an imbalance between A β production and clearance (6, 7). Both A β and tau may act synergistically to exacerbate neuronal degeneration (8); however, A β and tau alone cannot fully establish AD pathology. This is inferred from the fact that clinical trials targeting various A β and tau proteins have failed to restore brain function (9).

The brain is composed of neurons and glial cells that support neuronal functions. Inflammatory changes, such as microglial activation, astrogliosis, complement activation, cytokine elevation, and acute phase protein changes, have long been noted as a response, at least in part, to the initial accumulation of A β (1-42) in the brain (10). Furthermore, increasing evidence has revealed high levels of inflammatory markers and risk genes for AD associated with the innate immune system in patients with AD; neuroinflammation mediated by microglia and astrocytes is considered an important regulator of the development of A β plaques and abnormal neurofibrillary changes (11, 12). In addition to glial cells, other factors that cause neuroinflammation have been highlighted; T-cells may contribute indirectly to neuroinflammation through crosstalk with glial cells and may balance excessive neuroinflammation and neuroprotection. In particular, T-cells in the brain, called tissue resident memory T-cells (TRMs), have a different phenotype than that of peripheral circulating T-cells (13, 14) (Figure 1). Herein, we discuss

neuroinflammation and AD, with a focus on the role of T-cells.

Alzheimer's disease and neuroinflammation

1. Neurodegeneration and neuroinflammation

Central to the clinical manifestations of AD is the loss of synaptic plasticity and the loss of synapses themselves, which are closely associated with cognitive decline (3). An autopsy study comparing dendritic spines in patients with AD to control individuals who did not show a decline in cognitive function throughout life revealed that the density of dendritic spines was reduced in patients with AD, whereas it was comparable in non-dementia individuals with or without A β pathology (15). In other words, attention should be paid not only to avoiding AD pathology (cognitive resistance) but also to coping with it (cognitive resilience) (16).

In studies of AD pathology, several factors have been reported to promote neurotoxicity associated with cognitive decline, including oligomeric A β aggregates, hyperphosphorylated-tau species localized at synapses, and glial activation (17). Oligomeric A β or hyperphosphorylated tau has been shown to promote innate immune defense responses in the activation of pattern-recognition receptors that cause excessive inflammation (18, 19). Some studies have shown that both oligomeric A β and

hyperphosphorylated tau induce neuronal necroptosis, also known as immunogenic cell death (20, 21).

2. Increased blood-brain barrier (BBB) hyperpermeability and neuroinflammation

Factors that influence neuroinflammation in AD do not only come from within the CNS but also from external factors controlled by the integrity of the BBB. The BBB maintains a homeostatic environment that is necessary for normal CNS function (22). The endothelial, epithelial, and glial brain barriers constitute BBB compartments that exhibit different levels of accessibility to immune cell subsets (23). Within these compartments, brain endothelial cells (BECs) of the CNS microvasculature have been well studied, precisely regulating the movement of ions and molecules between the blood and the CNS to control the transportation of immune cells to the CNS in health and disease (24). BECs are tightly sealed by tight junctions such as claudin/occludin and adherens junctions, such as vascular endothelial cadherin (23).

The pathology of AD may directly promote vascular changes. For example, amyloid deposition near vessels is associated with MRI abnormalities in small-vessel disease, called cerebral amyloid angiopathy (CAA). (25). In rodent models of AD, A β has been reported to promote BBB permeability by altering tight junction binding or

promoting perivascular pericyte mitophagy (26, 27). Tau may also cause vascular abnormalities, leading to BBB breakdown and decreased clearance of abnormal proteins (28). In imaging studies using dynamic contrast-enhanced MRI, which is used to assess BBB permeability, increased vascular permeability was found in patients with early AD, so-called mild cognitive impairment (MCI) (29). Notably, vascular permeability was more pronounced in patients with one or more copies of the apolipoprotein E (APOE) $\epsilon 4$ gene, a known genetic factor in the development of AD (29). It has been reported that APOE4 proteins facilitate vascular permeability with or without A β pathology (30).

In terms of clearance, the paravascular interstitial fluid pathway facilitates the flow of cerebrospinal fluid (CSF) through the brain parenchyma, and the clearance of interstitial solutes, including A β (31). CSF drains from arachnoid granules in the dura mater. It is then excreted through the dural veins and a unique lymphatic drainage system from the CNS to the peripheral circulation and lymph nodes (23). Because dysfunction of these clearance systems increases the load of abnormal proteins in the CNS, astroglial dysfunction has been highlighted as a glymphatic dysfunction (32). Indeed, a longitudinal cohort study of individuals with enlarged perivascular spaces in the centrum semiovale correlated with the incidence of dementia, including AD (33).

In addition to BECs, capillaries, basement membrane (BM), astrocytes, pericytes

embedded in the BM, microglia, and neurons constitute the microenvironment that controls BBB integrity as the so-called neurovascular unit (NVU) (34). In early AD, soluble platelet-derived growth-factor receptor beta in the CSF, reflecting brain capillary damage, increased as a result of injurious stimuli for pericytes (35). These results suggest that early synaptic changes correlated with cognitive decline in AD are associated with BBB dysfunction and that this dysfunction may disrupt cognitive resilience to the remaining disease processes.

