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Review Article

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Inflammation Beyond Amyloid: Immune Cell Contributions to Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to a decline in various aspects of cognition, synaptic function, and neuronal survival, making it the most prevalent cause of dementia worldwide. While the accumulation of amyloid-β plaques and neurofibrillary tangles is a key pathological characteristic of AD, their roles do not comprehensively account for disease pathogenesis. Recent literature indicates the role of immune-related risk genes and innate immune response dysregulation such as complement activation, microglial and macrophage responses, natural killer (NK) cell dysfunction, and neutrophil-mediated inflammation in AD pathogenesis. In addition, the limitation of in vitro and in vivo models and inconsistent biomarker related data has hindered therapeutic progress for AD. However, novel immunomodulatory drugs targeting various signaling pathways have shown promising results. This review aims to provide comprehensive updated information on immune dysfunction in AD pathogenesis and the role of novel immunomodulatory therapies in managing this highly morbid and fatal disease.

Keywords: Alzheimer's Disease; Amyloid Plaques; Innate Immunity; Neuroinflammation; Anti-amyloid Therapies; Immunomodulatory Therapies

1. Introduction

Neurodegenerative conditions are a group of neurological disorders characterized by the gradual loss of neurons in the central and peripheral nervous systems [1]. These disorders have profound health effects globally. Alzheimer's disease (AD), a common cause of dementia, represents 60-70% of neurodegenerative cases. According to the World Health Organization (WHO), dementia affects more than 50 million people across the globe.

Alzheimer's disease affects the brain's medial temporal lobe, impairing memory formation and recall. It then gradually spreads to neocortical structures that control higher cognitive functions such as language, perception, and reasoning. The different phases of AD can be categorized into four stages. The first stage, commonly referred to as the pre-clinical phase, lasts for years and features minor memory loss and early abnormalities in the hippocampus and cortex, with no impairment of daily activities. The second stage is the early stage of AD, during which symptoms such as difficulty in conducting daily activities, memory loss, confusion about time and place, mood swings, and potential depression are observed. The third stage is characterized by the further spread of disease to the cerebral cortex regions, leading to advanced memory impairment and deteriorating language abilities. The fourth and final stage is the severe stage, during which the disease affects the entire cortical area, forming neuritic plaques and neurofibrillary tangles (NFTs). Individuals at this stage face significant challenges in daily functions and may not recognize family members. In addition, they may become bedridden and experience difficulties in

swallowing and urination [2]. While there is presently no definitive cure for AD, various medications to manage the symptoms are available to help patients with this condition.

Clinically, AD is characterized by the accumulation of specific proteins in the brain, which can cause damage to nerve cells and disrupt brain function. Amyloid-beta peptide (Aβ), produced by amyloid precursor protein (APP), accumulates and forms dense amyloid plaques that lead to reduced cognitive abilities and memory impairment [3]. Another protein, the tubulin-associated unit (tau) protein, normally responsible for stabilizing microtubules in neurons, becomes hyperphosphorylated in AD, leading to Neurofibrillary Tangles (NFTs) consisting of fibers that damage nerve cells and affect cognitive abilities [3]. **Figure 1** illustrates the connection between amyloid plaques, NFTs, and neuroinflammation.

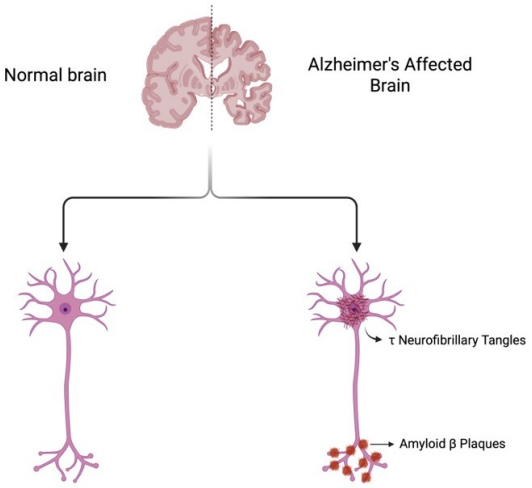

Figure 1: *Comparison between a normal and Alzheimer's-affected brain. The normal brain shows an intact cerebral cortex and hippocampus with undamaged neurons. In contrast, the AD brain shows cerebral cortex and hippocampus atrophy, along with enlarged ventricles. Additionally, it is characterized by tau NFTs and Aβ plaques (Illustrated using Biorender).*

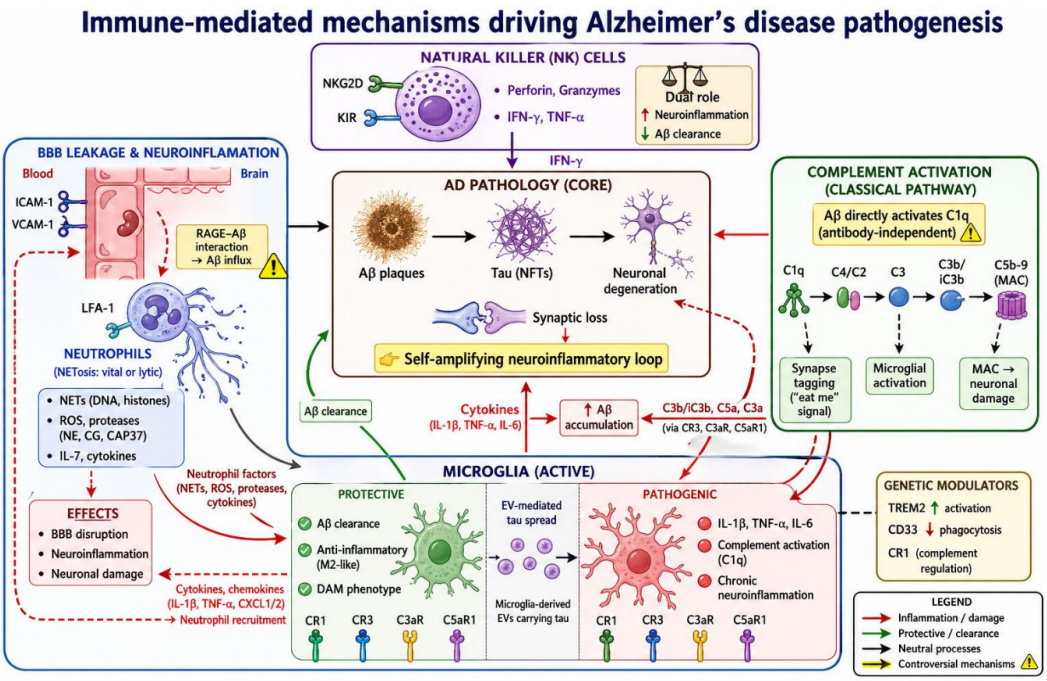

Figure 2: *A conceptual summary of immune cell interactions and mechanisms associated with AD (Illustrated using Biorender)*

Although amyloid-β plaques and tau tangles are widely recognized as key indicators of AD, they do not fully explain the full complexity of disease development and progression. Most traditional narratives emphasize neuronal damage, frequently neglecting the significance of immune-related aspects. However, AD is significantly linked to changes in immune system function and neuroinflammatory reactions. The buildup of amyloid-β can trigger innate immune mechanisms, such as complement and microglia signaling, which may initially aid in the removal of harmful proteins. However, when these immune responses are continuously activated, they can become ineffective, potentially leading to chronic neuroinflammation that hinders amyloid-β clearance and promotes the spread of tau pathology, ultimately accelerating neurodegenerative processes [4]. Therefore, innate immune cells and their dysregulation are increasingly being acknowledged as crucial players in the progression of AD (**Figure 2**).

