

THE IMMUNE SYSTEM IN ALZHEIMER'S DISEASE: INNATE AND ADAPTIVE IMMUNITY, NEUROINFLAMMATION, AND THERAPEUTIC APPROACHES

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized pathologically by extracellular amyloid- β (A β) plaques and intracellular tau neurofibrillary tangles. Beyond these hallmark lesions, a growing body of evidence indicates that the immune system plays a pivotal role in AD pathogenesis. Neuroinflammatory processes – driven by both the brain's innate immune cells (e.g. microglia, astrocytes) and components of the adaptive immune system (e.g. T and B lymphocytes) – are now recognized as key mediators of neuronal injury and disease progression. Genetic risk factors for late-onset AD notably include several genes associated with immune functions, underscoring the connection between immunity and neurodegeneration. Microglial activation in response to A β and tau can be double-edged: acutely, microglia may phagocytose A β and protect neurons, but chronic activation leads to release of pro-inflammatory cytokines, complement components, and other neurotoxic factors that exacerbate synaptic dysfunction and neuronal loss. Similarly, peripheral immune cells infiltrating the aging or diseased brain – including CD8⁺ and CD4⁺ T cells, natural killer cells, neutrophils, and others – have been implicated in amplifying neuroinflammation and modulating AD pathology. This review provides a comprehensive overview of the role of the immune system in AD, covering innate immunity (microglial activation states, inflammasome signaling, complement cascade, astrocyte-mediated responses), adaptive immunity (T cell and B cell responses within the central nervous system), the interplay between chronic neuroinflammation and AD pathogenesis, cytokine profiles in AD patients, disruption of the blood-brain barrier and immune trafficking, and the influence of peripheral immune factors. We also discuss emerging immune-based therapeutic strategies for AD – ranging from anti-amyloid immunotherapies and vaccines to approaches aiming to temper detrimental inflammation or boost beneficial immune responses. Understanding the multifaceted role of immunity in AD offers promising avenues for intervention and biomarkers. Therapeutic modulation of the immune system – carefully calibrated to suppress harmful inflammation while preserving or enhancing clearance of pathological proteins – may hold the key to altering the course of AD.

Key words: Alzheimer's Disease (AD), Amyloid- β (A β) plaques, Tau neurofibrillary tangles, Immune System, Neuroinflammation

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia, accounting for an estimated 60–70% of all dementia cases worldwide[1]. It is pathologically defined by the accumulation of amyloid- β (A β) peptide in extracellular plaques and hyperphosphorylated tau protein in neurofibrillary tangles. For decades, research centered on the “amyloid cascade” and neuronal processes; however, accumulating evidence now highlights a critical role for the immune system and chronic inflammation in AD pathogenesis[2][3]. Post-mortem and biofluid studies have shown increased levels of inflammatory markers (cytokines, acute phase proteins, complement components) in AD patients[2]. Converging with these findings, large-scale genomic studies of late-onset AD have identified multiple risk genes associated with innate immune functions and microglial biology[4]. Notably, rare variants in genes such as TREM2, PLCG2, ABI3, CR1, and others implicate microglia-mediated innate immunity in AD susceptibility[5][4]. Such discoveries have prompted a re-evaluation of AD as not merely a neuronal proteinopathy, but also a disease of dysregulated immunity and chronic neuroinflammation[2][6]. Innate immune cells within the central nervous system (CNS), especially microglia, are now recognized as major players in AD progression[7]. Microglia are the resident macrophages of the brain, constantly surveilling the microenvironment and responding to injury or protein aggregates. In early disease stages, microglia can uptake and clear A β , possibly containing pathology[8][9]. However, sustained activation of microglia is associated with the secretion of pro-inflammatory cytokines, chemokines, and reactive oxygen species that drive neuroinflammation and neuronal damage[7][10]. In parallel, astrocytes – though not classical immune cells – respond to AD pathology by entering reactive states and releasing inflammatory mediators (e.g. interleukins, complement proteins), further contributing to the chronic inflammatory milieu. The adaptive immune system is also involved. There is evidence of T lymphocyte infiltration in the brains of AD patients, particularly CD8⁺ cytotoxic T cells in close proximity to amyloid plaques and tau

aggregates[11][12]. CD4⁺ T helper cells and B cells have been found in the meninges and perivascular spaces, suggesting that the brain is not completely immune-privileged in AD[13][14]. These peripheral immune cells can modulate microglial activation and possibly directly contribute to neurodegeneration through cytotoxic effects or autoantibody production.

Neuroinflammation – a sustained inflammatory response within the brain – has emerged as a central feature linking innate and adaptive immunity to AD pathology[2][15]. Chronic neuroinflammation can disrupt synaptic homeostasis, impair phagocytic clearance of A β , promote tau phosphorylation, and compromise blood-brain barrier integrity, creating a feed-forward cycle of neuronal injury[16][10]. The blood-brain barrier (BBB) itself often becomes leaky in AD, particularly in individuals carrying the APOE4 allele, the strongest genetic risk factor for sporadic AD[17]. BBB breakdown enables peripheral immune cells and molecules to infiltrate the CNS, further exacerbating neuroinflammatory processes[18][12]. Indeed, in vivo imaging and cerebrospinal fluid studies indicate that BBB dysfunction and peripheral inflammatory signals are early events in the AD trajectory, potentially preceding cognitive symptoms.

In this review, we discuss in detail the multifaceted role of the immune system in AD. We first examine innate immunity in the brain – focusing on microglial activation, phenotypic states, inflammasome signaling, and interactions with protein aggregates. We then explore adaptive immunity, including T cell and B cell responses within the CNS and evidence of peripheral immune infiltration. Next, we describe the neuroinflammatory environment in AD and key cytokine and chemokine alterations that characterize the disease. We review how BBB impairment and meningeal lymphatic dysfunction contribute to immune-cell trafficking into the brain and AD progression. The influence of peripheral immune factors – such as systemic inflammation, infections, and immune aging – on AD pathology is also considered. Finally, we highlight current and emerging immune-based therapeutic strategies for AD, from monoclonal antibodies and vaccines targeting A β or tau, to novel approaches aiming to modulate microglia or peripheral immune cell function. By elucidating the complex interplay between the immune system and AD, we aim to provide insight into how immunomodulation could pave the way for effective therapies in this devastating disease.

Innate Immunity and Microglial Activation in AD

Microglia as double-edged sensors of pathology: Microglia play a central role in the innate immune response of the brain, and their involvement in AD is profound. In healthy conditions, microglia perform critical homeostatic functions: synaptic pruning, phagocytic clearance of debris, and support of neurons. Upon encountering A β oligomers or fibrils, microglia recognize these through pattern recognition receptors (such as TLRs, NLRs, and scavenger receptors) and become activated. Activated microglia can internalize and degrade A β , which in early stages may mitigate plaque growth[8][9]. For instance, studies in AD mouse models have shown that microglial depletion leads to an increased burden of diffuse A β plaques and neuritic dystrophy despite reducing overall amyloid load, suggesting that microglia help compact plaques and limit their toxicity[19]. This protective facet is further supported by the existence of a specialized microglial phenotype termed “disease-associated microglia” (DAM), first identified in transcriptomic studies, which is associated with upregulation of genes like TREM2, TYROBP, and APOE in response to A β pathology[20]. DAM cluster around plaques and may encapsulate and phagocytose A β deposits[20]. Notably, the transition to the full DAM phenotype requires signaling through the microglial surface receptor TREM2[21], highlighting a genetically supported pathway by which microglia respond to AD pathology.

