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Review

Review

The association of microbial infection and adaptive immune cell activation in Alzheimer's disease

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Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. Early symptoms include the loss of memory and mild cognitive ability; however, as the disease progresses, these symptoms can present with increased severity manifesting as mood and behaviour changes, disorientation, and a loss of motor/body control. AD is one of the leading causes of death in the UK, and with an ever-increasing ageing society, patient numbers are predicted to rise posing a significant global health emergency. AD is a complex neurophysiological disorder where pathology is characterized by the deposition and aggregation of misfolded amyloid-beta (Aβ)-protein that in-turn promotes excessive tau-protein production which together drives neuronal cell dysfunction, neuroinflammation, and neurodegeneration. It is widely accepted that AD is driven by a combination of both genetic and immunological processes with recent data suggesting that adaptive immune cell activity within the parenchyma occurs throughout disease. The mechanisms behind these observations remain unclear but suggest that manipulating the adaptive immune response during AD may be an effective therapeutic strategy. Using immunotherapy for AD treatment is not a new concept as the only two approved treatments for AD use antibody-based approaches to target Aβ. However, these have been shown to only temporarily ease symptoms or slow progression highlighting the urgent need for newer treatments. This review discusses the role of the adaptive immune system during AD, how microbial infections may be contributing to inflammatory immune activity and suggests how adaptive immune processes can pose as therapeutic targets for this devastating disease.

Keywords: Alzheimer's disease, immune system, neuroinflammation, immunotherapy, viruses

Abbreviations: ACE2: Angiotensin-Converting Enzyme 2; AD: Alzheimer's disease; ADCC: Antibody Dependent Cellular Cytotoxicity; ADRD: Alzheimer's Disease and Related Dementia; ALT: Alanine Aminotransferase; *Apoe*: Apolipoprotein E; APP: Amyloid Precursor Protein; ART: Anti-Retroviral Therapy; AST: Aspartate Aminotransferase; Aβ: amyloid-beta; BBB: Blood-Brain Barrier; CAR: Chimeric-Antigen-Receptor; CCL: Chemokine (C-C) Ligand; CCR: CC Chemokine Receptor; CDR3: Complementarity-Determining Regions; CNS: Central Nervous System; COVID: Coronavirus Disease; CSF: Cerebrospinal Fluid; CXCL-: Chemokine (C-X-C) Ligand; DAA: Direct-Acting Antivirals; Dtx: Diphtheria toxin; EBV: Epstein Barr Virus; EOAD: Early Onset AD; FDA: US Food and Drug administration; Foxp3: Forkhead Box Protein 3 gene; GWAS: Genome Wide Associated Studies; HAND: HIV-Associated Neurodegenerative Disorders; HCMV: Human Cytomegalovirus; HCV: Hepatitis C virus; HHV: Human Herpesviruses; HIV: Human Immunodeficiency Virus; HSV-1: Herpes Simplex Virus-1; IFITM3: Interferon Induced Transmembrane protein 3; IFN-: Interferons; IFNAR1/2: IFN1/2αβ- Receptor; IgM/G: Immunoglobulin-M/G; IL-: Interleukins; IP-10: Interferon-γ Inducible Protein-10; ISGs: Interferon Stimulated Genes; LOAD: Late Onset AD; MAITs: Mucosal-Associated Invariant T-cells; MCI: Mild Cognitive Impairment; MCP-1: Monocyte Chemoattractant Protein-1; MHC-I/II: Major Histocompatibility Complex I/II; MR1: MHC Complex Class I-related molecules; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; NFTs: Neurofibrillary Tangles; NHS: National Health Service; NK: Natural Killer cells; PAMP: Pathogen-Associated Molecular Pattern; PBMC: Peripheral Blood Mononuclear Cells; PD-1: Programmed Cell Death Protein 1; PRRs: Pattern-Recognition Receptors; PSEN1/2: Presenilin1/2; Rag: Recombination Activating Gene; RANTES: Regulated on Activation, Normal T-cell Expressed and Secreted; RNA-seq: RNA-sequencing; SARS-CoV2: Severe Acute Respiratory Coronavirus 2; SPP1: Secreted Phosphoprotein 1 Osteopontin; TAP: Transporter associated with Antigen Presentation; TCRs: T-cell Receptors; Tdap: Tetanus, Diphtheria, Pertussis; T_{EMRA}: Effector Memory T-cells; T_{FH}: T Follicular Helper T-cells; TGF-β: Transforming Growth Factor-β; T_H cell: $CD4^+$ helper T-cells; TNF: Tumour Necrosis Factors; Tregs: Regulatory T-cells; TRG: TCRγ-chain; UK: United Kingdom; VZV: Varicella Zoster Virus; γδ: Gamma-Delta T-cells.

Introduction

Dementia is currently the leading cause of death in women and the second in men in the UK [1] and represents a significant global health burden. The most recent up-to-date evaluation of dementia sufferers in the UK stated that there are approximately 900, 000 patients with dementia [2]. Long-term projections forecast this to rise to 1 million by 2025 and to 1.6 million people by 2040 [2]. Alzheimer's disease (AD) is the most common form of dementia and global estimates suggest there are close to 50 million AD patients worldwide that are predicted to reach 152 million by 2050 [3]. This devastating impact on human life is further exacerbated by the lack of any highly effective treatment and poses a significant financial burden to the UK economy, commanding £34.7 billion of the NHS annual budget [2] with global costs estimated near $1 trillion [3].

AD is a progressive neurodegenerative disease where pathology is driven by a combination of genetic, environmental, and immunological processes (reviewed in Ref. [3]). Neuropathology is defined by the presence of neuritic plaques

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and neurofibrillary tangles (NFTs) in the brain that have developed due to amyloid-beta accumulation (Aβ) and tau phosphorylation that leads to synaptic loss and dysfunction of neuronal cells, described below [3]. Early symptoms include loss of memory, language, visuospatial awareness, concentration, orientation, and mood. Late symptoms include delusions, hallucinations, personality loss, and loss of body/motor control [4].

There is no current cure for AD, but recent exciting advances have been made that focus on new immunotherapy-based anti-Aβ antibody treatments [5, 6]. The recent US Food and Drug Administration (FDA) approval of these treatments (discussed below) could not only potentially change the treatment outlook for AD patients but also highlight the key role that the immune system plays in the disease. This then raises the possibility that targeting other mechanisms within the immune system during AD could also be an effective way to treat disease.