Keeping the role of immune cell dysfunction in perspective, this review aims to provide updated insights into the roles of different immune cells in neuroinflammation and neurodegeneration, which contribute to the pathological progression of AD. Furthermore, evidence on targeting of immune dysregulation and the utility of novel drugs as potential therapeutic targets has been discussed.

2. Methodology

Electronic databases, including NCBI, PubMed, CORE, ScienceDirect, and ProQuest, were primarily searched using search terms/phrases "Alzheimer's disease," "immune cells' role in Alzheimer's," "immunotherapies in Alzheimer's," "neuroinflammation and immune cells," "complement and signaling pathways in Alzheimer's disease," and closely related immune mechanism-specific keywords. Articles included were filtered based on publication year, and the literature included in this manuscript ranges from 2012 to 2026. Exclusion criteria were defined as articles focusing mainly on other neurodegenerative diseases without clear relevance to AD, non-English, and non-open-access publications. The selected papers were read and critically evaluated by the authors, and key findings were organized according to cell type (e.g., macrophages, neutrophils, microglia) and biological process (neuroinflammation, blood-brain barrier (BBB) disruption, Aβ-tau pathology).

3. Role of Immune-Associated Genes in AD Pathogenesis

Genetic factors play a vital role in AD development by interacting with environmental and lifestyle factors. Instead of being associated with a single genetic factor, AD is influenced by various genetic factors, including *apolipoprotein E (APOE)*, *Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)*, *Amyloid Beta Precursor Protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2)* that collectively increase the risk of developing the condition [5]. Extensive genome-wide association studies (GWAS) have identified over 75 risk loci associated with AD and related dementias, providing insights into the underlying molecular processes. These discoveries underscore the genetic complexity of AD and reveal pathways associated with AD pathogenesis [6].

Of the major genes linked to AD pathogenesis, *TREM2* is identified as a key immune-related player in the central nervous system (CNS). It is well known to serve as a critical regulator of microglial activity and immune responses, and its dysregulation can therefore play a major role in AD. Mechanistically, TREM2 forms a signaling complex with TYRO protein tyrosine kinase-binding protein (TYROBP) to initiate proliferation and phagocytic activity of the microglia. Recent studies in preclinical settings have shown that Aβ serves as a ligand for TREM2, leading to microglial recruitment to Aβ plaques and enhancing their clearance through TREM2-mediated phagocytosis. It is suggested that dysfunction in TREM2 may impair this microglial response, resulting in reduced microglial accumulation around plaques and hindering Aβ clearance, thereby leading to AD-related pathogenesis [7].

Another significant genetic factor related to immune-related AD pathogenesis is *complement receptor 1 (CR1), which* functions through the complement system. CR1 is a membrane-bound receptor that binds to complement components, particularly complement component 3b (C3b) and complement component 4b (C4b). It plays a crucial role in facilitating the removal of immune complexes tagged for destruction by phagocytic cells and in the transport of red blood cells. Additionally, research suggests that variations in the *CR1* gene, such as the presence of *CR1*2* genetic variants, play a critical role in AD, due to their ability to display a significantly lower density of CR1 receptors on the surface of their red blood cells, which in turn hinders the clearance of amyloid proteins from the brain, leading to increased accumulation of amyloid plaques. This impairment may lead to and accelerate AD progression [8].

In addition to *TREM2* and *CR1*, recent studies have shown that Cluster of differentiation 33 (CD33) is linked with dysregulated immune responses in AD. GWAS has identified it as one of the most significant risk genes, particularly for late-onset AD. Mechanistically, CD33 is a receptor on the microglia that binds specific sialoglycan molecules. This receptor-ligand binding effectively inhibits microglial phagocytosis of toxic amyloid beta. Emerging evidence suggests that increased CD33 activity may impair microglial function and the removal of amyloid-β, resulting in increased accumulation of amyloid plaques in the brain. Additionally, specific polymorphisms of *CD33,* particularly the *rs2455069* variant, are associated with an elevated risk of AD, as these variants have been reported to modify the sialic acid binding, thus strengthening the inhibitory effect of CD33 and hindering the ability of microglia to clear toxic proteins, serving as critical players of AD progression [9].

3.1. Role of microglia and complement proteins in AD

Several studies have found that complement proteins play a crucial role in the developmental processes of synaptic function and pruning, as shown in **Figure 3**, where inactive synapses are cleared to allow stronger connections to strengthen and mature [10]. In lieu of this, the complement system, in conjunction with microglia, is increasingly recognized as a key factor in synaptic loss and cognitive impairments in AD. Over the past two decades, extensive research has evidenced the association of complement activation as a pathogenic trigger, indicating that it plays a significant role in AD. For example, in the initial stages of amyloid plaques, deposited complement proteins C1q, C3b, C3c, and C3d have been observed in amyloid plaques and dystrophic neurites of AD patients during disease progression [11].

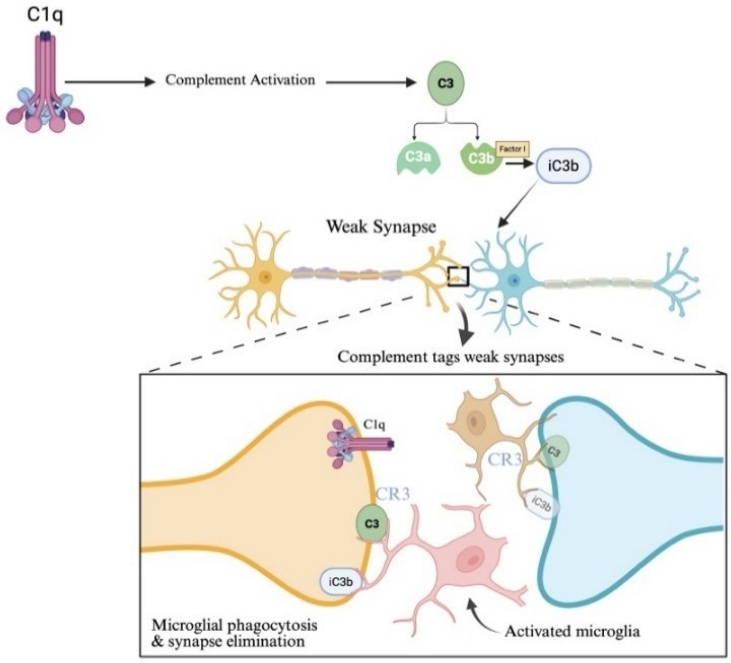

Figure 3: *The role of the complement system in synaptic function and pruning. Activation of the classical pathway induces complement component 1q (C1q) expression, leading to the cleavage of complement component 4 (C4) and complement component 2 (C2), which results in the expression of complement component 3 (C3) and inactive complement component 3b (iC3b). These molecules tag weak or damaged synapses, representing an "eat me" signal. Microglia possess complement receptor 3 (CR3) that recognizes tagged synapses and eliminates them by phagocytosis (Illustrated using Biorender).*

With respect to microglia, these are known as resident macrophages of the brain and are mainly present in the brain parenchyma. These play a vital role in brain development, homeostasis, and immune surveillance. However, these macrophages exhibit significant heterogeneity, consisting of resident populations, such as microglia and border-associated macrophages (BAMs), as well as infiltrating monocyte-derived macrophages under both physiological and pathological conditions [12]. Research on microglia has revealed their distinct development from primitive macrophages, local self-maintenance through proliferation, and unique functional states in response to

environmental changes, especially during aging and disease conditions [13].