However, microglial activation also has a darker side. Chronically stimulated microglia can adopt a pro-inflammatory phenotype that secretes cytokines (e.g. interleukin-1 β , IL-6, tumor necrosis factor- α), chemokines, and other toxic mediators that contribute to neuronal dysfunction and death[7][10]. In AD brains and mouse models, microglia surrounding plaques often show an dystrophic, overly activated morphology and upregulate markers of inflammation (such as MHC-II, CD68) while downregulating homeostatic genes[7][22]. These overactivated microglia release large amounts of IL-1 β , IL-18, TNF- α , nitric oxide, and reactive oxygen species, creating a neurotoxic environment. Such inflammatory microglia can damage synapses and neurons, and also inhibit their own ability to clear A β , forming a vicious cycle where inflammation begets more pathology[23][16]. The concept of microglial polarization into “M1” (pro-inflammatory) vs “M2” (anti-inflammatory or reparative) states has been used to describe this spectrum, although actual microglial states in AD are diverse and not strictly binary. Contemporary single-cell RNA sequencing studies reveal multiple microglial subpopulations in AD, including interferon-responsive microglia and lipid-droplet-accumulating microglia, each with distinct functional profiles[24][25]. Overall, microglia act as a double-edged sword: they are essential for containment and clearance of pathological proteins, but if overactivated or dysregulated, they significantly contribute to neuroinflammation and neurodegeneration in AD.

Genetic links to microglial function: The crucial role of microglia in AD is underscored by genetics. Several AD risk genes are either specifically or highly expressed in microglia[9]. The most prominent is **TREM2** (Triggering Receptor Expressed on Myeloid cells 2), a receptor on microglia involved in recognizing lipid and damage signals. Rare heterozygous TREM2 variants (such as R47H) confer a substantial increase in AD risk (comparable to one copy of APOE4). Mechanistic studies show TREM2 is activated by ligands including A β oligomers and APOE, triggering signaling that enhances microglial survival, chemotaxis, and phagocytosis[5][26]. In AD models, loss of TREM2 function impairs microglial clustering around plaques, reduces A β clearance, and results in more severe plaque-associated neuritic damage[26]. Conversely, activating TREM2 signaling (for example, with agonist antibodies) can boost microglial uptake of A β and mitigate amyloid accumulation[26][27]. Other microglial genes implicated in AD include **CD33** (a sialic-acid-binding immunoglobulin receptor that negatively regulates phagocytosis) and **CR1** (complement receptor 1). These genes point to pathways of A β clearance and inflammatory regulation – when certain alleles are present, microglial A β uptake

may be less efficient or pro-inflammatory responses heightened, thereby facilitating AD pathology. Importantly, a large 2022 meta-GWAS confirmed that innate immune processes and microglial activation pathways are significantly overrepresented among AD risk loci[4]. This provides strong evidence that microglial dysfunction is not a mere consequence of AD, but a driving factor in disease development.

Inflammasomes and innate inflammatory signaling: Among the innate immune pathways active in AD, the **NLRP3 inflammasome** has gained particular attention. NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) is a pattern-recognition receptor expressed in microglia that senses diverse danger signals, including A β aggregates. In AD brains, microglial NLRP3 is often activated, leading to assembly of the inflammasome complex and caspase-1-mediated maturation of IL-1 β and IL-18[10]. This amplifies the inflammatory cascade within the brain. Chronic IL-1 β elevation can drive tau hyperphosphorylation and synaptic dysfunction. In transgenic models, genetic deletion or pharmacological inhibition of NLRP3 has striking benefits: Nlrp3-knockout APP/PS1 mice show enhanced microglial A β clearance, reduced plaque burden, and improved memory performance[10][28]. Similarly, in a tau transgenic model, NLRP3 deficiency prevented tau aggregation and spreading[28][29]. These studies position NLRP3-driven inflammation as a key mediator of AD neurotoxicity. Other innate sensing pathways are also at play. Toll-like receptors (TLRs) on microglia (e.g. TLR2, TLR4, TLR9) can bind misfolded proteins or damage-associated molecular patterns and trigger inflammatory signaling via NF- κ B. Sustained NF- κ B activation in microglia has been shown to exacerbate tau pathology and neuronal damage in experimental models[24]. Indeed, inhibition of microglial NF- κ B or IL-1 signaling in some studies attenuated AD-like pathology and rescued cognitive function[30]. Together, these findings illustrate that innate immune signaling cascades are central in propagating AD-related neuroinflammation.

Complement system and synaptic pruning: The complement cascade, a component of innate immunity, is increasingly recognized for its role in the AD brain. Complement proteins, especially C1q and C3, are upregulated in AD and localize to synapses and plaques[31]. Microglia and astrocytes secrete these complement factors, which can tag synapses for elimination. In normal development, a complement-mediated mechanism helps microglia prune excess synapses; in AD, this mechanism may be aberrantly reactivated, leading to excessive synapse loss. Studies show that inhibiting complement signaling can be protective: for example, genetic or antibody-mediated inactivation of C3 (the central complement protein) in AD model mice preserved synapses and improved cognitive performance[31][32]. Complement receptor 3 on microglia (CR3, which binds iC3b) mediates engulfment of complement-tagged synaptic material; blocking this receptor or downstream signaling reduced neuroinflammation and tau pathology in mouse models of tauopathy[33][34]. These data suggest that aberrant complement activation in the AD brain contributes to neural circuit disruption. Indeed, APOE4 has been associated with elevated complement activation, and human studies find higher complement levels in AD cerebrospinal fluid correlating with worse cognition[35]. Therapeutic targeting of complement (e.g. C1q or C3 inhibitors) is being explored as a way to halt synaptic loss in early AD.

Astrocytes and innate immunity: Astrocytes in AD also undergo reactive transformation and participate in innate immune responses. In AD brains, astrocytes around plaques become hypertrophic and upregulate glial fibrillary acidic protein (GFAP) – a hallmark of astrogliosis. These reactive astrocytes can secrete pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6) and complement components (especially C3) that further modulate microglial activity[36][37]. A subset of reactive astrocytes termed “A1” neurotoxic astrocytes, induced by microglial cytokines, has been described; these A1 astrocytes lose normal neurotrophic functions and gain the ability to release factors that kill neurons and oligodendrocytes. Post-mortem AD analyses show an abundance of A1 astrocytes in affected regions, implicating astrocytic pathology in the disease. Moreover, astrocytes are crucial for BBB maintenance and for uptake of neurotransmitters – functions that are compromised when astrocytes become reactive. On the other hand, astrocytes also carry APOE, and APOE genotype influences astrocyte responses. APOE4 astrocytes have been found to produce higher baseline levels of inflammatory mediators and to less efficiently support synapses compared to APOE3 astrocytes[17][38]. Targeting astrocyte-specific pathways (for instance, inhibiting astrocytic NADPH oxidase or inflammatory cascades) has shown reductions in AD pathology in some preclinical studies. Thus, while microglia are the front-line innate immune cells, astrocytes significantly contribute to the inflammatory network and neuroimmune dysregulation in AD.

In summary, innate immunity is deeply intertwined with AD pathophysiology. Microglia and astrocytes sense accumulating A β and tau and mount responses that are initially protective but become dysregulated over time. Chronic microglial activation and astrocytic inflammation create a self-perpetuating cycle of neuroinflammation, oxidative stress, and metabolic impairment in neurons. Genetic risk factors highlight that when innate immune regulation is perturbed, the brain may be more susceptible to AD. These insights into innate immune mechanisms provide a foundation for therapeutic strategies aimed at modulating microglial activity, inflammasome signaling, or complement activation to slow AD progression.

Adaptive Immune Responses in AD

Traditionally, the brain has been considered an immune-privileged organ with limited involvement of the adaptive immune system. However, research over the past decade has overturned this notion, revealing that adaptive immunity – particularly T cell responses – plays a role in AD. While the healthy brain contains only sparse populations of lymphocytes, the AD brain shows an accumulation of T cells in certain contexts. Both **CD8⁺ cytotoxic T lymphocytes** and **CD4⁺ helper T cells** have been detected at increased numbers in the brains, cerebrospinal fluid, and meninges of AD patients compared to age-matched controls[11][13]. These T cells can influence AD pathology in various ways:

T cell brain infiltration: In mild to moderate AD, cytotoxic CD8⁺ T cells are frequently found in proximity to neurons and amyloid plaques, particularly in the hippocampus and entorhinal cortex[39][13]. Single-cell sequencing analyses of postmortem brains have shown clonal expansions of CD8⁺ T cells in AD, some of which bear T cell receptors specific for viral antigens (e.g. Epstein-Barr virus)[40][41]. This suggests that peripheral immune activation (such as chronic viral infections) could drive T cells into the brain in AD. The recruitment of T cells is facilitated by a compromised blood-brain barrier and by chemokines produced within the AD brain. Microglia and astrocytes in AD can secrete T cell-attracting chemokines like CXCL10, CCL2, CCL5, etc. For example, CXCL10 (IP-10) is upregulated in AD and blocking the CXCL10-CXCR3 axis in a 3D human neuroimmune model reduced T cell infiltration and consequent neuropathology[42]. In mouse models, neutralizing CCL2 and CCL8 or CCL3 also lessened T cell entry and neuroinflammation[43]. Once across the BBB, CD8 T cells can patrol the parenchyma and may directly interact with neurons and glia. Live imaging in models shows motile T cells scanning along blood vessels and through brain tissue in the presence of pathology.