It is widely accepted that both innate and adaptive immune cells are found within the central nervous system (CNS) in multiple neuropathological disorders including AD [7]. However, recent interest in the role of adaptive immune cells in AD and the emergence of the newly approved anti-Aβ immunotherapy has refocussed research attention on studying the key immunological mechanisms that contribute to pathology. This review discusses some of these recent findings and describes the inflammatory-mediated adaptive immune responses that are associated with viral, and to a lesser extent bacterial, infections during AD.

AD pathology

Neuropathology of AD can be classified into two main subsets: (i) an accumulation of NFTs, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients; (ii) atrophy of the brain leading to synaptic and neuronal loss [3].

Amyloid plaques are extracellular deposits of Aβ that are synthesized as a result of proteolytic cleavage of amyloid precursor protein (APP) peptide by alpha-, beta-, or gamma-secretases that gives rise to Aβ peptides of varying length (37–43 amino acids) [8]. In non-pathological conditions, Aβ40 is the most predominant peptide produced as compared to other varying length Aβ peptides that include the longer amyloidogenic Aβ42 peptide [9, 10]. However, genetic mutations or excessive overproduction of Aβ42 peptide in combination with longer Aβ isoforms versus shorter isoforms increases Aβ monomer aggregate formation [10].

Aβ monomers can then develop into amyloid fibrils forming the aggregate plaques or develop into insoluble oligomers that can spread throughout the brain and accumulate in the parenchyma [11]. As plaques form, reactive microglia and astrocytes are recruited to these sites generating curvature and distortion of both axons and dendrites (dystrophic neurites) [10, 12]. This damage leads to an impairment of neuronal function and synaptic loss (see below) [10, 12].

NFTs are formed as a result of hyperphosphorylation of the tau protein that develops into filament-like structures that can become twisted throughout the parenchyma forming paired helical filaments [3]. These are not only found to accumulate mostly in axons but are also found in dendrites and result in the loss of cytoskeletal microtubules and tubulin-associated proteins [3]. NFT development can progress from a pre-tangle phase to more mature NFTs and then later extracellular tangles [3]. This results in neuronal loss through destabilization of the neuronal microtubules due to excessive accumulation of tau that is resistant to proteolysis [3, 13, 14]. Aβ also initiates a pathway that leads to tau-dependant synaptic dysfunction that directly correlates with the symptoms of progressive cognitive decline in AD patients [13, 14].

Synaptic loss arises due to dysfunction of neuronal cell processes [3]. This can include defective axonal transport, mitochondrial function, oxidative stress, and as described above, accumulation of Aβ and tau at synaptic sites [3]. Combined, these lead to brain atrophy through a progressive loss of pre-synaptic terminals, dendritic spines, and axonal function resulting in neuronal cell death [3]. Understanding the interplay of Aβ and tau with the immune system may help identify novel ways to treat AD [13, 14].

Genetic risk factors in AD

There are multiple genetic risk factors affecting the risk of developing AD that can be classified and subtyped based on the patient's age of disease onset and the method of inheritance [15]. In genetic terms, these are classified as Early Onset AD (EOAD) and Late Onset AD (LOAD) (reviewed in Ref. [15]). EOAD is commonly referred to as Familial AD where the individual receives one risk allele from either parent in an autosomal dominant pattern [16]. Approximately 35–60% of EOAD patients have first-degree relatives with dementia that include 10–15% autosomal dominant families within three generations or more [17]. EOAD is a rare form of AD and is caused by mutations in either APP, presenilin1 (PSEN1), or presenilin 2 (PSEN2) and typically develops between the ages of 30 and 60 [10]. Importantly, only 5–10% of EOAD patients can be explained by the pathogenic mutations within these three familial genes [15]. This suggests that non-Aβ-pathways may contribute to AD pathology and are discussed below. LOAD, also referred to as Sporadic AD, is more polygenic and presents after the age of 65 with a genetic aetiology of up to 82% [15]. Multiple risk factors, including age, environmental factors, and multiple genetic variants, are also associated with LOAD [16].

Studies using large-scale genome-wide associated approaches (GWAS) and whole genome analyses have identified up to 75 risk loci with AD pathology with 42 new loci identified recently [18]. This study used 111, 326 AD patients and 677, 663 controls from 15 European country databanks [18]. Importantly, this study identified 22 immune-related risk loci that associate with immune functions and placed these into functional processes using gene ontology [18]. The authors described these as 'tier 1' related genes signifying a greater likelihood of being the causal risk gene responsible for AD [18]. 21 of these immune risk loci genes are novel [18] and complement the already described 28 immune risk loci genes reviewed by Frost *et al.* [19]. These include importantly *Apoe*, *Trem2*, *Cd33*, *Clu*, *Cr1*, *Plcg2*, *Abi3*, and the *Ms4a* and *Hla* families [10, 19] among others, and their association with AD are well described by Frost *et al.* and will not be discussed at length here [19].

The *Apoe* gene encodes apolipoprotein E and was the first genetic risk factor found associated with LOAD and is the most significant risk loci to AD [10]. APOE has been well described and is shown to play a role in both innate and adaptive immune function and can regulate levels of Aβ [20]. The main function of APOE is the regulation of lipid transport and in the brain is expressed mostly by astrocytes and oligodendrocytes; however, expression of APOE is greatly increased by reactive microglia during AD [10]. Importantly, individuals who carry the ε4 allelic isoform of the gene (*Apo*ε4) have a 3–4-fold increase in the likelihood of developing AD [20, 21]. It has also been shown in both mice and humans that *Apo*ε4 carriers also have increased Aβ aggregates and tau accumulation [22–24], whereas carriers of the ε2 allelic isoform (*APO*ε*2*) can enhance Aβ clearance and have lower AD risk [25].

APOE4 has also been shown to promote blood-brain barrier (BBB) dysfunction, even in individuals who are cognitively intact [26, 27]. However, in cognitively impaired individuals, APOE4 can result in more severe BBB dysfunction even though no effect on cerebrospinal fluid (CSF) Aβ and tau levels are seen [26, 27]. This could suggest that in APOE4 carriers the BBB dysfunction may allow recruitment of immune cells into the brain driving neuroinflammation. APOE has also been shown to influence the function of T-cells during AD and is discussed below.