Alzheimer's disease and T-cells

T-cells play a central role in the adaptive immune system, patrolling tissues, and serving a role in immune surveillance (36). The major class of T-cells has $\alpha\beta$ T-cell receptors and responds to pathogen-derived peptides presented by the major histocompatibility complex (MHC) on antigen-presenting cells; CD8⁺ cytotoxic T-cells respond to MHC class I molecules, whereas CD4⁺ helper T-cells respond to MHC class II molecules. After appropriate activation by antigens, T-cells differentiate into effector cells, which in the case of cytotoxic T-cells, exhibit direct cytotoxic activity and in the case of helper T-cells, elicit immune responses by producing cytokines (37).

1. Phenotypic changes of T-cells in the peripheral blood of patients with AD

In AD, there are several reports of changes in immunocompetent cells in the peripheral circulation, including enhanced adaptive immunity in patients with AD, such as increased activation of peripheral T-cells in response to A β and increased production of proinflammatory cytokines (38, 39). There are also reports of an imbalance between increased potential encephalitogenic T-helper 17 (Th17) cells and decreased regulatory T-cells (40). Dysfunctional regulatory T-cells in the peripheral blood of patients with AD have also been reported (41). Recently, it was reported that an increase in terminally differentiated, effector, memory re-expressing CD45RA (TEMRA) CD8⁺ T-cells in the peripheral blood of patients with MCI and AD is correlated with cognitive decline (42). Regarding antigen specificity, it has been reported that A β -responsive T-cells promote microglial activity in an IFN- γ -dependent manner, leading to A β clearance in a mouse model of AD overexpressing mutant amyloid-precursor protein (APP) and presenilin 1 (PS1) (APP/PS1) (43). In humans, A β (1-42)-reactive T-cells have been observed in patients with AD and healthy older adults, suggesting that intrinsic T-cell reactivity to the autoantigen A β may be associated with AD onset or may be a marker of the aging process (44). However, systemic immunization against A β - (1-42)-induced subacute meningoencephalitis and the clearance of A β did not prevent progressive dementia (45,

46). Tau peptide-specific T-cells have also been found in the general population, independent of neurodegenerative disease (47). To date, it has been reported that functional changes that enhance the function of immune cells, especially T-cells, in the peripheral circulation have been observed in patients with AD. These changes correlate with cognitive decline and antigen-specific responses to A β , but definitive evidence suggesting the cause and significance of these changes in peripheral T-cell function and their direct involvement in the brain, the primary site of AD pathogenesis, is undetermined.

2. Mechanisms of increased BBB permeability and T-cell infiltration in AD

Along with increased BBB permeability in AD, A β overload increases T-cells in the brain and simultaneously increases the expression of endothelial adhesion molecules that promote T-cell infiltration through the BBB (48). Furthermore, the CSF of patients with MCI and AD is enriched with clonality-expanded CD8⁺ TREMA cells (42). This suggests that antigen-experienced T-cells patrolling the intrathecal space are activated against antigens in the CNS and remain, at least partially, in the brain. Notably, the antigen-specific T-cells in the CSF may not necessarily respond to A β , but to virus antigens (42). The interactions between several cell surface molecules have been studied

as potential mechanisms of chronic inflammation and BBB permeability (49). For example, CD200 is expressed primarily in brain neurons, and CD200 receptors on microglia in the CNS; these interactions maintain brain homeostasis while promoting anti-inflammatory pathways. The reduced expression of CD200 and CD200 receptors has been reported in AD-affected brains (50). CD200-deficient mice show increased IFN- γ expression from infiltrated T-cells in the brain and activated microglia with increased BBB permeability (51). Such dysfunctional maintenance of the brain environment may affect AD pathology and induce T-cell infiltration into the CNS.

3. T-cells in the brain with AD

The brains of patients with AD have been shown to have a higher incidence of T-cells than that of patients with non-AD degenerative dementia and age-matched healthy brains. The percentage of CD8⁺ T-cells in the brain is significantly higher than that of CD4⁺ T-cells, with subtypes CD45RA-CD45RO⁺, indicating that T-cells infiltrating the brain are in an activated state (52). Moreover, the number of extravascular CD8⁺ T-cells in the hippocampus of patients with AD was reported to correlate with the amount of tau accumulation, not with the amount of A β (53). T-cell infiltration in the inferior parietal lobule, middle parietal gyrus, and medial frontal gyrus of patients with AD is positively

correlated with p-tau load (54). Thus, although A β is an initiator of immune changes in the peripheral circulation and may trigger T-cell infiltration through BBB and entrapment in the brain, T-cells in the brain may behave independently of A β and are correlated with the degree of neurodegeneration represented by tau accumulation.

Roles of T-cells in AD pathogenesis

While the CNS has long been considered an immune-privileged site, a growing body of evidence suggests that immune cells, including T-cells, contribute to the microenvironmental homeostasis of the brain in healthy and diseased states (55). However, no clear conclusions have been reached regarding the role of T-cells in AD pathogenesis. Multiple external signals received from cell surface molecules and cytokines play important roles in altering the host immune response. Co-stimulatory molecules are important for T-cell activation and the maintenance of an effective immune response, whereas co-inhibitory molecules prevent excess activation-induced cell death. The balance between co-stimulatory and co-inhibitory molecules on T-cells defines the T-cell state (56). In tissue microenvironments, such as in cancer tissues, T-cells become dysfunctional or exhausted due to high levels of clustered co-inhibitory molecules and specific gene profiles (57, 58). T-cells located in the perivascular space of the CNS have

been reported to express several co-inhibitory molecules, including programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), not only in healthy individuals but also in patients with neurological diseases, such as multiple sclerosis (MS) and AD (59).