Cytotoxic effects and microglial crosstalk: CD8⁺ T cells can exert direct cytotoxicity by releasing perforin and granzymes, which induce apoptosis in target cells. In AD, infiltrating CD8 T cells have been observed to form contacts with neurons, and increased granzyme-positive T cells correlate with greater neuronal loss[23]. These T cells, while attempting to eliminate cells perceived as abnormal (e.g. neurons laden with aggregated tau), may cause collateral damage and synaptic dysfunction. Moreover, CD8 T cells strongly interact with microglia. Microglia activated by A β deposits can express antigen-presenting molecules (MHC class I and II) and co-stimulatory signals, potentially presenting neuronal or aggregated-protein antigens to T cells. In a feed-forward loop, microglia-derived chemokines recruit more CD8 T cells, and the CD8 T cells in turn secrete interferon- γ (IFN- γ) and TNF- α , which further activate microglia[23][44]. This cross-talk amplifies neuroinflammation: IFN- γ -activated microglia increase their production of pro-inflammatory cytokines (IL-1 β , IL-6, TNF) and can impair A β clearance while enhancing A β production by stressed neurons[44][45]. The net result is a self-perpetuating cycle of inflammation and neuronal damage involving CD8 T cells and microglia. Supporting this deleterious role, an elegant study demonstrated that depleting T cells from a tauopathy mouse model (by anti-CD4/CD8 antibodies) led to reduced neurodegeneration and improved cognition[46], and similarly, CD8 T cell infiltration into neuron–glia cultures exacerbated neurodegeneration[47].

CD4⁺ T helper cells: CD4 T cells are versatile regulators that can differentiate into various effector subsets, each with distinct effects on inflammation. In the context of AD, both **pro-inflammatory** and **anti-inflammatory** CD4 T cell responses have been reported. On the pro-inflammatory side, **Th1** cells (which secrete IFN- γ and TNF- α) and **Th17** cells (which produce IL-17A along with IL-21, IL-22, and GM-CSF) appear to exacerbate AD pathology. Th1 cells activated by A β can initially assist microglia in clearing plaques via IFN- γ signaling[48]. However, excessive Th1 activation causes high IFN- γ /TNF levels that overstimulate microglia and astrocytes, leading to neurotoxic inflammation and even increased A β production[48]. Th17 cells, which are induced by IL-6 and TGF- β signals, have been found in greater numbers in AD patients' blood and brains, and secrete IL-17 and IL-21 that can reduce microglial A β phagocytosis and drive inflammation[49]. In APP/PS1 transgenic mice, adoptive transfer of A β -specific Th17 cells accelerated cognitive decline and raised CNS cytokine levels (TNF, IL-17, IFN- γ)[49]. IL-17 from Th17 and from other sources (like $\gamma\delta$ T cells, discussed later) appears particularly potent in AD models, as neutralizing IL-17 alleviated neuroinflammation and improved cognition in mice[50]. Additionally, other pro-inflammatory T cell phenotypes such as **Th22** (secreting IL-22) and **Th9** (secreting IL-9) have been noted to increase in AD and may contribute to glial activation and lymphocyte recruitment[51].

Counterbalancing these are the **anti-inflammatory T cell responses**, mainly **Th2** cells and **regulatory T cells (Tregs)**. Th2 cells produce IL-4 and IL-10, cytokines that suppress microglial activation. In experimental models, Th2-polarized cells attenuated AD pathology: administration of A β -stimulated Th2 cells to APP/PS1 mice reduced pro-inflammatory cytokine levels and A β burden, while improving cognitive performance[52][53]. These Th2 cells appear to inhibit Th1/Th17 responses, shifting the immune environment to a less inflammatory state. Tregs, which are CD4 T cells expressing FOXP3, serve as crucial brakes on immune activation. They limit effector T cell proliferation and cytokine release via IL-10 and TGF- β . In AD patients, Treg numbers (as a proportion of CD4 T cells) have been reported to be reduced in blood and brains relative to non-AD elderly[54]. A deficiency in Tregs can permit excessive inflammation – indeed, AD individuals with fewer Tregs showed higher levels of TNF- α , IL-1 β , and IL-6[55]. In APP/PS1 mice, the presence of Th1/Th17 cells was shown to diminish Treg populations and activity, thereby unleashing greater inflammation[56]. Augmenting Treg function has emerged as a potential therapeutic approach: for instance, treating AD model mice with low-dose IL-2 (which selectively expands Tregs) led to increased Treg counts, a rebalance of the Th17/Treg ratio, reduction in amyloid plaques, and attenuation of neuroinflammation[57]. This strategy has progressed to a phase 2 trial in AD patients (low-dose IL-2 to boost Tregs)[57]. Similarly, adoptive transfer of ex vivo expanded Tregs into 5 $\times$ FAD mice resulted in decreased amyloid load, suppression of microglial overactivation and complement activation, and improved cognitive outcomes[58]. Curiously, some studies suggest that transient Treg depletion can also benefit amyloid clearance by provoking an acute immune response that recruits peripheral phagocytes to the brain[59]. This paradox underscores the complexity of T cell regulation in AD – timing and context are critical. Early in disease, enhancing Tregs might quell harmful inflammation, whereas in advanced disease a temporary lifting of immune suppression might aid debris clearance. Regardless, it is clear that the balance of pro- versus anti-inflammatory T cell activity in the CNS can significantly influence AD progression[60].

B cells and humoral immunity: In addition to T cells, B lymphocytes and antibodies have been implicated in AD immunity. Normally, healthy CNS parenchyma has very few B cells. In AD, some B cells can be found in the meningeal spaces and occasionally in parenchyma near vessels or plaques[61]. These B cells in AD appear to be activated (expressing markers of stimulation) and some produce autoantibodies against brain antigens, including potentially A β . The role of these antibodies is complex. On one hand, B-cell-derived immunoglobulins recognizing A β could bind plaques and facilitate their clearance by microglia (opsonization), potentially slowing plaque growth[61]. On the other hand, antibody binding might also form insoluble immune complexes or activate complement, which can worsen inflammation and impede microglial uptake of A β [62]. There is also interest in the concept of AD as an autoimmune process, where the immune system might erroneously target neurons or synapses. Some autoantibodies against neuronal components (e.g. neurotransmitter receptors) have been detected in AD patients, but their pathogenic significance remains unclear.

Animal studies provide more insight into B cell function. In transgenic AD mice, depletion of B cells (using anti-CD20 antibodies) yielded somewhat stage-dependent effects. In models with established pathology, B cell depletion was associated with reduced amyloid burden, less microglial activation, and improved cognitive and motor function[63]. This suggests B cells (or antibodies) were contributing to sustaining the pathology or inflammation. Paradoxically, when B cells were removed at very early stages in some models, the mice actually showed an acceleration of amyloid deposition and cognitive decline[64]. One hypothesis is that B cells may have a protective role early (perhaps through antibodies that neutralize toxic A β species), but become net harmful later (via promoting immune complex deposition or chronic inflammation). It is also possible that B cells influence T cell responses, as they can act as antigen-presenting cells and modulate Treg and Th17 differentiation. Indeed, a recent study demonstrated that therapeutic B cell depletion could reverse cognitive deficits in an AD mouse model, aligning with the idea that the peripheral immune system sustains brain inflammation in AD[65]. At least one clinical trial is now exploring B cell depletion (with an anti-CD20 monoclonal antibody) in AD patients to test if reducing adaptive immune activation can slow disease (e.g., NCT03887455).