The immune system and AD

The brain was classically thought to be a site of immune privilege that was inaccessible to the systemic immune system. However, multiple studies have revealed a direct link between the brain and circulating immune cells [28–30]. The exposure of the brain parenchyma to the full force of the immune system can be further exacerbated through loss of homeostatic protective measures, including BBB damage and dysregulation, systemic and vascular inflammation or impaired meningeal lymphatic drainage, all of which are observed in AD [10]. This could promote infiltration and recruitment of systemic immune cells into the brain contributing, in the context of AD, to neuroinflammation and AD pathology [7].

Whilst the roles of both innate and adaptive arms of the immune system in AD have been well classified, this review will focus on recent work describing the neuroinflammatory properties of the adaptive immune system and the responses associated with microbial infections that contribute to AD pathology.

Adaptive immunity

One of the most described adaptive immune cells that contribute to AD pathology is T-cells (reviewed in Ref. [26, 31]. Multiple studies have shown the presence of T-cells in the leptomeninges and the hippocampus of brains collected post mortem from human AD patients [26, 32, 33]. This increase in T-cell presence is more prevalent in the $CD8^+$ lineage as compared to the $CD4^+$ lineage and is associated with more severe disease when found in the hippocampus [26, 32, 33]. This is also seen in AD mouse models where the increased prevalence of T-cells in the brain is associated with an increase of both Aβ and tau (reviewed in Ref. [26]). However, contrasting studies have described how the $CD8^+$ T-cell infiltrate correlates only with an increase in tau accumulation but not Aβ formation [32] and may potentially be linked to overall systemic "inflammaging" (chronic inflammation when ageing) [34].

Mouse studies have now shown that the infiltrate of $CD8^+$ T-cells into the brains of APP/PS1-21 AD mice can modulate neuronal and synapse-related gene expression [33]. This suggests that these infiltrating T-cells either directly interact with microglia or astrocytes, or neuroinflammatory properties mediated by cytokine/chemokine release are influencing neuronal cell function. This study went on to show that even when APP/PS1-21 AD mice were treated with depleting anti-CD8 antibodies, neither plaque formation nor cognition was altered [33]. This may suggest that $CD8^+$ T-cell function alone may not be sufficient to drive pathology. However, more recent data now suggests that T-cells can directly interact with microglia and that depleting both T-cells and microglia can reduce tau-mediated neurodegeneration [35]. This interaction now suggests a dual pathological role of T-cells contributing to AD pathology, by directly interacting with the brain-resident microglia influencing their function, whilst also simultaneously contributing to proinflammatory cytokine release.

This pathogenic role of $CD8^+$ T-cells in AD is also confirmed in studies that identified that this increased prevalence is restricted to the $CD8^+/CD45RA^+$ effector memory (T_{EMRA}) lineage and that these are found in both the blood and CSF of human AD patients [36]. This study went further and also identified that these $CD8^+$ T-cells found patrolling the CSF were clonally expanded and antigen experienced as they retained Epstein Barr Virus (EBV)-reactive T-cell receptors (TCRs) (discussed further below) [36].

However, there is conflicting evidence as to the role of T-cells in AD pathology. Marsh *et al.* took the approach of crossing *Rag2*$^{-/-}$ and *Il2rγ*$^{-/-}$ mice with 5xFAD AD mice to generate an AD mouse model system that is deficient of T-, B-, and Natural Killer (NK) cells [37]. They went on to show that the depletion of immune cells within this AD mouse results in an increase in severe Aβ pathology with enhanced neuroinflammation and decreased microglial activation [37]. They also showed that adoptive bone marrow transfer and restoration of T-, B-, and NK cells in these mice reduced Aβ pathology and increased microglial activation [37]. However, this study has taken an approach to delete all immune cells including $CD8^+$, $CD4^+$, and Regulatory T-cells (Tregs) and does not discriminate between the pathological or protective roles of these different immune subsets during AD. Similar studies also crossed *Rag2*$^{-/-}$ mice with APP/PS1ΔE9 AD mice (now only deficient in B- and T-cells) and showed that after adoptive bone marrow transfer, there is a significant reduction in Aβ levels [38]. These studies may point to discrepancies in the different AD mouse models used but also highlight that AD pathology can be significantly influenced by both T- and possibly B-cells. Direct antigenic stimulation of either T- or B-cells was not examined in these studies, so it is possible that activation of these cells via this route could drive an enhanced neuroinflammatory response exacerbating disease but requires further study.

It is also important to consider what effect $CD4^+$ helper T-cells (T_H) have during AD either in combination with $CD8^+$ T-cell function or in isolation. The pathological role of non-regulatory $CD4^+$ T-cells during AD has now revealed that $CD4^+$, T_H1, and T_H17 cells are directly contributing to pathology and are found within both human and mouse AD brains [31, 39]. Studies using APP/PS1-21 AD mice have shown that not only do the T_H1 and T_H17 cells enter the parenchyma but they also stimulate a range of proinflammatory cytokines including interleukins (IL-), tumour necrosis factors (TNF-), and interferons (IFN-) such as IL-6, IL-1β, TNF-α, IFN-γ, and monocyte chemoattractant protein-1 (MCP-1), that, in turn, influences microglia and astrocyte function [19, 39] (reviewed in Ref. [26]). However, conflicting studies have shown that adoptive transfer of Aβ-specific T_H1 cells into

5xFAD AD mice leads to an increase in T-cell mediated activation of MHC-II+ microglia that display increased phagocytic activity of Aβ [40]. This study may support the theory that enhanced T-cell activation is advantageous during AD in helping clear Aβ plaques and may provide an effective therapeutic strategy.

The role of T_H17 cell involvement in AD pathology is less well described. However, T_H17 cells have been shown to induce neuroinflammation and neurodegeneration through the production of IL-17 and IL-22 in rat AD models [41]. This study identified that the release of proinflammatory cytokines mediates neuronal function through the Fas/FasL apoptotic pathway [41]. More recent studies went further and developed clonal Aβ-specific T_H1 and T_H17 effector T-cells (Teffs) *in vitro*. The authors adoptively transferred these cells into APP/PS1-21 AD mice and showed that the presence of these Aβ-reactive Teffs accelerated systemic and brain inflammation, impaired cognition and increased amyloid burden and microglial activation [31]. Taken together this suggests the potential to either directly target and suppress the T-cell-mediated neuroinflammatory responses, the T-cell itself or block the Fas/FasL pathway. This may represent an innovative approach for the design of novel therapies for AD and contradicts the theory that increased T-cell activation in AD could be advantageous.