1. Pathogenic effects by T-cells in the brain

In chronic inflammatory diseases of the CNS, such as MS, T-cells play a vital role in long-term pathophysiology. Dysregulation of T-cells in peripheral lymphoid organs orchestrates leukocyte entry into the CNS, leading to immunopathology and neurological deficits (60). The mechanism of autoreactive T-cell entry into the CNS and immunopathology is initiated in a CNS antigen-dependent manner, with conventional dendritic cells of peripheral lymphoid organs serving as antigen-presenting cells, rather than NVU macrophages and microglia (61).

In general, pathogenic CD4⁺ T-cells in the brain communicate with microglia via MHC class II molecules and promote local inflammation (62). In contrast, neurons lack MHC class II and express MHC class I, so CD8⁺ T-cells can exhibit cytotoxic activity and destroy neurons (63). In addition to MHC class I-mediated mechanisms, CD8⁺ and CD4⁺ T-cells can induce neuronal death through cell-cell contact-dependent

mechanisms involving Fas and Fas ligands (64).

Furthermore, early studies have shown that the pro-inflammatory cytokine interferon-gamma (IFN- γ) from both CD4⁺ and CD8⁺ T-cells promotes astrocyte proliferation and activation, resulting in exacerbated neuroinflammation (65). IFN- γ induces microglial changes, including microglial proliferation and nitric oxide release; microglia stimulated by IFN- γ have been reported to impair neural network rhythms and cognitive function (66). CD4⁺ T-helper 1 (Th1) cells are important secretors of IFN- γ that activates microglia and astrocytes and may contribute to A β deposition, impaired synaptic plasticity, and cognitive deficits in APP/PS1 mice (67). On the other hand, increased Th17-cells have been reported in patients with MCI due to AD, defined by a low A β 1-42/1-40 ratio in CSF, suggesting that an alternative adaptive immune system is associated with neuropathological changes in AD (40). Th17-cells secrete the proinflammatory cytokine interleukin-17 (IL-17), which causes the activation of microglia (68) and decreases BBB tight junction molecules (69). IL-17 activates neutrophils in a manner dependent on lymphocyte function-associated antigen 1 integrin and plays a role in inducing neuronal apoptosis and neurodegeneration in rodent models of AD models: mice with three APP and two PS1 gene mutations associated with familial AD (5xFAD) and mice with APP, PS1, and tau gene mutations associated with familial AD or tauopathy

(3xTg) (70).

In rodent models of tauopathy observed in AD, T-cell infiltration promotes neuroinflammation and worsens cognitive function. T-cell depletion with anti-CD3 antibodies restores spatial memory deficits in the absence of tau pathology modulation (71). Moreover, the adoptive transfer of regulatory T-cells also improves cognitive function and reduces A β plaque deposition in 3xTg mice (72).

2. Neuroprotective effects of T-cells

Physiologically, T-cells play a vital role in the homeostasis of tissue microenvironments. Immunocompromised states impair the maintenance of hippocampal neurogenesis and spatial-learning abilities, but CNS-specific antigen-reactive T-cells restore adult neurogenesis (73). In rodent models of neurodegenerative diseases such as amyotrophic lateral sclerosis, T-cells exhibit neuroprotective effects by regulating glial-cell activation (74). In a rodent model of AD (5xFAD), the transient depletion of regulatory T-cells exhibited neuroprotective effects and improved cognitive function (75). Adoptive transfer of A β -specific Th1-cells into 5xFAD mice expanded MHC class II-positive microglia in the brain, which exhibited strong phagocytic activity upon interaction with brain-infiltrated T-cells and promoted A β phagocytosis (76). Thus, the

opposing actions of Th1 and regulatory T-cells in the AD model highlight the importance of an appropriate immune response to maintain CNS homeostasis in disease states. Another study using genetically engineered mice deficient in T- and B-cells revealed a worsening A β load and neuroinflammation, particularly microglial activation. Interestingly, this phenomenon is dependent on IgG-producing B-cells (77). Furthermore, the adoptive transfer of T-helper 2 (Th2) cells into APP/PS1 mice improved cognitive function and brain neuroinflammation without significant infiltration of T-cells into the CNS (78). These results suggest that both brain and peripheral immune phenotypes may be important for suppressing AD pathogenesis.

3. Brain resident memory T-cells

Immunological memory is a sophisticated mechanism of host defense, defined as a faster and stronger response when exposed to the same antigen (79). Circulating memory T-cells are classified as central-memory cells and effector-memory cells according to their homing and effector functions (80). Recently, another distinct subset, the so-called TRMs, which do not circulate in the body and remain in non-lymphoid tissues for lengthy periods, has been highlighted. TRMs are at the forefront of infection defense, promote fibrosis upon repeated antigen exposure, and are involved in

autoimmune responses to allergic diseases (81). In a rodent fatty liver model, a decrease in CD8⁺ TRM-like cells in the liver caused hepatitis and fibrosis, and the adoptive transfer of TRM-like cells restored this phenotype (82). This suggests that CD8⁺ TRMs are important for maintaining the steady state of an organ. Notably, CD8⁺ T-cells rather than CD4⁺ T-cells are a predominant subset of TRMs (81, 83). In addition to the memory function, as defined by CD45RO, TRMs express proteins associated with tissue retention: CD69 is a protein that functions in tissue retention by inhibiting sphingosine 1-phosphate signaling, thereby reducing tissue fluidity. CD103 is a protein that functions in tissue retention by contacting E-cadherin expressed on epithelial cells. These features have been observed in T-cells obtained from human brains with and without neurological diseases (59).