In summary, although neurons and glia are the primary cells affected in AD, the adaptive immune system is an important contributor to the disease's immunopathology. T cells infiltrating the brain can accelerate neurodegeneration through cytotoxicity and by driving microglial and astroglial inflammation. The fine balance between harmful (e.g., Th1/Th17-mediated) and protective (e.g., Th2/Treg-mediated) adaptive responses may influence how rapidly AD progresses in a given individual. B cells and antibodies add another layer, potentially influencing amyloid dynamics and glial activation. These insights suggest that modulating adaptive immunity – for instance, enhancing Treg activity or inhibiting pro-inflammatory T cell responses – could be a viable therapeutic strategy. However, given the dual nature of adaptive immune effects, any such approaches must be finely targeted and timed. The emerging picture is that AD is not simply a CNS-autonomous disorder, but rather a neuroimmune condition wherein peripheral immune cells and CNS immune responses jointly shape the disease course.

Neuroinflammation and Cytokine Dysregulation in AD

One of the defining features linking the innate and adaptive immune abnormalities in Alzheimer's disease is **neuroinflammation** – a state of chronic, widespread inflammation in the brain. Neuroinflammation in AD is mediated by activated microglia and astrocytes, infiltrating immune cells, and the plethora of inflammatory molecules they produce. Over the course of the disease, this inflammatory milieu becomes self-sustaining and contributes directly to neuronal injury and dysfunction[2][15].

Pro-inflammatory cytokines in AD: AD patients consistently show elevated levels of various pro-inflammatory cytokines in both the central nervous system and peripheral circulation. In the brain and cerebrospinal fluid, analyses have found higher concentrations of interleukins such as IL-1 β , IL-6, IL-8, IL-12, as well as cytokines like tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), compared to cognitively normal elders[2][66]. Many of these cytokines are also increased in the plasma of AD patients, and can cross into the brain across a compromised BBB, further fueling neuroinflammation[66][67]. For example, IL-6 is a key pro-inflammatory mediator consistently linked to AD; it promotes differentiation of Th17 cells and activation of microglia, and high IL-6 levels correlate with cognitive decline[68][69]. TNF- α , chiefly produced by microglia and infiltrating macrophages, can impair synaptic plasticity and drive neuronal apoptosis; its levels are often elevated in AD serum and brain tissue and have been associated with more rapid cognitive deterioration[70][71]. IL-1 β , one of the first cytokines recognized in AD pathology, is markedly upregulated by microglia around plaques. IL-1 β acutely triggers astrocytes and microglia to produce a cascade of other cytokines and also promotes tau phosphorylation via stress kinases. Sustained IL-1 signaling in AD models exacerbates plaque and tangle formation, whereas blocking IL-1 (for instance, with IL-1 receptor antagonists or genetic knockout) reduced neuropathology and improved memory in those models[30].

Interferons and immune polarization: Interferon- γ (IFN- γ), a Type II interferon, is another cytokine with a complex role in AD. At low or transient levels, IFN- γ can be beneficial – it enhances microglial uptake of A β and recruitment of blood-derived macrophages that help clear amyloid[16]. Indeed, IFN- γ can induce an “A β -clearing” phenotype in myeloid cells and has been shown to improve cognitive function in some mouse studies when present at physiological levels[16]. However, chronic elevation of IFN- γ is deleterious: it activates endothelial cells and disrupts tight junctions, contributing to BBB leakage[72]. Persistently high IFN- γ in the brain also leads to prolonged MHC II expression and antigen presentation by microglia, sustaining a feed-forward loop of T cell recruitment and inflammation[44][36]. Type I interferons (like IFN- α/β), typically produced during viral responses, have been found activated in some AD brains as well. Type I IFNs can drive microglia into a reactive state that excessively prune synapses (as seen in certain neurodegenerative models)[73]. Blocking the IFN- α/β receptor in APP transgenic mice reduced microglial activation and protected synapses[73], suggesting that an IFN-driven immune profile might contribute to cognitive decline in AD.

Chemokines: Alongside cytokines, chemokines are important in AD for mediating cell migration and positioning. Chemokines like CCL2 (MCP-1), CXCL8 (IL-8), CCL5 (RANTES), CXCL10 (IP-10) are upregulated in AD brains[14][12]. As discussed, these chemokines can attract peripheral monocytes, T cells, and other leukocytes into the brain. CCL2, for example, is produced by astrocytes and microglia in AD and can facilitate infiltration of CCR2⁺ monocytes; AD mice lacking CCL2 or CCR2 have reduced neuroinflammation but paradoxically often accumulate more amyloid due to impaired clearance (highlighting that some inflammation is part of a clearance response). Nonetheless, excess chemokine signaling likely enhances deleterious immune cell entry. Elevated CXCL8/IL-8 in AD may drive neutrophil chemotaxis to brain vessels, and higher CXCL10 correlates with more T cells in CSF[40].

Inflammatory amplifiers – NLRP3 inflammasome: A crucial intracellular mechanism in microglia for cytokine release is the NLRP3 inflammasome, as noted earlier. In AD, A β crystals and oligomers act as danger signals that trigger microglial NLRP3 activation[10]. This leads to caspase-1 activation and the maturation of the potent pro-inflammatory cytokine IL-1 β . Inflammasome activation also induces a form of cell death called pyroptosis in microglia, which can release HMGB1 and other inflammatory danger signals. The overall effect is a significant amplification of the inflammatory response. Pathologically, brains of AD patients and transgenic mice show evidence of active inflammasomes in microglia (e.g., ASC specks, cleaved caspase-1). The contributions of NLRP3 extend to tau pathology as well, since IL-1 β and related inflammasome products can facilitate tau phosphorylation and aggregation[36]. In a seminal study, blocking NLRP3 genetically or using a drug (MCC950) dramatically reduced tau-mediated neurodegeneration[36]. These findings have stimulated efforts to develop NLRP3 inhibitors as AD therapeutics[74].

Chronic inflammation and neuronal dysfunction: The persistent presence of pro-inflammatory cytokines in the AD brain has direct impacts on neurons. TNF- α and IL-1 β can downregulate neurotransmitter receptors and alter synaptic plasticity, contributing to cognitive symptoms. For instance, TNF- α causes internalization of synaptic AMPA glutamate receptors, weakening synaptic transmission. IL-1 β can disrupt long-term potentiation (LTP), a mechanism of memory encoding, and promote hyperexcitability that might lead to seizures (which are observed at higher incidence in AD patients). IFN- γ exposure on neurons induces inducible nitric oxide synthase (iNOS) in nearby glia, leading to nitric oxide production that damages neurons. Over time, this inflammatory stress can trigger apoptotic and necroptotic pathways in neurons. Additionally, inflammation affects brain metabolism and vascular function – cytokines like IL-1 β and IL-6 cause astrocytes to reduce support for neurons and can lead to alterations in blood flow and blood-brain barrier permeability.

Anti-inflammatory responses: In a healthy system, pro-inflammatory processes are counter-regulated by anti-inflammatory signals. In AD, however, these anti-inflammatory responses appear insufficient. Key anti-inflammatory cytokines include IL-10 and TGF- β . IL-10 is produced by certain microglia, astrocytes, and Treg lymphocytes, and acts to suppress microglial activation and promote tissue repair. Some AD patients paradoxically have elevated IL-10 in the brain, which might reflect a compensatory response; yet, if IL-10 is chronically high, it can also reduce microglial A β clearance ability (since inflammation and phagocytosis are somewhat linked). TGF- β is a pleiotropic cytokine that, in the brain, helps maintain homeostasis and inhibit immune cell effector functions. While early AD may see an increase in TGF- β signaling (e.g., elevated TGF- β 1 in plaque areas), later stages often show TGF- β pathway dysregulation, which correlates with more aggressive inflammation. Indeed, mice overexpressing TGF- β 1 in astrocytes showed reduced inflammation and amyloid burden[52], whereas TGF- β disruption exacerbated pathology. Enhancing anti-inflammatory pathways is a therapeutic angle under study – for example, a trial of an IL-10 gene therapy in a mouse model showed reduced plaques and inflammatory markers.