Recent findings indicate that microglia play a dual role in AD pathogenesis. While they help protect the brain by modulating the immune response and clearing Aβ plaques, excessive microglial activation can lead to persistent inflammation, worsening neuronal damage, and disease progression. Microglial activation is closely associated with Aβ plaque formation during the initial phases of AD. Emerging evidence also reveals that microglia recognize Aβ via various pattern recognition receptors and modulate local inflammation by releasing inflammatory and chemokine factors, thereby affecting Aβ clearance or accumulation in the brain [14].

M2-activated microglia promote anti-inflammatory responses and reparative processes that aid in Aβ clearance. Furthermore, disease-associated microglia (DAM) gather around Aβ plaques and regulate Aβ clearance and tau pathologies. However, when microglia are activated by pathological stimuli, they may cause excessive inflammatory responses and activate the complement system, leading to increased Aβ accumulation and neuronal damage [15]. The neuroinflammatory response is widely recognized as a key factor contributing to various diseases. In AD, activated microglia and increased cytokine production are significant contributors to neuroinflammation. Well-established studies have shown that inflammatory cytokines, including interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), are significantly upregulated in patients with AD. Furthermore, these cytokines not only amplify neuroinflammatory responses but also have direct, detrimental effects on neurons, leading to neuronal cell death and synaptic loss. It has been demonstrated that the Aβ peptide induces increased cytokine secretion from microglia, reinforcing the idea that Aβ is a substantial factor in microglial activation. This creates a feedback loop of ongoing cytokine release, resulting in a persistent neuroinflammatory state [14]. On the other hand, extracellular vesicles (EV) carrying hyperphosphorylated tau are crucial for the spread of tau pathology in AD. These tau-laden EVs can be taken up by adjacent cells, facilitating the transfer of tau-related abnormalities to neurons. Microglia play a significant role in this mechanism by internalizing and releasing tau via EVs. Research indicates that blocking the synthesis of these vesicles or depleting microglial cells diminishes tau propagation [15]. This process underlies the relationship between Aβ plaque accumulation and tau protein pathology. The presence of Aβ plaques stimulates microglial cells to release more EVs, which, in turn, facilitates the rapid dissemination of tau proteins [14].

The role of microglia has also been associated with complement protein depositions, leading to the pathogenesis of AD **(Figure 4).** The reported mechanism of action suggests that upon activation of microglia, either by the presence of pathogens in the CNS or by inflammatory signals released by injured or dying neurons/neurodegeneration, the microglia undergo morphological changes and secrete various complement proteins, such as C1q. In AD, oligomeric/fibrillar forms of Aβ and hyperphosphorylated tau proteins upregulate pathological C1q in surrounding microglia, thus activating the complement cascade. In addition to C1q, numerous complement proteins have been associated with AD. Among these are complement component 3a (C3a) along with its receptor C3aR, complement component 5a (C5a) and its receptor C5aR1, the C5b-C9 complex, complement component 9, factor B, and factor D. It has been documented in APP/PS1 mouse models that interactions between the astroglia nuclear factor κB (NFκB)-mediated release of complement C3 and neuronal C3aR receptors leads to altered dendritic structures and excitatory synaptic functions. This causes neuronal damage by binding to C3aR on neurons, leading to an increase in intraneuronal calcium levels that, in turn, exacerbates synaptic dysfunction and neuronal impairment through calcium dysregulation. Additionally, C3 generated by astrocytes binds to C3aR present on microglia, worsening Aβ pathology. Furthermore, the discovery of the terminal membrane attack complex (MAC), the endpoint of complement pathway activation, adjacent to near-fibrillar Aβ plaques and synaptic regions, underscores the involvement of all three complement pathways in the pathophysiology of AD [16]. Research utilizing APP knock-in (KI) mouse models of AD revealed increased concentrations of MAC, C1q, and C3 within brain synaptosomes. The detrimental impact of MAC on synaptic integrity was further validated using MAC-blocking antibodies and MAC component C6 depletion [17].

It is unknown whether complement plays a role in the initiation of AD pathology or promotes disease progression, resulting in neuronal loss. A comprehensive understanding of the relationship between the complement system and AD is essential for gaining insight into the molecular mechanisms underlying AD and for developing targeted therapeutic interventions [11].