Tregs have also been implicated in AD development (reviewed in Ref. [42]). These CD4+ T-cells express the transcription factor forkhead box protein 3 gene (Foxp3) and typically regulate the immune system through the production of immunosuppressive cytokines including transforming growth factor-β (TGF-β) and IL-10 [43]. Foxp3+ Tregs have been found to be systemically elevated in 5xFAD AD mice and also in elderly AD patients [44]. In these human studies, patients with mild cognitive impairment (MCI) were shown to have increased expression of programmed cell death protein 1 (PD-1)-negative Tregs [44]. This may suggest that in contrast to the studies described above that show increased numbers of proinflammatory CD4+ and CD8+ effector T-cells in the brain during AD, there is an overall increase in immunosuppression mediated by Tregs that may be contributing to pathology [44]. Baruch *et al.* went further by suggesting that due to the significant upregulation of Tregs, it would be appropriate to enhance the hosts' immune system to counter the immunosuppressive environment [45]. Based on this strategy, Baruch *et al.* treated 5xFAD and APP/PS1-21 AD mice with anti-PD-1 monoclonal antibodies [46]. They showed that PD-1 treatment developed elevated CD4+ IFN-γ responses that subsequently resulted in an overall decrease in Aβ plaque formation, rescued cognitive performance, and promoted monocyte recruitment into the brain [46]. The authors rightly state that this increased infiltrate of activated immune cells into the brain would need to be carefully monitored for any bystander damage [46, 47].

Another way to reduce Treg-mediated suppression has been performed in studies that deplete Tregs completely *in vivo* by crossing Foxp3-diphtheria toxin mice (*Dtx*) with 5xFAD AD mice [45]. These studies showed that when Tregs are depleted, 5xFAD AD mice not only displayed improved cognitive behaviour with reduced Aβ pathology, but also lead to an influx of macrophages and T-cells into the brain [45]. However, Treg-depleted mice will develop enhanced autoimmunity and non-specific T-cell activation [48], which in combination with enhanced immune cell infiltrate into the brain would need to be closely monitored [45] and would pose challenges if chosen as a treatment. IL-10 as mentioned above is an immunosuppressive cytokine and can be produced by multiple T-cell subsets including Tregs, and has been shown to be upregulated in the brains of AD patients [49]. Studies have also examined what effect depleting IL-10 *in vivo* has on AD pathology [49]. Using *Il-10*$^{-/-}$ mice crossed with APP/PS1-21 AD mice, the authors observed a preservation of synaptic ability, mitigated cognitive decline, and cerebral amyloid accumulation [49]. This data may suggest a mechanism behind the observation that Treg depletion, and thus IL-10 depletion restores cognitive function supporting the hypothesis described by Baruch *et al.* above [45]. Depleting IL-10 would be a more manageable strategy rather than targeting whole cell lineages such as Tregs. However, it is not known if Tregs are the main producers of IL-10 during AD as another source of IL-10 during AD could be T_H2 cells [50]. Studies have shown that the adoptive transfer of WT T_H2 cells into APP/PS1-21 AD mice can improve cognitive function and reduce AD pathology [51]. This study, therefore, suggests that immunosuppression elicited by IL-10 may be useful during AD. However, this may depend on whether the adoptively transferred T_H2 cells in this study are actually releasing IL-10 as this may only arise if the T_H2 cells are being activated. This highlights the therapeutic potential of targeting IL-10 *in vivo* in AD but suggests the direct impact of the cellular source of upregulated IL-10 needs further study. There are also ongoing studies that aim to enhance Treg function during AD to suppress immune activity that are discussed below.

The role of other subsets of the adaptive immune system in AD are more poorly understood. However, recent studies have suggested their potential role in disease. These include CD4+ T follicular helper T-cells (T_{FH}), B-cells, NK cells and gamma-delta (γδ) T-cells.

T_{FH} cells are the main source of proinflammatory IL-21 [52]. Systemic increases of IL-21 have been shown in both AD and MCI patients; however, these studies have not identified whether this was solely due to T_{FH} production and to date, no studies have shown the presence of T_{FH} cells in an AD brain [52]. These patients also displayed increases in both Aβ peptide-specific plasma IgM and IgG levels [53]. This is also seen in 5xFAD AD mice as compared to controls suggesting an IL-21 T_{FH}-mediated inflammatory response may be contributing to pathology [54]. IL-21 can also stimulate T_{FH} cells in an autocrine manner that could further exacerbate the presence and contribution of T_{FH} cells in AD [54, 55]. An excess production of IL-21 during an inflammatory response also mediates IL-17 release by T_H17 cells and thus could suggest that T_{FH} cells are an important immune mediator of excessive inflammation of other immune subsets in AD [54, 55].

B-cells are essential for the production of antibodies in mammalian biology [56]. The role of B-cells in AD is not fully understood; however, B-cells have been shown to be present in the brain parenchyma of 3xTG and APP/PS1-21 AD mice [57]. It was first thought that the presence of B-cells in the brain may produce immunoglobulins that were specific to, and interfere with Aβ plaque formation [57]. However, this study found that depletion of B-cells in AD mice by crossing 3xTG or APP/PS1-21 AD mice with J_HT mice (B-cell deficient) resulted in a lack of immunoglobulin deposition in the brain that subsequently reduced AD pathology. This result was also confirmed using anti-B-cell blocking antibodies in 5xFAD AD mice and suggests that B-cell production of immunoglobulins, an event that happens in response to microbial infections, can contribute to AD pathology [57].