Systemic inflammation and AD: It is also noteworthy that systemic inflammatory events (such as infections or comorbid conditions) can worsen neuroinflammation in AD. AD patients who experience infections or surgery often have transient delirium or accelerated cognitive decline, likely because peripheral cytokines (like IL-6, TNF) surge and impact the brain's immune environment. Markers of systemic inflammation (e.g., C-reactive protein, IL-6) are associated with higher risk of cognitive deterioration in longitudinal studies. This crosstalk between peripheral and central inflammation further emphasizes the importance of controlling overall immune activation in individuals at risk for or living with AD.

In conclusion, neuroinflammation in AD is characterized by a dysregulated cytokine network with excessive pro-inflammatory and inadequate anti-inflammatory signaling. The chronic production of cytokines and chemokines by activated glia and infiltrating immune cells creates an environment that is hostile to neurons and synapses. Neuroinflammation not only exacerbates the core AD pathologies of A β and tau but also independently impairs neural function. Targeting specific cytokines or their signaling pathways (for instance, via anti-TNF agents or inflammasome inhibitors) represents a rational strategy to break this vicious cycle. However, given the complex role of immune signaling (some inflammation is needed for repair and amyloid clearance), therapies must aim for a modulation rather than complete suppression of the immune response.

Blood-Brain Barrier Dysfunction and Immune-Brain Crosstalk

The **blood-brain barrier (BBB)** is a specialized endothelial barrier that tightly regulates the movement of cells and molecules between the bloodstream and the brain parenchyma. In AD, mounting evidence indicates that BBB integrity is compromised, which has significant implications for immune system interactions with the brain. A healthy BBB, composed of tightly connected endothelial cells with support from pericytes and astrocytic end-feet, maintains CNS immune privilege by restricting entry of peripheral immune cells[75][76]. In AD, however, multiple factors converge to disrupt the BBB: cerebrovascular degeneration, chronic inflammation, amyloid deposition in vessel walls, and APOE4-related vascular effects.

Cerebral amyloid angiopathy and BBB damage: Many AD patients (especially APOE4 carriers) exhibit **cerebral amyloid angiopathy (CAA)**, where A β deposits in the walls of cerebral blood vessels. These amyloid-laden vessels undergo structural weakening and inflammation, leading to endothelial damage and loss of tight junction proteins[77][78]. CAA is known to cause microhemorrhages (tiny brain bleeds visible on MRI) and capillary degeneration. Pathologically, CAA can be seen as a ring of amyloid around blood vessels, often accompanied by activated perivascular microglia and peripheral macrophages. The deposition of A β in vessel walls physically disrupts the BBB, as evidenced by leakage of plasma proteins like fibrinogen and immunoglobulins into the brain parenchyma in those areas[17][79]. Indeed, studies of cognitively normal APOE4 carriers (who do not yet have dementia) have found elevated albumin in the cerebrospinal fluid and subtle imaging signs of BBB leak, suggesting BBB impairment may start even before significant cognitive symptoms in genetically at-risk individuals[17].

APOE4 and vascular contributions: The APOE4 allele has direct detrimental effects on the cerebrovasculature. APOE4 has been shown to bind less effectively to receptors (like LRP1) that clear A β from the brain across the BBB, thereby slowing A β clearance[80]. Additionally, APOE4 is associated with damage to the BBB's cellular components: it promotes pericyte loss and downregulates endothelial tight junction proteins, resulting in increased permeability[79][81]. APOE4 also correlates with higher levels of pro-inflammatory mediators in brain vessels (e.g. cyclophilin A and matrix metalloproteinases) that can degrade the basement membrane and tight junctions[17]. Clinically, PET imaging with contrast agents and dynamic contrast MRI have shown that individuals with APOE4 have greater BBB leakage in the hippocampus even in mild cognitive impairment. Therefore, genetic risk factors like APOE4 link to AD in part via BBB breakdown.

Immune cell infiltration: When the BBB is impaired, peripheral immune cells gain increased access to the brain. Autopsy studies of AD brains reveal blood-derived **macrophages** and **lymphocytes** within the parenchyma and perivascular spaces that are rarely seen in healthy brains[12][82]. **Monocyte-derived macrophages** can enter through leaky capillaries or meningeal vessels; in late-stage AD, these peripheral macrophages are found around plaques and often contain A β , indicating they attempt to phagocytose amyloid[82]. However, their efficiency in clearance might be lower or their presence might also contribute to inflammation (macrophages release cytokines similar to microglia). Interestingly, substituting microglia with peripheral monocytes in some experiments did not markedly reduce plaque load[83], suggesting that while peripheral macrophages can assist, they may not replicate all functions of microglia.

T cells traverse into the AD brain via multiple routes. Besides direct crossing of a compromised BBB, research in mouse models indicates that **dural venous sinuses and meningeal lymphatic vessels** are pathways for immune cell trafficking[84][85]. The meninges (the protective membranes around the brain) are an active interface of the immune system and CNS. In AD models, T cells have been observed accumulating in the meninges and then penetrating into the brain along perivascular spaces. The meningeal **lymphatic system**, which normally helps drain interstitial fluid and immune cells to cervical lymph nodes, appears to deteriorate with age and even more so in AD. Impaired meningeal lymphatic drainage in AD mice led to reduced clearance of A β from the brain and increased deposition of amyloid in the meninges and parenchyma[86]. Conversely, enhancing lymphatic drainage – for example, by growth factors or surgical intervention – improved A β removal and even potentiated the effects of anti-A β immunotherapy[87]. These findings highlight that the boundary between the CNS and peripheral immune system becomes more porous in AD, both due to BBB breakdown and lymphatic dysfunction.

With a leaking BBB, **circulating cytokines and complement proteins** also flood into the CNS. Peripheral inflammation (from infections, etc.) can thus acutely worsen AD pathology because factors like IL-6 or TNF- α from the blood enter the brain and activate microglia[66]. This may explain why AD patients often experience cognitive dips during systemic illnesses (sometimes termed “sickness behavior” on top of dementia). Chronic BBB leak may allow a slow drip of such factors maintaining brain inflammation continuously.

Neutrophils and vascular inflammation: Neutrophils, the acute responders of the innate immune system, have emerged as surprising contributors to AD, particularly at the BBB interface. In AD models, neutrophils adhere to the brain's capillary endothelium (a phenomenon known as “neutrophil plugging”), which can reduce cerebral blood flow[78]. This exacerbates the already reduced perfusion seen in AD and can lead to localized ischemia. Neutrophils release proteases and oxidants that degrade tight junctions (e.g., neutrophil elastase can cleave occludin and claudins), further opening the BBB[78]. They also form neutrophil extracellular traps (NETs) in vessel walls near plaques, which consist of DNA and enzymes that are highly pro-inflammatory[88]. Elevated interleukin-17 from neutrophils (and $\gamma\delta$ T cells) has been observed in AD mice, linking neutrophils to the adaptive immune axis as well[89]. Reducing neutrophil recruitment to the brain – either by transient neutrophil depletion or blocking adhesion molecules like LFA-1 – led to improved cerebral blood flow and reduced amyloid pathology in AD mice[90]. These results indicate that neutrophil activity at the neurovascular interface is another mechanism by which peripheral immunity can inflict damage in AD.

Peripheral immune aging (immunosenescence): Aging of the immune system in general (termed immunosenescence) might also impact AD. Elderly individuals often have a higher proportion of late-differentiated, senescent T cells (for example, CD8⁺ effector memory CD45RA⁺ cells, called T_{EMRA}) that produce high levels of inflammatory cytokines[40]. AD patients show expansions of such T_{EMRA} cells in blood, and intriguingly, some of these cells are clonally expanded with specificity to latent viruses like EBV[40]. This suggests chronic peripheral antigen exposure (like herpesviruses) might lead to a pool of reactive T cells that later cross into the brain. Additionally, immunosenescence involves reduced diversity in T and B cell receptors, which may impair the ability to respond to new threats but can allow clonal domination of potentially autoreactive cells. AD patients, despite overall

immune senescence, paradoxically have heightened T cell responses to A β peptides[91] – perhaps due to persistent exposure to accumulating A β providing a chronic antigen stimulus.