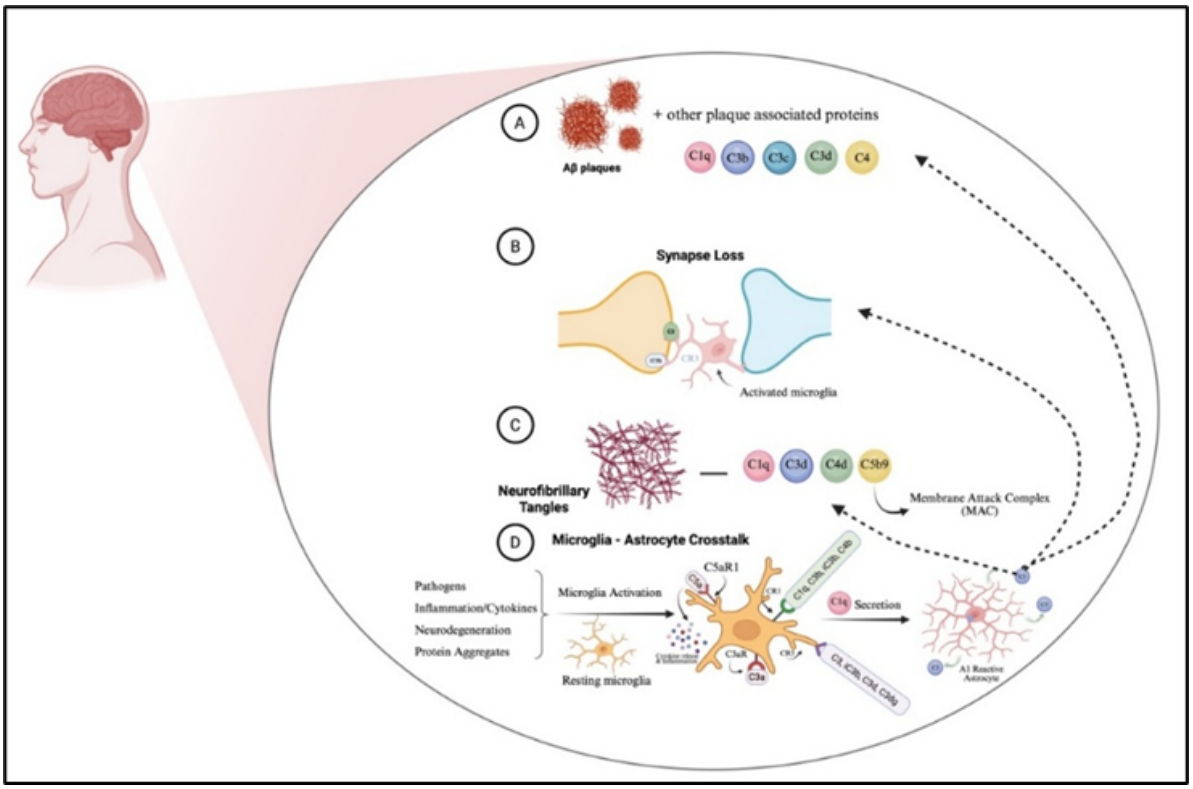

Figure 4: *The role of the complement system in AD pathogenesis. Complement proteins (C1q, C3d, C4d, and C5b-9) are deposited on amyloid plaques, weakened synapses, and NFTs. Microglia, activated by pathogens, cytokines, neurodegeneration, Aβ protein, and tau aggregates, secrete C1q and express complement receptors CR1, CR3, C3aR, and C5aR1 to facilitate phagocytosis and inflammation. C1q induces A1-reactive astrocytes, which release C3, further contributing to synaptic damage and NFT deposition (Illustrated using Biorender).*

3.2. Natural Killer (NK) Cells

Another immune cell reported to be involved in AD pathology is the NK cell, which is well known for its cytotoxic activity. As illustrated in **Figure 5**, NK cell behavior is under very precise control by the presence of both activating receptors (e.g., KIR, NKG2D, and CD94/NKG2) and cytokine-mediated stimulation (such as IL-2, IL-12, IL-15, and IL-18), which collectively drive NK cell activation. Upon activation, NK cells exert their effector functions through two main mechanisms: a) killing of target cells through cytolytic molecules such as perforin, granzymes, FasL, and TRAIL, and b) cytokine production, including interferon-gamma (IFN-γ), TNF-α, GM-CSF, and interleukins (IL-5, IL-10, IL-13, and IL-22), thereby linking innate and adaptive immunity [18].

Previous studies have reported reduced NK cell activity and dysfunction in its cytotoxic pathways, especially those related to perforin and granzyme-mediated killing, in the immunopathogenesis of AD. Additionally, alterations in lymphocyte subset distribution and increased concentrations of pro-inflammatory cytokines in AD patients further support the involvement of NK cell dysregulation in disease pathogenesis. Several studies have demonstrated that Tacrine (THA), a treatment for neurological disorders, inhibits NK cell expansion and cytotoxic activity in patients with AD compared with healthy controls. Other studies have also indicated that although NK cell frequency appears similar between patients with AD and healthy individuals, their functional capacity may be reduced, contributing to AD pathogenesis [19].

Conversely, some findings indicate that NK cells in patients with AD retain responsiveness to cytokine stimulation, particularly IL-2 and IFN-γ, which are critical activators. Functional impairment of NK cells has been reported to be partially reversible after such stimulation. Furthermore, NK cells in individuals with AD exhibit resistance to specific immunosuppressive agents, such as cortisol, suggesting possible changes in intracellular signaling pathways, including altered protein kinase C (PKC) expression. Such dysregulation may enhance NK cell responsiveness under cytokine-driven conditions. Moreover, evidence regarding IL-2–dependent cytokine production by NK cells in AD remains inconsistent, with some studies suggesting increased IL-2-induced production

of IFN- γ and TNF-α by NK cells with decreased production of vascular endothelial growth factor (VEGF) in AD patients as compared to healthy individuals. Moreover, IL-12, another key cytokine, may stimulate IFN-γ production by NK cells and promote a TH1-type immune response during the acute phase of AD. Notably, a positive correlation between IL-12 levels and the number of T cells in the cerebrospinal fluid (CSF) has been reported, suggesting a potential interaction between innate and adaptive immune responses in AD [19].

During the pathogenesis of AD, although the number of NK cells remains consistent, their cytotoxic function undergoes dynamic changes. Studies have revealed increased production of granzyme B and inflammatory cytokines in NK cells of patients with amnestic moderate cognitive impairment (MCI) and mild AD; however, the results in severe AD remain uncertain. This indicates a possible detrimental effect of NK cells on cognitive function. Moreover, in mouse models, NK cells exacerbate neuroinflammation and cognitive deterioration. In contrast, anti-NK cell therapy enhances cognitive function and alleviates neuroinflammation, suggesting a detrimental role of NK cells in AD [20].

In patients with mild AD, NK cell activation capacity remains unchanged, as shown by the constant expression of CD107a, granzyme B, and IFN-γ. However, the condition of NK cells in patients with severe AD remains unclear. Mouse models deficient in NK, T, and B cells have increased Aβ levels, suggesting a possible role of NK cells in controlling Aβ accumulation. Interestingly, these mice exhibit altered microglial morphology, suggesting that NK cells are involved in microglial activation. However, further research is needed to determine whether these effects are directly linked to NK cell deficiency or the absence of other lymphocyte subpopulations. Contrary to expectations, mice lacking T and B cells but retaining functional NK cells have a lower burden of Aβ plaques. Nonetheless, unlike models lacking NK cells, their microglial activation remains unchanged, demonstrating a differential effect on microglial function. These findings show a nuanced role for NK cells in AD pathogenesis, potentially affecting microglial activation pathways that differ from those of T and B cells [20]

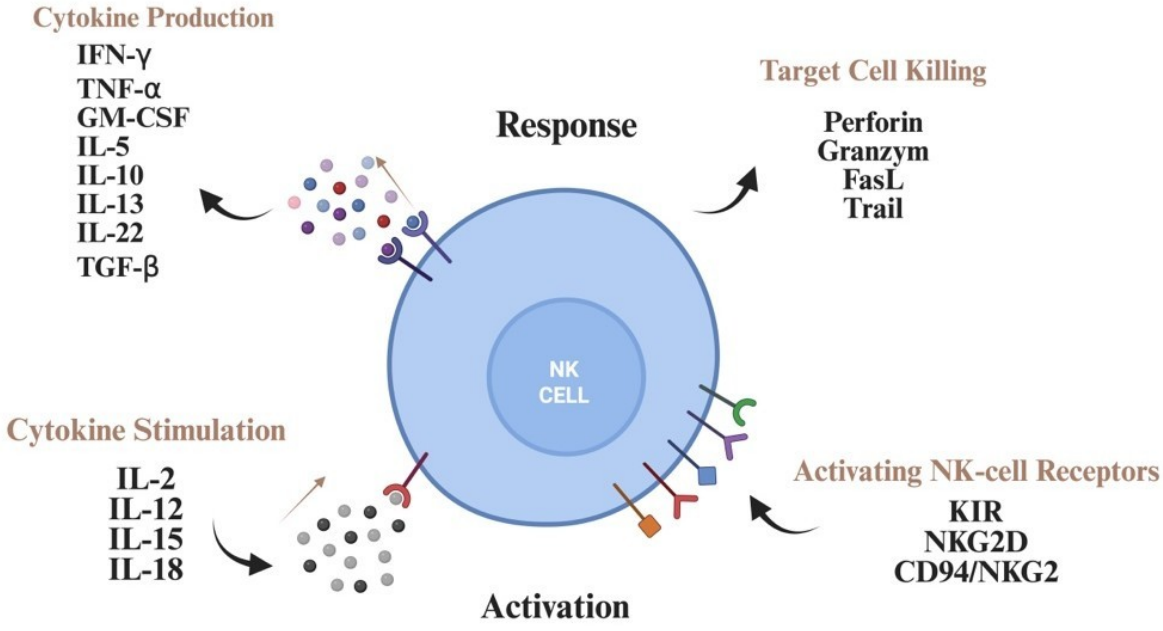

Figure 5: *NK cells can be stimulated by a variety of inflammatory cytokines and/or by engaging with ligands of NK receptors. Consequently, they can produce a variety of pro-inflammatory and inhibitory cytokines or directly kill the target cells (Illustrated using Biorender).*