NK cells are another subset of immune cells that play a vital role in host defence and bridges the gap between the innate and adaptive immune response [58]. NK cells can kill an infected cell directly via production of cytokines or mediate antibody-dependent cellular cytotoxicity (ADCC) [58]. The role of NK cells in AD is poorly understood, but studies have shown that depletion of NK cells using anti-NK1.1 antibodies dramatically improves the cognitive function of 3xTG AD mice [59]. This depletion of NK cells was also associated with a decrease in microglial proliferative capacity and rescued inflammatory cytokine production [59]. It has also been shown that in human AD patients most systemic NK cell numbers contract; however, RNA-sequencing (RNA-seq) analysis has revealed an expansion of a unique NK cell subset expressing *Cx3cr1*, *Tbx21*, *Myom2*, *Dusp1*, and *Zfp36l2* that may potentially drive NK-mediated AD pathology [60]. Together these studies imply that NK cells play an important role in AD pathology, but similarly to T-cells their effect may be restricted to proinflammatory cytokine release or ADCC-mediated damage. It may be, therefore, useful to target for deletion the expanded NK subset described above or define the specific proinflammatory cytokines released by these cells.

γδ T-cells are less abundant than $CD4^+$ T_H or $CD8^+$ T-cells but they play an important role in anti-microbial defence but can also support wound healing and immune tolerance [61]. Using TCR deep sequencing of both human blood and brain samples from AD patients, analysis of the TCR revealed clonal diversity and somatic variability within the TCR γ-chain (TRG) and identified putative TCR clonotypes that were more specific in both the brain and blood [61]. Whilst this highlights that a biased γδ TCR subset may contribute to disease, further studies are needed to elucidate the importance of these findings and whether any dominance of the TRG region or other TCR complementarity-determining regions (CDR3) can be used as markers of AD pathology [61].

There are other immune cells not discussed at length here that may potentially contribute to AD pathology including mucosal-associated invariant T-cells (MAITs). Interestingly, brain astrocytes and microglia can express functional MHC complex class I-related molecules (MR1) that present microbial antigens to MAIT cells [62]. This raises the possibility that microglial antigen recognition by MAITs, similar to that seen with T-cells [35], may contribute to AD pathology, but any mechanism for this has not been described and would need further study to dissect any link.

It is also worth considering what influence AD genetic risk loci factors have on T-cell function. T-cell activation is elevated in individuals that express *Apo*ε4 (risk allele) as compared to those that express *Apo*ε2 or *Apo*ε3 [63]. This activation is also seen *in vivo* using *Apoe*$^{-/-}$ mice that have increased levels of T_H1 and T_H17 cells in their brains with concurrent increases in proinflammatory cytokine release (IL-17, IFN-γ, TNF-α, IL-12, IL-1β, and IL-6) [64]. This data show that APOE can modulate T_H1 and T_H17 proinflammatory-mediated cytokine responses [64] and is a key regulator of T-cell activation; however, *in vitro* studies suggest that APOE lipoproteins can actually inhibit T-cell activation by limiting inflammatory cytokine release [65, 66]. More work is needed to discover whether activated T-cells and neuroinflammation seen during AD are a consequence of the individual expressing *Apo*ε4.

Cytokines, inflammation, and AD

As mentioned throughout, AD pathology can be exacerbated by the production of cytokines and chemokines that can drive neuroinflammation. These are released either through: (i) the activated systemic innate and/or adaptive immune response which then recruits to the brain; (ii) through the interaction of the immune cells with brain-resident cells; or (iii) released via aberrant brain-resident microglia and astrocytes themselves. These include those that are most well described, that are either proinflammatory, including IL-1β/α, IL-6, IL-18, TNF-α, and IFN-γ; and those that are anti-inflammatory, including IL-4, IL-10, and TGF-β [19, 67].

There are 15 cytokines that have been associated with AD with at least 23 cytokine polymorphisms associated with disease risk [67, 68]. Zheng *et al.* classified all cytokines associated with AD into three main conditions "(1) having polymorphisms that are significantly associated with AD, (2) having corresponding genotype/phenotype data, and (3) having previous records of the changed levels in AD patients" [67, 68]. Dysregulation of these cytokines can then contribute to excessive Aβ production in an inflammatory manner that subsequently leads to further increases in IL-1β, IL-6, TNF-α, and IFN-γ production by glial cells, creating a vicious cycle of pathogenic events [67].

New data have suggested a role of the proinflammatory cytokine secreted phosphoprotein 1 Osteopontin (SPP1) in AD [69]. This study showed that SPP1 is upregulated by perivascular macrophages and is required by microglia for synaptic phagocytosis in the hippocampus of APP-NL-F AD mice [69]. The authors suggest that SPP1-microglia crosstalk mediates aberrant microglial activity during AD [69]. SPP1 release has also been shown to promote the survival of autoreactive T-cells in the brain of multiple sclerosis (MS) mouse models [70]. This may suggest that the microglia may also become activated by the presence of these autoreactive T-cells further exacerbating microglial synaptic phagocytosis, but would need further studies to confirm any association.

Recent studies have also suggested that IFN release plays a key role in Aβ-mediated pathology (reviewed in Ref. [71]). The IFN family have widespread anti-viral or immune-modulatory functions and is released upon pathogen-associated molecular pattern (PAMP) recognition (reviewed in Ref. [71]). Microglia and astrocytes both express pattern-recognition receptors (PRRs) that can recognize PAMPs and their engagement results in transcription of cytokines (described above) including type-I IFNs [71]. There are three major classes of IFN: type-I IFNs comprising IFN-α and IFN-β, type-II IFN (IFN-γ) and type-III IFN (IFN-λ) [72]. Cell signalling is induced when type-I IFNs bind to the IFN-αβ receptor (IFNAR1 and IFNAR2) and initiate transcription of interferon-stimulated genes (ISGs) [72].

Multiple studies have shown that ISGs are elevated in the brains of AD patients as compared to healthy controls [73, 74]. These findings were supported using *in vivo* 5xFAD AD mouse models where type-I IFN activation was shown to induce Aβ pathology in microglia and other neuronal cells [75]. The authors showed that blocking IFNAR signalling in 5xFAD AD mice reduces both microglial cell accumulation and synapse loss [74] and that specific deletion of IFNAR1 expressed on microglia can rescue memory and reduce synaptic defects [75]. IFNAR1 deletion on other neuronal cells has also been shown to restore synaptic terminals and decrease Aβ plaque formation [75]. The importance of type-I IFN signalling in AD pathology was shown in studies using APP/PS1-21 AD mice where primary microglia isolated from the brains of mice with ablated type-I IFN signalling displayed increased phagocytic capacity to uptake Aβ1-42 [76].