Feedback on BBB function by CNS immune cells: Once peripheral immune cells infiltrate the brain, they can further affect BBB integrity. For instance, activated T cells in the CNS produce matrix metalloproteinases and vascular endothelial growth factor (VEGF), which can degrade the basement membrane and loosen tight junctions, respectively. Microglia activated by A β can release TNF and IL-1 that act on endothelial receptors to reduce junctional protein expression[72]. In this way, neuroinflammation can create a feedback loop worsening BBB permeability.

In summary, the BBB in AD becomes a leaky border through which peripheral and central immune factors continuously interact. This loss of compartmentalization means that systemic inflammation can directly aggravate brain pathology, and conversely, CNS-derived antigens (like A β , tau) can egress to lymph nodes to induce peripheral immune responses. Therapeutically, stabilizing the BBB and improving waste clearance (e.g., enhancing meningeal lymphatics) are emerging strategies. Some experimental drugs (such as inhibitors of MMP-9 or agents that boost endothelial tight junctions) are being tested to protect the BBB in AD models[79][81]. Moreover, the recognition that peripheral cells like neutrophils and monocytes contribute to AD suggests that targeting these cells or their adhesion to the BBB (for example, with integrin blockers) could mitigate neuroinflammation. Ultimately, the interplay of a failing BBB and immune infiltration is a crucial component of AD pathophysiology, linking cerebrovascular health to neurodegeneration.

Peripheral Immune Modulation of AD Pathology

Beyond the localized events at the BBB, the broader state of the peripheral immune system can significantly influence Alzheimer's disease progression. AD does not occur in isolation from the rest of the body; rather, peripheral immune signals and cells can modulate the neuroinflammatory environment and vice versa. Several lines of research illustrate this bidirectional “crosstalk” between the peripheral immune system and the AD brain:

Systemic inflammation and cognitive decline: Epidemiological studies have found that elevated peripheral inflammatory markers, such as high-sensitivity C-reactive protein (CRP) and pro-inflammatory cytokines, are risk factors for accelerated cognitive decline and dementia conversion. Individuals with autoimmune diseases or chronic infections (which involve systemic inflammation) often have higher incidence of cognitive impairment in late life. Experimentally, peripheral administration of lipopolysaccharide (LPS, a mimic of bacterial infection) to AD model mice results in increased brain A β deposition and microglial activation, suggesting that systemic immune activation can exacerbate AD pathology. This is thought to be due to circulating cytokines like IL-6 and TNF- α crossing into the brain and “priming” microglia to a more reactive state[66][67]. Additionally, during peripheral infections, monocytes are activated and can more readily migrate into the brain, where they intensify plaque-associated inflammation. Clinically, AD patients often experience episodes of delirium or sudden cognitive worsening during urinary tract infections or pneumonia; these episodes correspond to surges in systemic cytokines and typically subside with resolution of infection, but they may leave lasting damage.

Peripheral monocytes and macrophages: Monocytes circulating in the blood can be attracted to the AD brain by chemokines (CCL2, CCL5, etc.) and by endothelial adhesion molecules upregulated in response to A β and inflammation. Once they enter the CNS and differentiate into macrophages, these cells function similarly to microglia in ingesting A β and secreting cytokines. There is evidence that bone-marrow-derived monocytes can partially compensate for dysfunctional microglia in clearing plaques[82]. However, the ability of peripheral macrophages to traffic to the brain is limited; it occurs more during breach of the BBB or when microglia are depleted. Therapeutic approaches have aimed to enhance this recruitment – for example, short-term depletion of microglia causes blood monocytes to infiltrate and assume plaque-cleaning roles, which in some models reduced A β burden. On the other hand, these monocyte-derived macrophages may also release enzymes (like elastase, myeloperoxidase) that contribute to tissue damage. AD brains often show perivascular iron deposits and hemosiderin-laden macrophages (signs of microbleeds being cleaned up by macrophages), reflecting chronic vascular damage and repair by peripheral immune cells. Overall, while peripheral macrophages can aid in A β clearance under certain conditions, their recruitment is a double-edged sword – beneficial in removing debris, but potentially harmful via inflammatory byproducts.

Neutrophils: As described, neutrophils have been implicated in AD through their impact on cerebral blood flow and BBB integrity[78]. AD transgenic mice display an accumulation of neutrophils in cerebral vessels, and neutrophil depletion improved memory function[92]. In humans, AD patients have higher neutrophil counts and neutrophil-related inflammation in peripheral blood, which some studies correlate with faster cognitive decline. Neutrophils may also carry peripheral inflammatory signals into the brain; for example, a neutrophil's lifespan is short, but as it transmigrates it can leave behind enzymes and cytokines in the brain tissue. Targeting neutrophil adhesion (e.g., with LFA-1 integrin inhibitors) is being explored in preclinical studies as a means to protect the microcirculation in AD[90].

Natural killer (NK) cells: NK cells are innate lymphocytes that typically attack virally infected or tumor cells. Their role in AD is not fully defined, but recent studies suggest they are present in higher numbers in AD brains and CSF compared to controls. NK cells can produce IFN- γ and TNF, and one report indicated that NK cell depletion in an AD mouse model led to reduced neuroinflammation and improved neurogenesis[93]. Curiously though, another study found that boosting NK cell activity in APP/PS1 mice (via injecting activated NK cells) led to reduced A β deposition[94]. This implies a paradoxical role: NK cells might kill stressed neurons or glial cells (worsening damage), but they might also help clear pathological cells or stimulate phagocytosis (aiding clearance). An early-phase human trial (ASK-AD) has tested infusions of autologous NK cells in AD, with preliminary reports suggesting possible lowering of amyloid and tau levels[95]. Much remains to be learned about NK cells in AD, but their production of inflammatory mediators and interactions with microglia (through cytokines like GM-CSF or direct cytotoxicity) add another layer to peripheral immune influence.

Innate-like T cells (MAIT and $\gamma\delta$ T cells): Beyond conventional T cells, innate-like T lymphocytes have been linked to AD. **Mucosal-associated invariant T (MAIT) cells**, which respond to bacterial metabolites, are increased in number and activation in the 5 $\times$ FAD mouse model as disease progresses[96]. MAIT cells require the MR1 molecule for antigen presentation, and interestingly, MR1 expression is up in microglia around plaques in both mice and human AD[97]. When MR1 is knocked out, amyloid pathology is reduced in mice[98], suggesting MAIT cell–microglia interactions might exacerbate plaque deposition or related inflammation. **Gamma-delta ($\gamma\delta$) T cells**, another innate T cell subset, are a major source of IL-17 in the meninges and help with normal memory in healthy animals[99]. In AD models, $\gamma\delta$ T cells massively accumulate in the brain and meninges, producing IL-17A, which has been tied to early synaptic and cognitive dysfunction[99]. These $\gamma\delta$ T cells may be responding to AD pathology or chemokines, and in doing so, they amplify the Th17-type inflammatory environment. Blocking IL-17 or depleting $\gamma\delta$ T cells in 3 $\times$ Tg AD mice ameliorated memory deficits, underscoring their contribution.

Peripheral metabolic factors and immunity: Metabolic conditions such as obesity, diabetes, and hyperlipidemia, which are often accompanied by chronic low-grade inflammation, are risk factors for AD. Adipose tissue produces inflammatory cytokines (like TNF and IL-6) that can influence neuroinflammation. Moreover, metabolic dysfunction can activate the NLRP3 inflammasome in peripheral immune cells, potentially “priming” the innate immune system such that microglia in the brain are more reactive. Some peripheral molecules act as immune modulators in the brain: for example, leptin (an adipokine) has neuroimmune effects and its dysregulation in metabolic syndrome might impact AD pathways.

Beta-2 microglobulin (B2M): B2M is a component of MHC class I molecules and a factor that increases with age systemically. Notably, B2M levels are elevated in AD patients’ blood and CSF, and research has shown that B2M can cross the BBB and negatively affect cognition[100][101]. In AD models, high B2M promotes A β aggregation (it can co-aggregate with A β) and neuroinflammation[100]. Reducing B2M (genetically or with antibodies) in AD mice improved memory and reduced amyloid load[102]. B2M is thus a peripheral immune-related molecule that modulates AD pathology, representing a link between systemic immune aging and AD progression. It exemplifies how peripheral immune **mediators** (not just cells) can drive central pathology.