However, the role of NK cells in AD pathogenesis remains controversial. Certain studies have shown decreased cytotoxic capability in patients with AD compared to healthy individuals, while others have reported increased cytotoxic capacity in patients with AD. NK cells may contribute to chronic inflammation in the CNS of AD by activating macrophages. On the other hand, NK cells have been reported in mouse model studies to eliminate Aβ plaques. Although NK cell infiltration in the brains of AD mouse models has been documented, few studies have investigated NK cell infiltration in patients. Single-cell RNA sequencing (scRNA-seq) results indicate that peripheral NK cells may enter the brain in AD patients, leading to neuroinflammation; however, more studies are needed to validate these findings [20].

3.3. Neutrophils

In contrast to the resident immune cells described earlier, neutrophils are non-resident, peripheral immune cells that are both highly abundant and first responders to the site of inflammation. The pathology of AD is often associated with chronic systemic inflammation, partly contributed to by non-resident immune cells, such as neutrophils, monocytes, and T cells, crossing the BBB, which is thought to contribute to further cognitive damage and decline. Notably, given their location outside the brain, they are promising therapeutic targets. In AD, initial neutrophil recruitment can be triggered by Aβ pathology through receptors such as Toll-like Receptors (TLRs), including TLR2 and TLR4, with TLR6 potentially contributing as a TLR2 binding partner in some inflammatory contexts, such as vascular inflammation [21]. The inflammatory environment in the brain, along with plaques and vascular amyloids, activates microglia and endothelial cells, which release cytokines and chemokines to attract neutrophils to the injury site. Simultaneously, upregulation of endothelial adhesion molecules, namely Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), occurs, while neutrophil adhesion receptors such as Lymphocyte Function-Associated Antigen 1 (LFA-1) help the cells attach to the endothelium and allow passage across the BBB [22] as shown in **Figure 6**. These active neutrophils become involved in capillary stall formation, which affects cerebral blood flow, in addition to abnormal neutrophil signaling, further progressing the pathology [23]. Earlier studies have shown that AD mouse models with neutrophil depletion and therapeutic inhibition of LFA-1 integrin have significantly reduced AD neuropathological features [24].

Documented reports indicate that neutrophils can accumulate in brain vessels and may transmigrate into the parenchyma. Here, they release reactive oxygen species (ROS), proteases, and enzymes such as myeloperoxidase through the formation of NETs [25]. These NETs release DNA, histones, and granule proteins and have been detected in both AD mouse models and human AD brain tissues (cortical vessels and parenchyma). According to these studies, the regions that accumulate include the cerebellum, temporal cortex, and hippocampus in both the parenchyma and the vasculature. This conclusion was largely based on staining NET-associated markers, which are most often found proximal to BBB-disrupted sites [24]. However, it is important to note that the identification of NETs in AD does not definitively establish their role as purely detrimental, as neutrophils are a heterogeneous population and thus have functionally distinct subsets. Therefore, some subsets cause obvious pathological associations, but those involved in clearing plaques or immune regulation. Therefore, their overall role in AD remains context-dependent rather than strictly damaging [24]. This supports the idea that neutrophil-driven mechanisms are not limited to the periphery but may directly affect the diseased brain [26]. As mentioned earlier regarding the involvement of neutrophil granules in AD pathology, some of them are Cationic Antimicrobial Protein of 37 kDa (CAP37), Cathepsin G (CG), and Neutrophil Elastase (NE). These bind directly to the Aβ_{1-42} peptide upon detection. Along with these proteins, another transporter receptor called the Receptor for Advanced Glycation End-products (RAGE) is said to be involved in the influx of peripheral Aβ_{1-42} across the BBB into the brain. Hence, the RAGE-Aβ_{1-42} peptide interaction could potentially induce chronic pro-inflammatory signaling in the brain. Therefore, theoretically, introducing interference with the RAGE-Aβ_{1-42} interaction, as well as its interactions with CAP37, CG, and NE, could help attenuate inflammatory signaling and potentially slow the progression of AD [27].