GWAS studies have also shown that viral-mediated IFN responses are associated with an increase in microglial-mediated tau pathology [77], and as discussed below, viral infections can play a critical role in exacerbating AD. More recent studies went further and used transcriptomic approaches to reveal polymorphisms in ISGs within the hippocampus in multiple mouse models of AD and compared these findings to human GWAS AD datasets [78]. These studies suggest that ISG polymorphisms may increase the overall risk of AD [78]. However, these require further study to describe the mechanisms underpinning their involvement and whether these are associated with microbial infection or microglia function. This is now of significant importance given that Interferon-induced transmembrane protein 3 (IFITM3), a key anti-viral restriction factor, is activated by inflammatory cytokines in neurons and astrocytes and binds gamma-secretase subsequently upregulating Aβ production [79]. The authors showed that IFITM3 is upregulated in LOAD patients and that crossing *Ifitm3*$^{-/-}$ mice with 5xFAD AD mice results in reduced gamma-secretase activity with reduced amyloid plaque formation [79]. This study suggests a key role for IFN-induced risk of neuroinflammation and exacerbation of AD pathology. Recent studies have suggested a mechanism behind this type-I IFN-mediated effect whereby pathogenic tau stimulates microglia to release type-I IFN that is mediated by cGAS-STING signalling in 5xFAD AD mice [80]. This study suggested that deletion of cGAS induces a myocyte enhancer factor 2c gene (*Mef2c*) network that promotes cognitive resilience and thus suggests that cGAS signalling may be an effective therapeutic target in AD [80]. Whilst this new study does reveal new mechanistic insight, and as described by Sandford *et al.* [71], it is still not fully understood how IFN production directs the immune system to exacerbate AD pathology and tauopathy and requires further study [71, 78].

Chemokine signalling is another major component of adaptive immune function. Mononuclear phagocytes such as monocytes and macrophages are some of the primary inducers of inflammation-mediated via chemokine release/signalling and have been shown to influence AD pathology (reviewed in Ref. [47]). Several chemokines such as CCL2 (MCP-1), CXCL8 (IL-8), CXCL10 (IP-10), and CCL5 (RANTES) are also produced in response to Aβ peptide deposition and have been shown to regulate both microglial and astrocyte migration and the recruitment of other peripheral immune cells into the brain [67]. Activated microglia have also been shown to contribute to pathology mediated via a chemokine axis and can inhibit neuronal activity through expression of CCL-3/-4/-5 binding to neuronal CCR5 [81]. This study showed that genetic deletion of CCR5, whose expression is increased in mouse models of tauopathy, ameliorates tau pathology [81]. This suggests a paracrine signalling effect by activated microglia that influences neuronal function. Microbial infections are known to infect monocytes, macrophages, and microglia with some microbes exploiting chemokine receptors for viral entry [82]. AD pathology may, therefore, be induced as a side effect of neuroinflammation via infection-mediated chemokine release, similar to that seen with cytokines released during infection (discussed below).

Viral infection and AD

Recent data now highlights the potential role of viral infections in exacerbating cognitive decline and AD [83]. It is well known that many viruses are neurotropic and can access the brain driving neurological impairment including herpes simplex virus-1 (HSV-1), SARS-CoV-2, Polio, and West Nile Virus [84–86]. Further evidence suggests that human herpesviruses (HHV), which establish life-long chronic infections, can be found in the brains of deceased AD patients including HSV-1, HHV-6A, and HHV-7 [84, 87].

It was first suggested over 40 years ago that HSV-1 infection can induce encephalitis in the brain that displays similar properties to AD [88]. Later studies went on to confirm this discovery showing that HSV-1 genomic DNA and a functional HSV-1 genome is found in AD patient brains [89, 90]. Studies next went on to investigate the mechanisms behind these observations and identified that direct HSV-1 infection in primary neurons increases protein kinase A that mediates tau phosphorylation giving rise to dystrophic neurites and AD pathology [91, 92]. Lövheim *et al.* went on to state that HSV-1 plays an important role in early AD development and were able to detect the presence HSV-1-specific antibodies in plasma samples taken 6.6 years prior to the onset of dementia [93]. This, therefore, could suggest that HSV-1 circulating antibodies can potentially serve as risk biomarkers of AD in those patients who are also at genetic risk of developing AD.

More recent studies have examined what effect co-infection has on AD pathology and neuroinflammation [94]. Using human-induced neural stem cell cultures that were infected with quiescent HSV-1 and/or varicella-zoster virus (VZV), the authors showed that VZV infection alone displayed no typical characteristics of AD such as Aβ and tau accumulation but was able to induce gliosis and proinflammatory cytokine release [94]. The authors also showed that HSV-1 infection alone is enough to induce typical AD-like features, as stated before, and strikingly they showed that VZV infection of cells was able to reactivate HSV-1, which then drives Aβ and tau accumulation [94]. They went on to state that shingles induced by VZV infection could indirectly contribute to AD by promoting sufficient neuroinflammation to reactivate HSV-1 which then directly drives AD pathology [94]. Epidemiological studies have also shown that in patients over the age of 50 with an untreated active HSV-1 or VZV infection, the overall risk of dementia is increased 1.5-fold [94]. These studies have also shown that anti-viral medication could also lower the risk of dementia by 25% as compared to the untreated herpes-infected individuals [95].

Due to the very high seroprevalence of other herpes viruses within the human population, studies have shown that infection with the common β-herpesvirus human cytomegalovirus (HCMV) is also associated with AD [96–98]. HCMV infection results in increased localized viral-specific inflammation found in both the blood and brain of AD patients that is associated with worsening rates of cognitive decline and an increased accumulation of Aβ [96–98]. However, there are conflicting epidemiological studies that suggest CMV seroprevalence alone is not associated with AD pathology and that a co-infection hypothesis of CMV with HSV-1 is the driver of AD development and is similar to what is described above with HSV-1 and VZV [99]. Though chronic infection with HCMV results in viral latency, the virus is reactivated upon a host becoming immunocompromised or in a co-infection setting may reactivate by a host's redirection of the immune system to another active viral infection [100]. However, more studies are needed to confirm the mechanisms behind these findings. This co-infection hypothesis is further supported by a recent study showing that HSV-1 and SARS-CoV-2 infection in human CSF can result in amyloid aggregation of proteins known to be involved in AD, including APOE [101]. This may suggest that active site-specific viral replication within the CNS may be enough to trigger AD pathology.