The role of CD8⁺ T-cells in the brain is widely known in neuroimmune diseases, such as MS, where CD8⁺ T-cells are the predominant type in MS brain lesions rather than CD4⁺ T-cells (84). CD8⁺ T-cells with TRM characteristics located in active MS lesions may correlate with the compartmentalization of the inflammatory response in established lesions (85). Thus, in chronic progressive MS, demyelinated lesion load is associated with an increased number of TRM-like activated T-cells that accumulate in the perivascular space (86). In support of the pathogenic role of cytotoxic T-cells, myelin-specific CD8⁺

T-cells induce severe CNS inflammation in rodents with a pathology resembling MS (87).

These TRM-like cells are also characterized by increased expression of co-inhibitory receptors, such as PD-1 and CTLA-4, but still have the potential ability to secrete proinflammatory cytokines (59). T-cells present in the brain lesions of patients with MS express multiple co-inhibitory molecules including PD-1 (88). PD-1+ CD8+ T-cell presence in the CSF of patients with MS has been reported to correlate with treatment responsiveness (89). This highlights the potential immune regulatory role of CD8+ T-cells in the CNS. A patient with metastatic melanoma who received four doses of nivolumab, a PD-1 immune checkpoint inhibitor, showed TRM-like T-cell infiltration with demyelination and macrophage activation (90). In a rodent model of AD (5xFAD), while the role of TRMs was not described, PD-1 immune checkpoint inhibitors enhanced systemic IFN- γ dependent immune responses and recruitment of monocyte-derived macrophages recruitment to the brain, resulting in increased phagocytosis of A β protein, reduced A β plaque levels and improved cognitive function (91). Transcriptome analysis of brain TRMs revealed a gene profile distinct from circulating CD8+ T-cells, but comparable between APP/PS1 mice and wild-type controls (92). As mentioned above, brain resident memory T-cells exhibit repertoires that react to virus epitopes (42). This means that CNS TRMs localize as bystander cells that increase with age and may play a

role in several injurious stimuli. Pathological TRM induction has been reported to promote inflammation and leukocyte mobilization after ischemic injury (93). In AD, a more complex brain microenvironment may induce distinct roles for TRMs, which remain to be investigated.

Conclusion

The evidence suggesting immune alterations and BBB impairment in patients with AD prompted us to further investigate the role of immune cells in AD. T-cells infiltrating the CNS may be involved in the regulation of AD pathogenesis, and T-cell-derived proinflammatory cytokines are involved in inflammatory responses in astrocytes and microglia. On the other hand, a preferable immune phenotype in the peripheral circulation and memory T-cells in the brain contributes to physiological homeostasis through appropriate immune surveillance in the brain microenvironment. In addition to the synergistic effects of A β and tau on neuronal degeneration, various processes, including T-cell immune responses, are thought to trigger the onset of AD. Once lost, cognitive function cannot be restored; therefore, it is necessary to clarify the point of no return that triggers the onset of dementia and to find appropriate preventive treatments.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (20H03562) and the Japan Science and Technology Agency (Moonshot R&D) (JPMJMS 2024).

Disclosure of Ethical Statements

1. Approval of the research protocol: N/A
2. Informed Consent: N/A
3. Registry and the Registration No. of the study/trial: N/A
4. Animal Studies: N/A

Conflict of Interest: None declared

Reference

1. Organization WH. Newsroom "Dementia" [updated Sep 2022. Available from: <https://www.who.int/news-room/fact-sheets/detail/dementia>.
2. Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018;25(1):59-70.
3. Soria Lopez JA, Gonzalez HM, Leger GC. Alzheimer's disease. *Handb Clin Neurol*. 2019;167:231-55.
4. Japan Co. Section 2 current state and trends on the elderly and their environment, situation on aging, annual report on the aging society: 2017 [Available from: <https://www8.cao.go.jp/kourei/english/annualreport/2017/pdf/c1-2-1.pdf>.
5. Goedert M, Spillantini MG. A century of Alzheimer's disease. *Science*. 2006;314(5800):777-81.
6. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184-5.
7. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-6.
8. Busche MA, Hyman BT. Synergy between amyloid-beta and tau in Alzheimer's disease. *Nat Neurosci*. 2020;23(10):1183-93.
9. Andrade S, Ramalho MJ, Loureiro JA, Pereira MDC. Natural Compounds for Alzheimer's Disease Therapy: A Systematic Review of Preclinical and Clinical Studies. *Int J Mol Sci*. 2019;20(9).
10. Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, Murphy GM, Jr., et al. Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. *Glia*. 2001;35(1):72-9.
11. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimers Dement*. 2016;12(6):719-32.
12. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157-72.
13. Dai L, Shen Y. Insights into T-cell dysfunction in Alzheimer's disease. *Aging Cell*. 2021;20(12):e13511.
14. Stojic-Vukanic Z, Hadzibegovic S, Nicole O, Nacka-Aleksic M, Lestarevic S, Leposavic G. CD8+ T Cell-Mediated Mechanisms Contribute to the Progression of Neurocognitive Impairment in Both Multiple Sclerosis and Alzheimer's Disease? *Front Immunol*. 2020;11:566225.
15. Boros BD, Greathouse KM, Gentry EG, Curtis KA, Birchall EL, Gearing M, et al. Dendritic spines provide cognitive resilience against Alzheimer's disease. *Ann Neurol*. 2017;82(4):602-14.
16. Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: Clarifying terminology for preclinical studies. *Neurology*. 2018;90(15):695-703.
17. Perez-Nievas BG, Stein TD, Tai HC, Dols-Icardo O, Scotton TC, Barroeta-Espar I, et al. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain*. 2013;136(Pt 8):2510-26.
18. Salminen A, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T. Inflammation in Alzheimer's disease:

amyloid-beta oligomers trigger innate immunity defence via pattern recognition receptors. *Prog Neurobiol*. 2009;87(3):181-94.

19. Meng JX, Zhang Y, Saman D, Haider AM, De S, Sang JC, et al. Hyperphosphorylated tau self-assembles into amorphous aggregates eliciting TLR4-dependent responses. *Nat Commun*. 2022;13(1):2692.

20. Salvadores N, Moreno-Gonzalez I, Gamez N, Quiroz G, Vegas-Gomez L, Escandon M, et al. Abeta oligomers trigger necroptosis-mediated neurodegeneration via microglia activation in Alzheimer's disease. *Acta Neuropathol Commun*. 2022;10(1):31.

21. Dong Y, Yu H, Li X, Bian K, Zheng Y, Dai M, et al. Hyperphosphorylated tau mediates neuronal death by inducing necroptosis and inflammation in Alzheimer's disease. *J Neuroinflammation*. 2022;19(1):205.

22. Persidsky Y, Heilman D, Haorah J, Zelivyanskaya M, Persidsky R, Weber GA, et al. Rho-mediated regulation of tight junctions during monocyte migration across the blood-brain barrier in HIV-1 encephalitis (HIVE). *Blood*. 2006;107(12):4770-80.

23. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. *Nat Immunol*. 2017;18(2):123-31.

24. Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS*. 2020;17(1):69.

25. Boulouis G, Charidimou A, Jessel MJ, Xiong L, Roongpiboonsopit D, Fotiadis P, et al. Small vessel disease burden in cerebral amyloid angiopathy without symptomatic hemorrhage. *Neurology*. 2017;88(9):878-84.

26. Marco S, Skaper SD. Amyloid beta-peptide1-42 alters tight junction protein distribution and expression in brain microvessel endothelial cells. *Neurosci Lett*. 2006;401(3):219-24.

27. Li J, Li M, Ge Y, Chen J, Ma J, Wang C, et al. beta-amyloid protein induces mitophagy-dependent ferroptosis through the CD36/PINK/PARKIN pathway leading to blood-brain barrier destruction in Alzheimer's disease. *Cell Biosci*. 2022;12(1):69.

28. Bennett RE, Robbins AB, Hu M, Cao X, Betensky RA, Clark T, et al. Tau induces blood vessel abnormalities and angiogenesis-related gene expression in P301L transgenic mice and human Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2018;115(6):E1289-E98.

29. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71-6.

30. Montagne A, Nikolakopoulou AM, Huuskonen MT, Sagare AP, Lawson EJ, Lazic D, et al. APOE4 accelerates advanced-stage vascular and neurodegenerative disorder in old Alzheimer's mice via cyclophilin A independently of amyloid-beta. *Nat Aging*. 2021;1(6):506-20.

31. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med*. 2012;4(147):147ra11.

32. Reeves BC, Karimy JK, Kundishora AJ, Mestre H, Cerci HM, Matouk C, et al. Glymphatic System

Impairment in Alzheimer's Disease and Idiopathic Normal Pressure Hydrocephalus. Trends Mol Med. 2020;26(3):285-95.