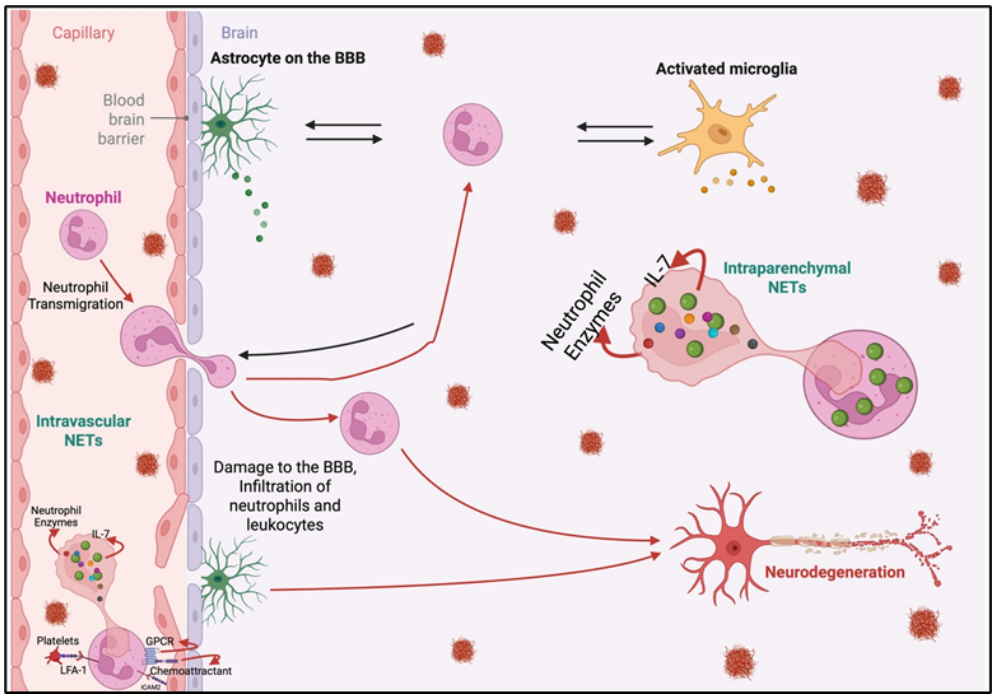

Figure 6: *Neutrophil-mediated mechanisms of BBB disruption and neurodegeneration in AD. In a neuroinflammatory environment, circulating neutrophils in the capillary lumen transmigrate across the BBB with aid from adhesion molecules such as ICAM and LFA-1, and chemoattractant signaling via G protein-coupled receptors (GPCRs), with platelet interactions further exacerbating neutrophil recruitment in the brain. Within the intravascular compartment, these cells form neutrophil extracellular traps (NETs) - designated here as intravascular NETs. These NETs release neutrophil enzymes and pro-inflammatory cytokines such as IL-7, collectively fueling BBB disruption. Simultaneously, astrocytes anchored to the BBB's abluminal surface engage in bidirectional crosstalk with the infiltrating immune cells and hence modulate the barrier permeability. Once neutrophils cross the barrier, they contribute to parenchymal damage and facilitate further leukocyte infiltration. Now, within the brain parenchyma, intraparenchymal NETs continue releasing neutrophil enzymes and IL-7, possibly sustaining a pro-inflammatory microenvironment. The activated microglia respond to these signals via bidirectional communication with infiltrating immune cells, thereby amplifying the Neuroinflammatory response. Overall, the combined efforts from BBB breakdown, continuous NET formation, and microglial activation, coupled with the generation of neurotoxic mediators, ultimately drive progressive neuronal damage. This is evident by the illustration of neuronal loss and axonal fragmentation. BBB, blood-brain barrier; NETs, neutrophil extracellular traps; IL-7, interleukin-7; LFA-1, lymphocyte function-associated antigen 1; ICAM-2, intracellular adhesion molecule 2; GPCR, G protein-coupled receptor (Illustrated using Biorender).*

To further understand this, it's important to note that different populations of neutrophils exist, each possibly playing distinct roles in disease progression. Approximately 297 differentially expressed genes (DEGs) were AD-related, of which 18 exhibited diagnostic potential [28]. Multiple studies conducted on patients with AD, using transcriptomic and single-cell analyses, revealed elevated DEGs linked to neutrophil signaling pathways, many of which are involved in pro-inflammatory processes, cell adhesion (e.g., CD11b), and other processes. In addition, these DEGs in AD neutrophils were high for AD-related pathways, such as ATP metabolic pathways and mitochondrion organization [24, 29, 30]. Further supporting this, emerging studies have identified certain neutrophil subtypes, namely C-C motif chemokine ligand 2 (CCRL-2)- positive populations, suggesting that neutrophil heterogeneity might contribute to neuroinflammation [31]. Furthermore, NET formation has been shown to be upregulated to some extent in AD, according to gene expression profiles, alongside inflammatory mediators such as CCL2 and TLR2 (Toll-Like Receptor 2), and a reduction in brain-derived neurotrophic factor (BDNF). Thus, suggesting a range of inflammatory and neurotoxic neutrophil phenotypes [28, 31]. Moreover, the coupling of ROS production and NET release, along with reduced phagocytic activity, suggests that neutrophils may become dysregulated, contributing to chronic inflammation rather than effective clearance of pathological components [24]. On the other hand, well-known AD-related genes, such as *APOE*, influence risk parameters and amyloid dynamics; however, their direct interactions with neutrophil-specific functions remain unclear. Equally important, alterations in the above-mentioned neutrophil signaling, oxidative responses, and other pathways collectively create an environment conducive to prolonged inflammation, impaired plaque clearance, and progressive neurodegeneration.

More recent human studies have elucidated the influence of neutrophils beyond findings in brain tissue. For instance, a 2025 study linked immune markers, such as neutrophil percentage and the neutrophil-to-lymphocyte ratio (NLR), to BBB-associated markers, suggesting that neutrophil impairment may reflect, or even influence, central disease processes [32]. Another 2025 review on the NLR in AD supported this association with disease pathology; however, it emphasized that NLR can only be a supportive biomarker and not yet a standalone diagnostic tool [33]. Overall, newer literature strengthens the involvement of neutrophils and related processes as active contributors to AD-related neuroinflammation and neurodegeneration, shifting from broad claims that these cells are solely harmful to a more nuanced view of neutrophil states, adhesion pathways, and NET-related programs as important, evolving therapeutic targets in AD.

To provide a concise, integrative overview of immune cell involvement in AD pathogenesis, **Table 1** summarizes the key roles, mechanisms, and effects.

Table 1: Summary of immune components and their physiological roles, mechanisms, and contributions to AD.

Immune Component	**Physiological Role**	**Role in AD**	**Key Mechanisms / Molecules**	**Overall Impact in AD**
Complement System	Synaptic pruning, immune defense, clearance of pathogens	Overactivation, synapse loss, neuronal damage	C1q, C3, C3aR, MAC CR1/CR3, calcium dysregulation	Predominantly detrimental (synaptic loss, neurodegeneration)
Microglia (Brain Macrophages)	Immune surveillance, debris clearance, CNS homeostasis	Dual role in Aβ clearance and neuroinflammation	Aβ recognition, inflammatory cytokines, DAM extracellular vesicles, tau spread	Dual role (protective early, detrimental when persistently activated)
Macrophages (Peripheral & CNS-associated)	Immune regulation, tissue repair, homeostasis	Heterogeneity, CNS infiltration, neuroinflammatory contribution	Monocyte-derived macrophages, BAMs, DAM inflammatory mediators	Context-dependent (often detrimental when dysregulated)
Natural Killer (NK) Cells	Cytotoxicity, cytokine production, innate–adaptive immune link	Altered cytotoxicity, cytokine dysregulation, context-dependent role	IFN-γ, TNF-α, IL-2, IL-12 granzyme B, perforin, PKC, VEGF	Uncertain / context-dependent (mixed evidence)
Neutrophils	First-line defense, pathogen clearance, ROS production	Brain infiltration, BBB disruption, oxidative stress, NETs	ROS, NETs, TLR2/4, LFA-1 ICAM-1, VCAM-1, CAP37, CG, NE, RAGE	Largely detrimental (inflammation, vascular damage) subset-dependent

AD: Alzheimer's disease; C1q: complement component 1q; C3: complement component 3; C3aR: complement component 3a receptor; MAC: membrane attack complex; CR1: complement receptor 1; CR3: complement receptor 3; CNS: central nervous system; Aβ: amyloid-beta; DAM: disease-associated microglia; tau: tubulin-associated unit; BAMs: border-associated macrophages; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor alpha; IL-2: interleukin 2; IL-12: interleukin 12; PKC: protein kinase C; VEGF: vascular endothelial growth factor; ROS: reactive oxygen species; BBB: blood–brain barrier; NETs: neutrophil extracellular traps; TLR2/4: toll-like receptors 2 and 4; LFA-1: lymphocyte function-associated antigen 1; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule 1; CAP37: cationic antimicrobial protein of 37 kDa; CG: cathepsin G; NE: neutrophil elastase; RAGE: receptor for advanced glycation end-products.

4. Future Perspectives

Understanding the pathology of AD has been of great help in developing medications that could change the progression of the disease and not simply control the symptoms, although it is still a challenge when tailoring a treatment plan. According to the Food and Drug Administration (FDA), approved drugs for Alzheimer's fall into two categories: a) drugs that temporarily control the symptoms of Alzheimer's dementia (the most common), and b) drugs that slow the progression of Alzheimer's by affecting its biology.