This theory is supported by studies showing that EBV-specific TCRs are found to be both antigen experienced and clonally expanded within the CNS of AD patients [36]. Tiwari *et al.* support this theory and suggest that EBV-encoded proteins (e.g. BNLF-2A) can induce AD by interfering with antigen processing and presentation by inhibiting cellular TAP (transporter associated with antigen presentation) functions and downregulating MHC-I and MHC-II expression [102]. The authors showed that upon infection, this process can lead to an accumulation of neuronal cells and viral polypeptides that subsequently promote a build-up of oligomers and amyloid-like aggregates using *in vitro* Thioflavin-S fluorescence assays [102]. EBV infection is also known to be associated with a range of neurodegenerative conditions such as Parkinson's disease, viral-induced encephalitis, and Meningitis (reviewed in Ref. [103]). Recent large-scale epidemiological studies in over 10 million people show the risk of MS is increased 32-fold in EBV-infected individuals and suggest that EBV is the leading cause of MS [104]. The neurodegenerative events seen during infection may potentially arise due to systemic EBV-infected peripheral blood mononuclear cells (PBMC) crossing the BBB and replicating within brain endothelial cells promoting cytokine release and a loss of neurons [103, 105]. The constant systemic switch from latency to reactivation events associated with infection can, therefore, continually drive systemic stress further exacerbating BBB crossover and cognitive deficits seen with AD and other neurodegenerative diseases [103, 106]. Taken together, these studies highlight how herpes viruses that establish life-long infection increase the overall risk of developing AD. Future work must be performed in this area to identify the key viral-induced mechanisms behind these observations and whether anti-viral treatment could be useful in AD.

Recent attention has been extended to examine what effect the recent circulating pandemic SARS-CoV-2 virus has on AD pathology. Whilst all seven members of the *Coronaviridae* family have been shown to be neurotropic [107], the association of SARS-CoV-2 infection with AD is still in its infancy due to the recent emergence of the virus. However, it has been well described that cognitive deficits and dysfunction are observed in patients post-SARS-CoV-2 infection even after mild infections [108]. This neuroinflammatory nature of the infection has been shown to be driven by increased levels of CCL11 in the CSF and serum that leads to microglial activation and loss of neuronal function in mouse brains [109]. Whether these same viral-induced processes apply in exacerbating AD is not yet known, but they provide useful mechanistic insights to help inform future AD studies.

In the context of AD, recent epidemiological studies in over 6.2 million people >65 years of age, have suggested SARS-CoV-2 infection is associated with a nearly 2-fold increased risk of AD (0.35% (non-COVID-19) to 0.68% (COVID-19+) and these risks are significantly elevated within 360 days of infection, especially in people >85 years of age and in women [110]. Further studies have shown that within UK biobank cohorts, *Apo*ε4 homozygotes were 2.31 times more likely to test positive for SARS-CoV-2 than *Apoε3* homozygotes [111]. Studies that have used human-induced pluripotent stem cells have shown that APOE4 isogenic neurons and astrocytes observe a higher rate of SARS-CoV-2 infection compared to *Apo*ε3 genotype with increased astrocytic apoptosis [112]. This is supported by studies that show Aβ42 can bind with high affinity to the S1 subunit of SARS-CoV-2 and membrane-bound ACE2 (angiotensin-converting enzyme 2 receptor – S1 binds to ACE2 for viral entry) resulting in increased viral ingress and proinflammatory IL-6 production [113, 114]. ACE2 has also been shown to be significantly upregulated in the brains of AD patients irrespective of disease severity, gender, or age and has the potential to be potentially neuroprotective [115]. Furthermore, *in vivo* AD studies in non-SARS-CoV-2 infection models have shown that Aβ43 and Aβ42, the two longer forms of Aβ, can be converted by ACE2 into the less toxic Aβ40 isoform and slow down Aβ42 aggregation in APP-transgenic J20 PDGF-APPSw AD mice [116]. Whilst this neuroprotective property of ACE may be useful in AD upon no infection, ACE2 upregulation may exacerbate AD upon SARS-CoV-2 infection with the virus exploiting this upregulated receptor for entry into endothelial cells in the brain to drive neuroinflammation. Combined, these studies demonstrate that SARS-CoV-2 infection can directly exploit the cellular factors that are associated with AD pathology.

The existence and now continued prevalence of SARS-CoV-2 circulating within the human population poses a risk to AD patients given the neurotropic nature of the virus. Studies that examine co-infection of SARS-CoV-2 with herpes virus family members that are associated with elevated risk of AD are now, therefore, of vital importance. This is due to the high level of seroprevalence of these viruses that are known to independently contribute to AD and where the likelihood of co-infection within humans remains high.

Epidemiological studies have also associated hepatitis C virus (HCV) and intestinal infections with AD [83] (reviewed in Ref. [117]). In bipolar patient cohorts that go on to potentially develop AD, 31% of AD patients were found to be HCV+ as compared to 16% of non-AD patients who were HCV+ [118]. These findings may suggest that an HCV-specific neuroinflammatory response similar to that seen with herpes virus infections is contributing to AD as no study has yet reported any HCV within the brains of deceased AD patients. Importantly, however, predictive markers of HCV liver cirrhosis (elevated aspartate aminotransferase [AST] to alanine aminotransferase [ALT] ratio) have been associated with AD diagnosis [119]. Here, AD patients were assessed for a correlation between HCV predictive markers with neuroimaging scores, cognitive ability, CSF biomarkers, brain function/atrophy, and amyloid accumulation and found an elevated AST to ALT ratio of 7.932 is associated with AD diagnosis [119]. More mechanistic studies have identified that APOE has also been shown to be heavily involved in HCV virion assembly and directly interacts with HCV envelope glycoproteins [120], but the role this mechanism plays in AD is not understood. This, therefore, points to a potential HCV-AD link, but this requires much further study. Due to the recent emergence and success of direct-acting antivirals (DAA) for the treatment of HCV, as mentioned above, it would be important to examine the influence of DAA treatment in patients who go on to develop AD.