In summary, the peripheral immune system’s state – whether it be acute inflammation from an infection, chronic inflammation from diseases, or immune senescence from aging – can greatly modulate the course of Alzheimer’s disease. Peripheral immune cells such as monocytes, neutrophils, NK cells, and unconventional T cells participate in AD-related inflammation when given access to the brain. Soluble factors from the periphery can either exacerbate (e.g. pro-inflammatory cytokines, B2M) or potentially ameliorate (e.g. some anti-inflammatory signals) the neuronal environment. This systemic influence on AD suggests that treating peripheral inflammation (for example, through anti-inflammatory drugs or management of comorbidities) might have positive effects on AD outcomes. It also raises caution that systemic infections or stressors in AD patients should be swiftly addressed, as they could hasten neurodegenerative processes. The interplay between the peripheral immune system and the AD brain reinforces the concept of AD as a whole-body disorder of aging, not solely confined to the brain.

Immune-Based Therapeutic Strategies in AD

With the recognition of the immune system’s central role in AD pathogenesis, numerous therapeutic approaches have been proposed or are under development to target immune-related mechanisms. These **immune-based therapies** aim either to reduce the deleterious aspects of the AD immune response (e.g. dampening harmful inflammation) or to enhance beneficial immune functions (e.g. promoting clearance of pathological proteins). Below, we outline key immunotherapeutic strategies, ranging from those already in clinical use to experimental approaches in preclinical stages.

1. Anti-amyloid Immunotherapies: The most advanced immune-based treatments for AD are the monoclonal antibodies targeting A β . These include **passive immunotherapies** such as aducanumab, lecanemab, and donanemab, which are laboratory-made antibodies administered to patients to bind A β . By tagging A β aggregates, these antibodies facilitate microglial phagocytosis of plaques. Recently, clinical trials have demonstrated that such antibodies can significantly clear brain amyloid and modestly slow cognitive decline in early-stage AD[103]. For example, lecanemab (an antibody against A β protofibrils) in an 18-month Phase 3 trial (Clarity AD) resulted in a 27% reduction in the rate of cognitive decline compared to placebo, alongside a robust lowering of amyloid PET signal[103][104]. These outcomes led to lecanemab’s FDA approval in 2023. Donanemab, targeting A β plaque “cores,” likewise showed positive Phase 3 results, slowing clinical decline by around 35% in early AD and removing amyloid plaques in many patients. Such results provide proof-of-concept that engaging the immune system to remove pathological protein aggregates can affect disease progression. However, these therapies also underscore the complexities of immune modulation: a significant fraction of patients receiving anti-A β antibodies experience **ARIA (amyloid-related imaging abnormalities)**, which are MRI-detected brain edema or microhemorrhages[105]. ARIA is thought to result from antibody-triggered microglial activation and complement engagement around blood vessels where plaques are being removed, essentially an immune-mediated side effect. Most ARIA-E (edema) cases are asymptomatic and resolve, but a few can be serious. Thus, while anti-amyloid immunotherapies represent a major breakthrough, they must be managed carefully to balance efficacious plaque clearance with the risk of immune-related adverse effects.

Active A β vaccines are another approach, wherein patients’ own immune systems are stimulated to produce anti-A β antibodies. The first such vaccine (AN1792) in the early 2000s did generate antibodies and clear some plaques, but it was halted when ~6% of patients developed meningoencephalitis – likely an autoreactive T cell response to A β peptide[106]. This taught researchers that vaccine design must avoid strong T cell epitope activation. Second-generation vaccines (CAD106, UB-311, etc.) use shorter A β fragments or conjugates to focus the immune response on B cell (antibody)

production while minimizing T cell help. These have shown safer profiles in trials, with CAD106 demonstrating amyloid reduction without major inflammation, although clinical benefit remains to be proven. A recent innovative vaccine strategy packaged A β fragments in a nanocarrier that also promoted regulatory T cell responses specific to A β , aiming to induce a more tolerogenic immune reaction[107]. In mouse models, such approaches generated antibodies that cleared plaques and concurrently boosted A β -specific Tregs, reducing neuroinflammation. Active vaccination could provide long-term immunity against amyloid buildup, but challenges include variability in patient immune responses and ensuring safety.

2. Anti-tau Immunotherapies: Tau pathology follows amyloid and correlates strongly with neuronal loss and cognitive symptoms. Thus, immunotherapies targeting abnormal tau have been pursued. Several anti-tau monoclonal antibodies (e.g., gosuranemab, tilavonemab, semorinemab) have undergone clinical trials. The goal is to bind extracellular tau or tau fragments and facilitate their clearance or prevent neuron-to-neuron spread of tau aggregates. So far, results have been mixed – some antibodies did not significantly slow cognitive decline in Phase 2 trials despite engaging tau, whereas one (semorinemab) showed a modest slowing of decline in mild dementia. It's possible that tau immunotherapy might need to be given earlier or that targeting specific tau species (like oligomers or propagation-competent fragments) is critical. Vaccines against tau (ACI-35, AADvac1) are also in trials and have shown that they can induce anti-tau antibody responses. The field is still determining if reducing tau with antibodies will translate to clinical benefit, but it remains a promising avenue especially as tau imaging can now identify the right patients.

3. Modulating Microglia and Innate Immune Receptors: Given microglia's central role, therapies aim to shift microglial activity from a neurotoxic to a neuroprotective mode. One approach is via **TREM2 agonists**. As noted, TREM2 activation enhances microglial uptake of debris and clustering around plaques. Pharmaceutical companies are developing antibodies or Fc-fusion proteins that activate TREM2 signaling. Preclinical studies with a TREM2-activating antibody (with BBB-penetrant modifications) showed it could increase microglial metabolic fitness and reduce plaque burden in AD models[26][27]. A phase 1 trial of such an agent (by Alektor) indicated it engaged microglia in humans; further efficacy trials are ongoing. Another strategy is **CSF1R inhibitors** which transiently deplete microglia (since CSF1R signaling is needed for microglial survival). In mouse models, CSF1R inhibitors reduced neuroinflammation and could even mitigate tau pathology by temporarily removing microglia. However, wholesale removal of microglia may have downsides in humans (risk of impairing repair or clearing functions), so this approach would likely be short-term or in specific contexts.

Microglial **checkpoint molecules** like CD22 have also emerged as targets. CD22 (normally a B cell inhibitory receptor) was discovered to be upregulated on aging microglia where it suppresses phagocytosis[108]. Inhibiting CD22 function via antibodies in aged mice enhanced microglial clearance of aggregated proteins and improved cognition[109]. CD22 shedding into blood (soluble CD22) is higher in AD and correlates with worse outcomes[110][111]. Thus, blocking microglial inhibitory receptors (CD22, SIGLEC-3/CD33, etc.) could rejuvenate microglial activity in clearing A β and other debris.

Inflammasome inhibitors: As the NLRP3 inflammasome is a major driver of microglial inflammatory output, small-molecule inhibitors targeting NLRP3 or caspase-1 are being explored[74]. One such inhibitor, dapansutrile, is in clinical testing for other inflammatory conditions and could be repurposed for AD if brain-penetrant forms are developed. Likewise, generic anti-inflammatory drugs (e.g., colchicine, a broad anti-inflammasome drug) are under trial in dementia prevention (e.g., COLCOS-AD study).

4. Targeting Pro-inflammatory Cytokines: Therapies that directly neutralize pro-inflammatory cytokines have revolutionized autoimmune disease treatment (e.g., anti-TNF in rheumatoid arthritis). In AD, small exploratory trials have examined this approach. Etanercept (an anti-TNF biologic) delivered perispinally was reported in case series to improve cognition transiently in AD, though this route and data are controversial. More rigorously, a trial of an anti-IL-1 β monoclonal (canakinumab) is planned, based on the observation that IL-1 β is key in AD and cardiovascular patients on canakinumab had lower dementia incidence. Another target is IL-6: tocilizumab (anti-IL6R) is being tested in a sub-study of an AD trial. The challenge with systemic cytokine blockade is ensuring enough drug reaches the brain and does not overly suppress beneficial inflammation needed for A β clearance. An alternative is intrathecal delivery of cytokine inhibitors, but that is invasive. So far, no large trial has shown clear cognitive benefit from cytokine targeting, but these attempts are still in early phases.