To date, there are three FDA-approved treatments under the second category, all of which are anti-amyloid antibody therapies, also referred to as monoclonal antibodies (mAbs): Aducanumab (Aduhelm), Lecanemab (Leqembi), and Donanemab (Kisunla) [34]. The following sections discuss FDA-approved therapies and other therapeutic targets in clinical trials and in preclinical stages, including their mechanisms, side effects, limitations, and potential improvements to better implementation.

4.1. FDA-approved Monoclonal Antibodies (mAbs)

Aducanumab (Aduhelm) is a human immunoglobulin (Ig) G1 monoclonal autoantibody (IgG1-mAb) that binds to the N-terminal epitope of the Aβ42 (Aβ42) peptide. It was the first approved Aβ-targeting mAb, granted accelerated approval in June 2021. Lecanemab (Leqembi) and Donanemab (Kisunla) are humanized IgG1 antibodies derived from mouse mAb158 and mE8-IgG2a, respectively. Lecanemab targets amyloid protofibrils and received full approval in July 2023. Lastly, Donanemab, which was approved in July 2024, was designed to target N3pG amyloid. Preclinical studies and clinical trials of all three therapies showed a dose- and time-dependent decrease in Aβ plaques, along with slower cognitive decline. Aducanumab showed an approximate 22% slowed cognitive decline, Lecanemab showed 27%, and Donanemab showed 33%. Anti-amyloid mAbs represent a revolutionary step towards precision medicine for AD; nevertheless, their potential and safe utility remain to be fully understood. Therefore, there is a demand for the use of safety biomarkers for early detection and prevention of ARIA. Expectantly, safety and preventive guidelines are being established for future clinical trials and treatment approvals [35–39].

4.2. Therapies under clinical trials and preclinical stages

4.2.1 Sargramostim (Leukine)

Sargramostim is a granulocyte macrophage colony-stimulating factor (GM-CSF) and an FDA-approved drug used for bone marrow stimulation. GM-CSF binds to receptors on progenitor cells (GM-CSF-R), which activate the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway, stimulating the proliferation, differentiation, and maturation of most phagocytes, namely granulocytes, macrophages, neutrophils, and eosinophils. This drug is mainly used for acute myelogenous leukemia (AML), myeloid reconstruction after allogeneic bone marrow transplantation (BMT), following engraftment failure, and for mobilizing peripheral blood stem cells after transplantation [40, 41].

Sargramostim is currently undergoing clinical trials for AD to assess its safety and efficacy in individuals with mild-to-moderate disease. Potter et al. (NCT04902703) found that short-term Sargramostim use increased immune cell counts and cytokine levels and was safe and tolerable in participants. The reported adverse events included dermatological issues, gastrointestinal symptoms, and headaches. No ARIAs were observed. Potter et al. emphasized the need for long-term trials with larger sample sizes to more accurately define the safety and efficacy of Sargramostim [42].

4.2.2 TLR9 Agonists (CpG1018)

Toll-like receptor 9 (TLR9) is a receptor involved in innate immunity activation. It recognizes unmethylated CpG motifs (commonly found in bacterial and viral DNA), triggering chemotaxis and phagocytosis. A TLR9 agonist (CpG1018) is being investigated as a potential aid in Aβ plaque clearance. This agonist is a synthetic, unmethylated oligonucleotide containing CpG motifs, which are usually used in vaccines (e.g., hepatitis B). In mouse models of AD, a TLR9 agonist reduces Aβ plaques in brain regions associated with memory and cognition. Furthermore, preclinical evidence by Patel et al. assessing the efficacy and long-term safety of the TRL9 agonist in squirrel monkey models concluded that stimulation of innate immunity with the TLR9 agonist improves cognition and reduces amyloid pathology, validating the beneficial outcomes. Since CpG1018 does not cross the BBB, two hypotheses are proposed to explain its mechanism in relation to AD: (1) the binding of CpG1018 to TLR9 on peripheral immune cells induces the secretion of inflammatory mediators that can pass the BBB and enter the CNS, stimulating microglia to clear Aβ plaques, and/or (2) inducing the recruitment of peripheral immune cells to the CNS, influencing protective mechanisms. Although the mechanism remains to be fully understood, a clinical trial (NCT05606341) is underway, with an estimated completion date of November 2026. Expected measurable outcomes include ARIA, changes in cognitive assessment, changes in amyloid concentrations in plasma and CSF, and changes in Tau biomarker concentrations in plasma and CSF [40, 43].

4.2.3 CSF1R Inhibitors

Colony-stimulating factor 1 receptor (CSF1R) is primarily involved in microglial survival, proliferation, and functionality. Prolonged CSF1R activation is thought to contribute to neuroinflammation in AD. In AD mouse

models, decreasing pro-inflammatory microglial activity by inhibiting CSF1R has been linked to enhanced Aβ clearance, reduced cytokine expression, and preservation of neuronal viability, with some studies suggesting improved cognition. However, some studies suggest that CSF1R antagonism in 5xFAD models can increase Aβ plaques resembling cerebral amyloid angiopathy (CAA), raising safety concerns. In non-AD models, CSF1R inhibitors are associated with improved neuronal function and cognition. In a clinical trial (NCT04121208), the drug JNJ-40346527 showed measurable effects, including changes in CSF1 levels; however, caution is advised, as the CSF1R mechanism remains incompletely understood [40].

4.2.4 C1q inhibitors

In both tauopathy and amyloidosis mouse models, C1q knockout appears to restore synaptic density and diminish disease pathology. Petrisko et al. examined the long-term effects of microglial C1q deletion in young adult aggressive AD mouse models, documenting reduced phagocytosis of hippocampal synapses and improved cognition. This study also reports an unchanged amyloid load but altered amyloid plaque structure and glial amyloid phagocytosis. Furthermore, a study targeting mGluR5 with BMS-984923 to prevent C1q synaptic localization without altering total C1q levels in AD mouse models reported promising results [44, 45].

The dual function of C1q in neurodevelopment, neuroprotection, and neuroinflammation could be a key factor in supporting the safe use of C1q inhibitors as both a treatment and a diagnostic tool for neurodegenerative diseases, including AD. For example, in human clinical trials, a phase 1 trial (NCT05804383) was completed in October 2025, assessing the safety and tolerability of the C1q inhibitor BMS-984923 in healthy volunteers and patients with AD to determine the use of synaptic density, measured using positron emission tomography (PET), as an early marker of therapeutic response to treatments that target synapse restoration.

4.2.5 Multi-modal therapy

Immune mechanisms function coherently, influencing pathology and disease progression. Understanding these interactions creates opportunities for new interventions when it comes to neurodegenerative diseases, including AD. For example, in AD, extracellular aggregates of Aβ plaques are surrounded by activated microglia and astrocytes. These clusters release ATP, and high extracellular ATP levels signal activation of purinergic receptors. Depending on the physiological environment, ATP concentration, receptor subtype, and cell type, purinergic receptors behave differently and can be involved in neurotransmission, neuromodulation, or neuronal injury [46].