- 33. Romero JR, Pinheiro A, Aparicio HJ, DeCarli CS, Demissie S, Seshadri S. MRI Visible Perivascular Spaces and Risk of Incident Dementia: The Framingham Heart Study. Neurology. 2022;99(23):e2561-71.**
- 34. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12(12):723-38.**
- 35. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019;25(2):270-6.**
- 36. von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. N Engl J Med. 2000;343(14):1020-34.**
- 37. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3-23.**
- 38. Speciale L, Calabrese E, Saresella M, Tinelli C, Mariani C, Sanvito L, et al. Lymphocyte subset patterns and cytokine production in Alzheimer's disease patients. Neurobiol Aging. 2007;28(8):1163-9.**
- 39. Ciccocioppo F, Lanuti P, Marchisio M, Gambi F, Santavenere E, Pierdomenico L, et al. Expression and phosphorylation of protein kinase C isoforms in Abeta(1-42) activated T lymphocytes from Alzheimers disease. Int J Immunopathol Pharmacol. 2008;21(1):23-33.**
- 40. Oberstein TJ, Taha L, Spitzer P, Hellstern J, Herrmann M, Kornhuber J, et al. Imbalance of Circulating T(h) 17 and Regulatory T Cells in Alzheimer's Disease: A Case Control Study. Front Immunol. 2018;9:1213.**
- 41. Ciccocioppo F, Lanuti P, Pierdomenico L, Simeone P, Bologna G, Ercolino E, et al. The Characterization of Regulatory T-Cell Profiles in Alzheimer's Disease and Multiple Sclerosis. Sci Rep. 2019;9(1):8788.**
- 42. Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, et al. Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. Nature. 2020;577(7790):399-404.**
- 43. Fisher Y, Nemirovsky A, Baron R, Monsonogo A. T cells specifically targeted to amyloid plaques enhance plaque clearance in a mouse model of Alzheimer's disease. PLoS One. 2010;5(5):e10830.**
- 44. Monsonogo A, Zota V, Karni A, Krieger JJ, Bar-Or A, Bitan G, et al. Increased T cell reactivity to amyloid beta protein in older humans and patients with Alzheimer disease. J Clin Invest. 2003;112(3):415-22.**
- 45. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology. 2003;61(1):46-54.**
- 46. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet. 2008;372(9634):216-23.**
- 47. Lindestam Arlehamn CS, Pham J, Alcalay RN, Frazier A, Shorr E, Carpenter C, et al. Widespread Tau-Specific CD4 T Cell Reactivity in the General Population. J Immunol. 2019;203(1):84-92.**

48. Ferretti MT, Merlini M, Spani C, Gericke C, Schweizer N, Enzmann G, et al. T-cell brain infiltration and immature antigen-presenting cells in transgenic models of Alzheimer's disease-like cerebral amyloidosis. *Brain Behav Immun.* 2016;54:211-25.
49. Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal 'On' and 'Off' signals control microglia. *Trends Neurosci.* 2007;30(11):596-602.
50. Walker DG, Dalsing-Hernandez JE, Campbell NA, Lue LF. Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: a potential mechanism leading to chronic inflammation. *Exp Neurol.* 2009;215(1):5-19.
51. Denieffe S, Kelly RJ, McDonald C, Lyons A, Lynch MA. Classical activation of microglia in CD200-deficient mice is a consequence of blood brain barrier permeability and infiltration of peripheral cells. *Brain Behav Immun.* 2013;34:86-97.
52. Togo T, Akiyama H, Iseki E, Kondo H, Ikeda K, Kato M, et al. Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. *J Neuroimmunol.* 2002;124(1-2):83-92.
53. Merlini M, Kirabali T, Kulic L, Nitsch RM, Ferretti MT. Extravascular CD3+ T Cells in Brains of Alzheimer Disease Patients Correlate with Tau but Not with Amyloid Pathology: An Immunohistochemical Study. *Neurodegener Dis.* 2018;18(1):49-56.
54. Zotova E, Bharambe V, Cheaveau M, Morgan W, Holmes C, Harris S, et al. Inflammatory components in human Alzheimer's disease and after active amyloid-beta42 immunization. *Brain.* 2013;136(Pt 9):2677-96.
55. Louveau A, Harris TH, Kipnis J. Revisiting the Mechanisms of CNS Immune Privilege. *Trends Immunol.* 2015;36(10):569-77.
56. Driessens G, Kline J, Gajewski TF. Costimulatory and coinhibitory receptors in anti-tumor immunity. *Immunol Rev.* 2009;229(1):126-44.
57. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol.* 2015;15(8):486-99.
58. Chihara N, Madi A, Kondo T, Zhang H, Acharya N, Singer M, et al. Induction and transcriptional regulation of the co-inhibitory gene module in T cells. *Nature.* 2018;558(7710):454-9.
59. Smolders J, Heutink KM, Fransen NL, Remmerswaal EBM, Hombrink P, Ten Berge IJM, et al. Tissue-resident memory T cells populate the human brain. *Nat Commun.* 2018;9(1):4593.
60. Chihara N. Dysregulated T cells in multiple sclerosis. *Clin Exp Neuroimmunol.* 2018;9:20-9.
61. Mundt S, Mrdjen D, Utz SG, Greter M, Schreiner B, Becher B. Conventional DCs sample and present myelin antigens in the healthy CNS and allow parenchymal T cell entry to initiate neuroinflammation. *Sci Immunol.* 2019;4(31).
62. Schetters STT, Gomez-Nicola D, Garcia-Vallejo JJ, Van Kooyk Y. Neuroinflammation: Microglia and T Cells Get Ready to Tango. *Front Immunol.* 2017;8:1905.
63. Cebrian C, Loike JD, Sulzer D. Neuronal MHC-I expression and its implications in synaptic function,

axonal regeneration and Parkinson's and other brain diseases. *Front Neuroanat.* 2014;8:114.

64. Giuliani F, Goodyer CG, Antel JP, Yong VW. Vulnerability of human neurons to T cell-mediated cytotoxicity. *J Immunol.* 2003;171(1):368-79.

65. Yong VW, Moudjian R, Yong FP, Ruijs TC, Freedman MS, Cashman N, et al. Gamma-interferon promotes proliferation of adult human astrocytes in vitro and reactive gliosis in the adult mouse brain in vivo. *Proc Natl Acad Sci U S A.* 1991;88(16):7016-20.