5. Enhancing Regulatory/Protective Immune Elements: On the adaptive side, strategies to bolster protective immunity are under investigation. One example given earlier is low-dose **IL-2 therapy** to expand Tregs (Phase 1/2 trials such as the "ADIL2" study). Another concept is adoptive cell therapy: infusing autologous ex vivo expanded **Treg cells** or **myeloid cells** engineered for enhanced A β uptake. These are complex and at experimental stages. There is also interest in boosting anti-inflammatory cytokines: a small trial delivered **intranasal insulin** (insulin has anti-inflammatory and neurotrophic properties) and noted some cognitive stabilization, positing that it modulated brain inflammation indirectly.

6. Complement inhibition: As complement-mediated synaptic loss is a contributor to AD, drugs that inhibit complement activation are being tested. A monoclonal antibody against C1q (the initiator of classical complement cascade) called ANX005 has been through Phase 2 in mild AD. Interim results showed it could reduce synaptic loss markers and was relatively safe; cognitive outcomes are pending. Likewise, inhibitors of C3 (the central complement component) are in development. If these can preserve synapses, they might slow cognitive decline, especially in early AD.

7. Checkpoint inhibition and immune rejuvenation: A provocative line of study from preclinical work is the use of **immune checkpoint blockade** (such as anti-PD-1 antibodies) to modulate peripheral immunity. In 2016, Baruch et al. reported that blocking PD-1 (which normally restrains T cells) in AD model mice caused a burst of peripheral immune activity that subsequently infiltrated the brain and reduced pathology[112]. Essentially, releasing the brakes on the immune

system allowed peripheral macrophages to enter the brain and help clear A β . This approach improved cognition in mice[112]. While translating this to humans is risky (checkpoint inhibitors can cause systemic inflammation and autoimmunity), it opens the idea of amplifying the body's immune clearance mechanisms in a controlled way. Perhaps partial and transient checkpoint blockade, or targeted to the CNS, could be considered in the future.

8. Microbiome-based approaches: Recognizing that gut microbiota profoundly influence systemic immunity and inflammation, some exploratory AD therapies aim to alter the microbiome. Probiotics or synbiotics have shown small effects on inflammatory markers and cognition in pilot studies. Fecal microbiota transplantation (FMT) is also being investigated for its immune-modulatory effects (a small trial in AD is underway). The theory is that a healthier gut microbiome might reduce peripheral inflammation and production of bacterial metabolites that could affect the brain's immune state.

9. Broad lifestyle and anti-inflammatory strategies: Though not a drug per se, controlling vascular risk factors and systemic inflammation through lifestyle (exercise, diet rich in anti-inflammatories like omega-3 fatty acids, etc.) is thought to create a less inflammatory milieu that could delay AD onset or progression. Epidemiological data famously suggested chronic use of NSAIDs was associated with lower AD risk, though clinical trials of NSAIDs in AD did not show benefit – likely because by the time of dementia, the inflammatory process is entrenched and not easily reversed by mild anti-inflammatories.

Combinatorial and stage-specific therapy: As our discussion shows, AD involves multiple arms of the immune system; thus, combination therapies might be needed. For example, one could envision a treatment regimen that includes an anti-amyloid antibody (to remove the trigger), plus an anti-inflammatory agent (to suppress the harmful response to removed amyloid), and perhaps an immune stimulant in early stages (to boost clearance) followed by an immune suppressant in late stages (to reduce bystander damage). Already, trials are being planned that add an anti-inflammatory (like an NSAID or microglial modulator) on top of anti-amyloid antibody therapy to see if it improves tolerability and efficacy.

In summary, immune-based therapeutic strategies in AD are diverse – reflecting the complex role of immunity in the disease. Recent successes in immunotherapy validate the approach of engaging the immune system to fight AD, yet also highlight the need for precision in how we modulate immunity. The field is moving toward an era where treating AD may involve not only removing toxic proteins but also “rebalancing” the immune environment of the brain. As many of these therapies are in trials, the coming years will reveal which immune targets can be safely and effectively harnessed to alter the trajectory of AD.

CONCLUSION

Research over the last several years leaves little doubt that Alzheimer's disease is as much a disorder of the immune system as it is a disease of protein aggregation. Innate immune activation, chronic neuroinflammation, and adaptive immune engagement are deeply intertwined with the classical amyloid-tau pathology in AD. Microglia – the brain's resident immune cells – have a pivotal influence on whether amyloid plaques and tau tangles are contained or propagate, and genetic studies implicate microglial genes in disease risk. Meanwhile, peripheral immune cells and signals continuously communicate with the CNS, especially as the blood-brain barrier breaks down during aging and AD. T cells, monocytes, and other immune cells infiltrating the brain can either help clear debris or add fuel to the inflammatory fire, depending on their phenotype and the context. Cytokine and chemokine networks in AD brain create an environment that can drive a self-perpetuating cycle of neuronal injury and further immune activation.

A key theme that emerges is one of balance and timing. Immune responses that are acute and well-regulated might be beneficial – for instance, transient inflammation can help mobilize clearance of A β or stimulate repair processes. However, in AD this balance tips toward chronic, unresolving inflammation that becomes maladaptive. The same immune components that initially serve protective roles (phagocytosis of A β , restriction of infections) transition into drivers of damage (engulfing synapses, secreting neurotoxins). There is also a spatiotemporal shift: early in AD, innate immunity predominates (microglial and complement responses to emerging plaques), whereas later on, as pathology accumulates and the BBB falters, adaptive immunity kicks in more strongly, with T cells and B cells contributing to disease progression[11][13]. Understanding this dynamic can guide stage-specific interventions.

Clinically, the burgeoning success of immunotherapies like anti-amyloid antibodies provides a welcome proof that targeting the immune-related aspects of AD can alter disease pathology and potentially clinical outcomes. At the same time, the side effects encountered (ARIA from inflammation) remind us that the immune system must be carefully guided – simply activating it or suppressing it wholesale can backfire. The next generation of AD treatments will likely aim for immune modulation: fine-tuning immune cells to a state that promotes debris clearance and tissue repair without excessive collateral damage. Examples include activating microglia's restorative pathways (e.g. via TREM2) while blocking their pro-inflammatory triggers (e.g. NLRP3 or TNF), or boosting regulatory T cell activity to keep peripheral inflammation in check.

Another important implication of the immune involvement in AD is the potential for novel biomarkers. Inflammatory cytokines in blood or CSF, markers of microglial activation (like soluble TREM2[113] or sCD14), or even circulating immune cell profiles could serve as indicators of disease stage or progression. They might also help identify which patients are likely to benefit from immunotherapies – for instance, a patient with high neuroinflammation might respond well to an anti-inflammatory strategy, whereas one with low inflammation might not need it. Precision medicine approaches could stratify patients based on an “immune signature” of their AD.

In conclusion, the role of the immune system in Alzheimer's disease is multi-faceted and significant. Innate and adaptive immune mechanisms contribute to both the propagation and the potential containment of AD pathology. Therapeutically, targeting these mechanisms offers hope for altering the course of AD, as evidenced by recent breakthroughs. However, given the immune system's complexity, therapies must achieve a delicate balance – mitigating the harmful aspects of the immune response while preserving or enhancing its reparative functions. Continued research is critical to unravel the remaining complexities: for example, what are the antigenic triggers for T cells in AD? How do we optimally toggle microglia between inflammatory and phagocytic states? Can peripheral immune rejuvenation in the elderly reduce AD risk? The answers to these questions will guide the development of next-generation immunotherapies. By marrying classic neuropathological insights with modern immunology, we move closer to a future where Alzheimer's disease can be effectively treated, or even prevented, by calibrating the immune system to protect the aging brain.

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