In AD, the purinergic P2X receptor (P2XR) on microglia is thought to play a role, specifically by contributing to the neuroinflammation. In contrast, this receptor is also thought to play a neuroprotective role in AD by producing soluble amyloid precursor protein alpha (sAPPα), a neurotrophic and neuroprotective fragment, and aiding in Aβ clearance [46, 47].

In APPS1 mice, P2XR deficiency resulted in reduced Aβ pathology and had no effect on sAPPα levels. Martin et al. hypothesize that short P2X7R stimulation may induce beneficial sAPPα release, whereas prolonged activation in the mouse model can lead to toxic Aβ release. Therefore, P2X antagonists may be a target for AD treatment. However, astrocyte-derived ATP functions as a ligand for purinergic receptors on microglia, thereby hindering microglial Aβ clearance. In theory, combining P2X antagonists with a compound that neutralizes astrocyte-derived ATP, such as HT-ALZ, can enhance the P2X-mediated degradation of Aβ by microglia [40, 46].

Targeting purinergic receptors as a treatment approach is still in the preclinical stage for AD and other neurodegenerative conditions, such as Multiple Sclerosis (MS), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS). However, different research gaps concerning P2X7R should be investigated to better understand its utilization in neurodegenerative diseases. For example, how does its dual role (neurotoxicity and neuroprotection) affect the development and progression of the disease. In addition, brain-penetrant antagonists need to be developed [47].

5. Limitations

Although research into the role of the immune system in AD has grown very rapidly in recent years, it is important to note the several major limitations associated with this type of immune-related research. The field is rapidly evolving, with limited integration of findings across immune pathways and a lack of consensus on the precise

contribution of immune dysregulation to disease initiation and progression. Moreover, the potential role of genetic variants that influence immune cell function and downstream neuroinflammatory cascades in AD is an important consideration. The existing literature provides limited insight into whether population-specific genetic backgrounds modulate immune-mediated mechanisms. This underscores a critical gap in understanding disease heterogeneity across different ethnic and geographical groups.

A major challenge is the heavy reliance on preclinical and animal models for research. Although these models offer significant insights, they do not fully represent the complexity of AD pathology in humans, thereby limiting the translational applicability of many findings in clinical settings.

In addition, there is a notable lack of longitudinal human studies investigating the immune system alterations associated with the progression of AD. Consequently, most research is predominantly cross-sectional, making it challenging to establish a causal relationship between immunological changes and disease.

Another significant limitation is the considerable variability in biomarker findings between studies. Differences in study design, sample populations, and detection methods also lead to variable results, particularly regarding cytokine levels and immune cell activity, complicating the standardization of biomarkers for clinical applications. Moreover, the heterogeneous populations of certain immune cells, namely neutrophils, hinder their identification as a reliable early-phase AD marker despite its heavy involvement in the overall pathology [24].

Finally, the underlying mechanisms of immunity in AD remain incompletely understood. Despite the involvement of numerous immunological pathways, the specific functions of these pathways remain ambiguous, hindering the development of effective therapeutic options.

6. Conclusion

In conclusion, AD is a neurodegenerative condition that has been observed to be associated with dysregulated immune response. The role of immune components in the development, progression, and potential treatment of AD has been discussed extensively in the review. Many treatments are being developed to slow disease progression rather than control symptoms and are being investigated in clinical trials, with some gaining FDA approval. Currently, there are three FDA-approved anti-amyloid antibody therapies, and numerous drugs targeting immune components are being investigated.

7. Declarations

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Author Contributions

Conceptualization and writing original draft: H.P., L.M., O.A., O.I., S.A., T.A.; Writing, review, and editing: H.P., L.M., O.A., O.I., S.A., T.A.; Illustration and visualization: H.P.; Supervision: H.P., L.M., O.A., O.I., S.A., T.A.; All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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Schematic figures illustrating the involvement of macrophages, neutrophils, microglia, and other immune cells in AD pathology were generated using BioRender (BioRender.com). These figures were designed to visually summarize key mechanisms described in the manuscript, including immune cell trafficking across the BBB and interactions between different immune cell populations.

Use of Artificial Intelligence

During the preparation of the manuscript, the authors used ChatGPT and Grammarly for language editing, clarity, and graphic preparation. After using the tool, the authors reviewed and edited the content as needed and took full responsibility for the publication's content. The authors confirm that no content in this manuscript was generated using artificial intelligence (AI) tools and take full responsibility for the accuracy and integrity of the work.

8. Abbreviations

The following abbreviations are used in this manuscript:

Aβ	Amyloid beta
AD	Alzheimer's disease
AE	Adverse event
ALS	Amyotrophic Lateral Sclerosis
AML	Acute Myelogenous Leukemia
ApoE	Apolipoprotein E
APP	Amyloid Precursor Protein
ARIA	Amyloid-Related Imaging Abnormalities
BAMs	Border-Associated Macrophages
BBB	Blood-brain barrier
BDNF	Brain-Derived Neurotrophic Factor
BMT	Bone marrow transplantation
C1q	Complement component 1q
C2	Complement component 2
C3	Complement component 3
C4	Complement component 4
CAA	Cerebral Amyloid Angiopathy
CAP37	Cationic Antimicrobial Protein of 37 kDa
CCRL-2	C-C motif Chemokine Ligand-2
CD33	Cluster of Differentiation 33
CG	Cathepsin G
CNS	Central nervous system
CR1	Complement Receptor 1
CR3	Complement Receptor 3
CSF	Cerebrospinal fluid
CSF1R	Colony-Stimulating Factor-1 Receptor
DAM	Disease-Associated Microglia
DEGs	Differentially Expressed Genes
EMPs	Erythroid Myeloid Progenitors
EVs	Extracellular Vesicles
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GWAS	Genome-Wide Association Studies
iC3b	Inactive Complement Component 3b
ICAM-1	Intercellular Adhesion Molecule-1
IFN-γ	Interferon-Gamma
IL	Interleukins
JAK/STAT	Janus Kinase/Signal Transducers and Activators of Transcription

KI	Knock-in
LFA	Lymphocyte Function-Associated Antigen
MAC	Membrane attack complex
MCI	Moderate Cognitive Impairment
mGluR5	Metabotropic Glutamate Receptor 5
MS	Multiple Sclerosis
NE	Neutrophil Elastase
NET	Neutrophil Extracellular Traps
NF-κB	Nuclear Factor kappa B
NFTs	Neurofibrillary Tangles
NK	Natural killer cells
NLR	Neutrophil to Lymphocyte Ratio
PD	Parkinson's disease
PET	Positron emission tomography
PKC	Protein kinase C
PSEN	Presenilin
RAGE	Receptor for Advanced Glycation End-products
ROS	Reactive oxygen species
SAPPα	Soluble Amyloid Precursor Protein alpha
scRNA-seq	Single-cell RNA sequencing
Tau	Tubulin-Associated Unit
THA	Tacrine
TLRs	Toll-like Receptors
TNF-α	Tumor Necrosis Factor-alpha
TREM2	Triggering Receptors Expressed on Myeloid cells 2
TYROBP	TYRO protein tyrosine kinase-Binding Protein
VCAM-1	Vascular Cell Adhesion Molecule-1
VEGF	Vascular Endothelial Growth Factor

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