66. Kann O, Almouhanna F, Chausse B. Interferon gamma: a master cytokine in microglia-mediated neural network dysfunction and neurodegeneration. *Trends Neurosci.* 2022;45(12):913-27.

67. Browne TC, McQuillan K, McManus RM, O'Reilly JA, Mills KH, Lynch MA. IFN-gamma Production by amyloid beta-specific Th1 cells promotes microglial activation and increases plaque burden in a mouse model of Alzheimer's disease. *J Immunol.* 2013;190(5):2241-51.

68. Sun J, Zhang S, Zhang X, Zhang X, Dong H, Qian Y. IL-17A is implicated in lipopolysaccharide-induced neuroinflammation and cognitive impairment in aged rats via microglial activation. *J Neuroinflammation.* 2015;12:165.

69. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, et al. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol.* 2008;172(1):146-55.

70. Zenaro E, Pietronigro E, Della Bianca V, Piacentino G, Marongiu L, Budui S, et al. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. *Nat Med.* 2015;21(8):880-6.

71. Laurent C, Dorothee G, Hunot S, Martin E, Monnet Y, Duchamp M, et al. Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. *Brain.* 2017;140(1):184-200.

72. Baek H, Ye M, Kang GH, Lee C, Lee G, Choi DB, et al. Neuroprotective effects of CD4+CD25+Foxp3+ regulatory T cells in a 3xTg-AD Alzheimer's disease model. *Oncotarget.* 2016;7(43):69347-57.

73. Ziv Y, Ron N, Butovsky O, Landa G, Sudai E, Greenberg N, et al. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nat Neurosci.* 2006;9(2):268-75.

74. Beers DR, Henkel JS, Zhao W, Wang J, Appel SH. CD4+ T cells support glial neuroprotection, slow disease progression, and modify glial morphology in an animal model of inherited ALS. *Proc Natl Acad Sci U S A.* 2008;105(40):15558-63.

75. Baruch K, Rosenzweig N, Kertser A, Deczkowska A, Sharif AM, Spinrad A, et al. Breaking immune tolerance by targeting Foxp3(+) regulatory T cells mitigates Alzheimer's disease pathology. *Nat Commun.* 2015;6:7967.

76. Mittal K, Eremenko E, Berner O, Elyahu Y, Strominger I, Apelblat D, et al. CD4 T Cells Induce A Subset of MHCII-Expressing Microglia that Attenuates Alzheimer Pathology. *iScience.* 2019;16:298-311.

77. Marsh SE, Abud EM, Lakatos A, Karimzadeh A, Yeung ST, Davtyan H, et al. The adaptive immune

system restrains Alzheimer's disease pathogenesis by modulating microglial function. *Proc Natl Acad Sci U S A*. 2016;113(9):E1316-25.

78. Cao C, Arendash GW, Dickson A, Mamcarz MB, Lin X, Ethell DW. Abeta-specific Th2 cells provide cognitive and pathological benefits to Alzheimer's mice without infiltrating the CNS. *Neurobiol Dis*. 2009;34(1):63-70.

79. Dutton RW, Bradley LM, Swain SL. T cell memory. *Annu Rev Immunol*. 1998;16:201-23.

80. Sallusto F, Geginat J, Lanzavecchia A. Central memory and effector memory T cell subsets: function, generation, and maintenance. *Annu Rev Immunol*. 2004;22:745-63.

81. Schenkel JM, Masopust D. Tissue-resident memory T cells. *Immunity*. 2014;41(6):886-97.

82. Koda Y, Teratani T, Chu PS, Hagihara Y, Mikami Y, Harada Y, et al. CD8(+) tissue-resident memory T cells promote liver fibrosis resolution by inducing apoptosis of hepatic stellate cells. *Nat Commun*. 2021;12(1):4474.

83. Yang K, Kallies A. Tissue-specific differentiation of CD8(+) resident memory T cells. *Trends Immunol*. 2021;42(10):876-90.

84. Lucchinetti CF, Popescu BF, Bunyan RF, Moll NM, Roemer SF, Lassmann H, et al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med*. 2011;365(23):2188-97.

85. Machado-Santos J, Saji E, Troscher AR, Paunovic M, Liblau R, Gabriely G, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. *Brain*. 2018;141(7):2066-82.

86. Fransen NL, Hsiao CC, van der Poel M, Engelenburg HJ, Verdaasdonk K, Vincenten MCJ, et al. Tissue-resident memory T cells invade the brain parenchyma in multiple sclerosis white matter lesions. *Brain*. 2020;143(6):1714-30.

87. Huseby ES, Liggitt D, Brabb T, Schnabel B, Ohlen C, Goverman J. A pathogenic role for myelin-specific CD8(+) T cells in a model for multiple sclerosis. *J Exp Med*. 2001;194(5):669-76.

88. van Nierop GP, van Luijn MM, Michels SS, Melief MJ, Janssen M, Langerak AW, et al. Phenotypic and functional characterization of T cells in white matter lesions of multiple sclerosis patients. *Acta Neuropathol*. 2017;134(3):383-401.

89. Koto S, Chihara N, Akatani R, Nakano H, Hara A, Sekiguchi K, et al. Transcription Factor c-Maf Promotes Immunoregulation of Programmed Cell Death 1-Expressed CD8(+) T Cells in Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4).

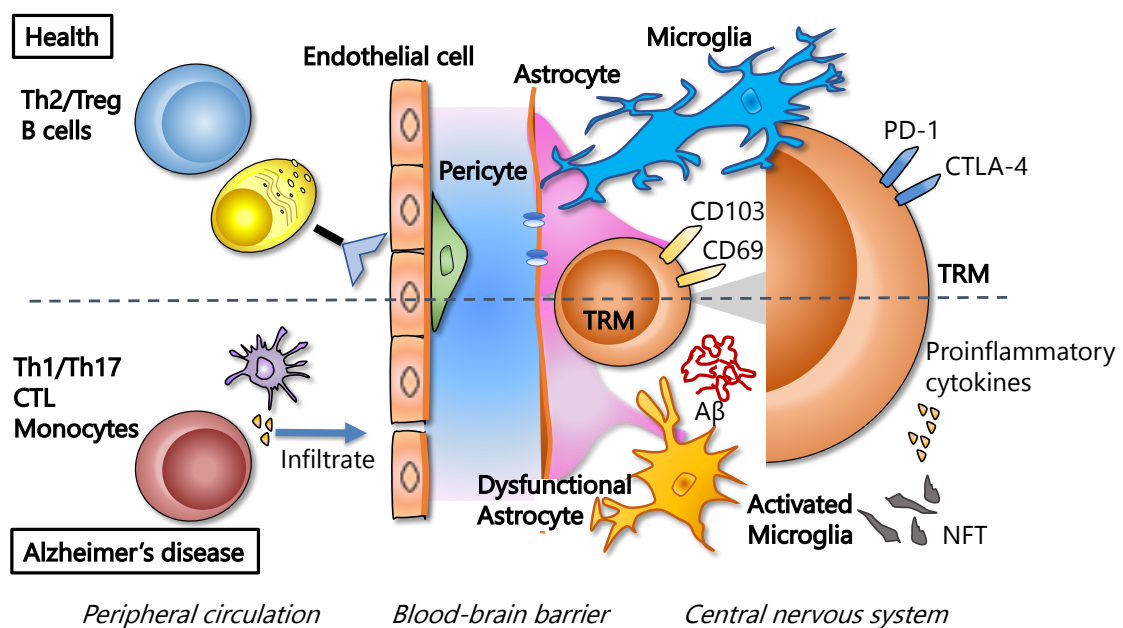
90. Maurice C, Schneider R, Kiehl TR, Bavi P, Roehrl MH, Mason WP, et al. Subacute CNS Demyelination after Treatment with Nivolumab for Melanoma. *Cancer Immunol Res*. 2015;3(12):1299-302.

91. Baruch K, Deczkowska A, Rosenzweig N, Tsitsou-Kampeli A, Sharif AM, Matcovitch-Natan O, et al. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nat Med*. 2016;22(2):135-7.

92. Altendorfer B, Unger MS, Poupardin R, Hoog A, Asslaber D, Gratz IK, et al. Transcriptomic Profiling

Identifies CD8(+) T Cells in the Brain of Aged and Alzheimer's Disease Transgenic Mice as Tissue-Resident Memory T Cells. *J Immunol.* 2022;209(7):1272-85.

93. Ritzel RM, Crapser J, Patel AR, Verma R, Grenier JM, Chauhan A, et al. Age-Associated Resident Memory CD8 T Cells in the Central Nervous System Are Primed To Potentiate Inflammation after Ischemic Brain Injury. *J Immunol.* 2016;196(8):3318-30.



	Immunological changes found in Alzheimer's disease or AD models
Peripheral circulation	Increase in Th17 cells and decrease in Treg cells (human)⁴⁰⁾ Treg cells dysfunction (human)⁴¹⁾ Increase in CD8⁺TEMRA cells correlated with cognitive decline⁴²⁾
Blood-brain barrier	Early AD promotes BBB permeability²⁹⁾ APOE4 proteins facilitate vascular permeability (human)³⁰⁾ Pericytes damage correlated with BBB permeability³⁵⁾ A β promotes BBB permeability^{26), 27)} Tau promotes BBB permeability²⁸⁾
Central nervous system	Th1 exacerbated AD model (mouse)⁶⁷⁾ Th1 ameliorated AD model (mouse)⁷⁶⁾ Interleukin-17 activated neutrophils cause neuronal damage (mouse)⁷⁰⁾ Treg depletion ameliorated AD model (mouse)⁷⁵⁾

Figure 1. T-cells in healthy tissue and tissue of patients with Alzheimer's disease

T-cells play a vital role in the immune system and patrol tissues for immune surveillance.

Dysregulated pro-inflammatory T-cells cause blood-brain barrier impairment and glial-cell activation or dysfunction. T-cells in Alzheimer's disease do not necessarily react to

abnormal A β and tau peptides to exhibit their pathogenic effects. TRMs increase with aging and contribute to maintaining homeostasis of the brain microenvironment; however, they may become proinflammatory cells in diseases. Th: helper CD4⁺ T cells, CTL; cytotoxic T lymphocytes (CD4⁺ and CD8⁺ T cells); Treg, regulatory T cells; TRM, tissue resident memory T cells; TEMRA, terminally differentiated, effector, memory re-expressing CD45RA; A β , amyloid beta; NFT, neurofibrillary tangles; PD-1, programmed cell death-1; CTLA-4, cytotoxic T-lymphocyte associated antigen-4.