The association of human immunodeficiency virus (HIV) and AD within humans is less well defined. However, there are similarities that exist between the cognitive dysfunctions seen during HIV infection and AD termed HIV-associated neurodegenerative disorders (HAND) [121]. Though no large-scale epidemiological study has shown a direct link between HIV and AD [83], a recent meeting abstract has shown that HIV+ individuals had a higher prevalence of AD and related dementia (ADRD) [122]. The clinical scores of ADRD that the authors used to describe AD are not classified in this study; however, this data may now suggest a direct association of HIV infection with AD but requires more detailed analysis upon data availability [122].

There are also many similarities between the brain-specific pathways and mechanisms associated with HIV infection and AD, which have been extensively studied in mice (reviewed in Ref. [123]). Multiple murine studies have shown that HIV infection results in an increase in Aβ synthesis and tau phosphorylation that is mediated by the HIV-specific Tat protein (reviewed in Ref. [123]). Importantly, *in vivo* studies show that expression of the lentiviral-vector derived Tat protein in the hippocampus of APP-PS1 AD mice increases Aβ1-42 synthesis and the overall size of amyloid plaques [124]. More recent studies went further to describe how the HIV-specific Gag polyprotein can also increase Aβ expression and modulate APP metabolism. Whilst the increase in Aβ expression was shown to be neurotoxic, the increase in APP was shown to sequester the Gag protein to restrict HIV-1 release [125]. This suggests the potential of Aβ to act in an anti-microbial manner and is described further below.

These *in vivo* studies strongly suggest a direct link between HIV infection and AD; however, human studies remain less convincing. Similar levels of Aβ1-42 have been shown in the CSF of both HAND and AD patients [126]; however, it is important to consider that the HAND patients would all have been undergoing anti-retroviral therapy (ART) meaning interpretation of this data is influenced by therapeutic treatment for infection and different ART treatments can result in 50–200% increase in Aβ production in mouse neuronal cells [127]. Studies have shown that any accumulation of amyloid aggregates in HIV patient brain samples begins prior to ART [128]. This again suggests the true function of overproduction of Aβ during HIV-1 infection is currently unknown as to its relationship with AD onset.

Human studies went on to show that in samples taken from the brains of HIV-infected individuals, the presence of accumulated amyloid was mostly found within neurons, whereas in AD, the neuritic plaques associated with AD pathology are mostly found outside of neurons [129]. This accumulation of Aβ may arise due to dysregulation of microglia that would normally remove any excessive Aβ [129]. The authors described how microglia can act as HIV reservoirs and that infection may activate microglia which then promotes a neuroinflammatory environment and failed removal of Aβ [121, 129].

These studies suggest a strong overlap between HIV+ HAND and AD. However, important studies are needed to examine in more detail whether there is a distinction between HAND and AD. As suggested in Ref. [121], Turner *et al.* have been actively recruiting patients to evaluate this very point and to build on machine learning techniques that distinguish between magnetic resonance imaging (MRI) morphometric differences in the brains of HAND and MCI AD patients [130]. Taken together the question of whether HIV can cause AD currently remains as a strong association rather than a definitive direct causation. As the HIV+ cohorts are now becoming aged individuals and HIV can prematurely age brains [131], this may create an opportunistic environment that would be suitable for AD development/onset.

Current epidemiological studies suggest that at least 45 different viral exposures can be significantly associated with neurodegenerative disorders, with some associated up to 15 years after infection [83]. This, therefore, raises the possibility that vaccination strategies aimed at viral infections may help reduce the onset of dementia and AD. Human studies have shown that vaccination to herpes zoster or a tetanus, diphtheria, and pertussis (Tdap) vaccine was associated with a 25% and 18% lower risk, respectively, for dementia than compared to no vaccine controls [132]. A recent epidemiological study went further and calculated that vaccination with Zostavax against VZV, lowered dementia occurrence by 19.9%, with the vaccine being found to be more effective in women under the age of 80 [133]. The researchers stated that this was a more natural experiment as the data were obtained in a non-biased way where other factors that can reduce the risk of dementia in the vaccinated group (such as healthier lifestyles) were eliminated using unique natural randomization [133]. These studies show exciting promise and suggest that anti-viral treatment and viral-based vaccines, of which there are multiple available for a range of different infections, including those mentioned above, need to be urgently extended to examine their influence in more detail on AD development. However, it is also possible that the host systemic anti-viral inflammatory response may stimulate the immune system to elicit cytokine-mediated neuroinflammation that contributes to AD pathology. There does, however, remain a lack of clear data regarding the viral-induced immune mechanisms that directly drive AD development and thus require further study.

Non-viral infections and AD

Whilst the association of bacterial and fungal infections with AD risk have gathered recent interest, less information exists examining their impact on AD as compared to viral infections. It has been shown that infection with gram-negative bacteria, including *Porphyromonas gingivalis*, the main cause of chronic periodontitis, can induce neuroinflammation increasing the risk of developing AD with elevated Aβ1-42 levels shown in *Apoe*$^{-/-}$ mice brains [134]. This can induce lipopolysaccharide production that stimulates the release of proinflammatory cytokines at the site of infection, but also in the periphery, which may then be directed to the brain [135, 136]. The presence of *Chlamydia pneumoniae*, has also been found post mortem in the brains of deceased AD patients [137] and other bacteria have also been implicated in contributing to AD including *Propionibacterium acnes* and *Helicobacter pylori* (reviewed in Ref. [138]). Studies have also shown using APP/PS1-21 AD mice that polymicrobial activation can increase fibrillar Aβ plaque formation in the hippocampus that activates astrocytes contributing to increased brain-specific inflammation [135]. Combined these studies support the hypothesis that similarly to some anti-viral responses, active anti-bacterial activity may be indirectly contributing to AD via a neuroinflammatory response (reviewed in Refs. [138, 139]).

Conflicting data suggests, however, that during AD, the presence of Aβ can actually be protective against invading pathogens [140]. The anti-microbial hypothesis of Aβ is supported by *in vitro* studies whereby synthetic Aβ peptide treatment exhibits potent anti-microbial activity towards eight common and clinically relevant microbial pathogens [141]. This protective hypothesis was later supported using transgenic human Aβ expressing cell lines where overexpression of Aβ increased host cell resistance to *Candida albicans* infection [142]. The authors went on to show that in 5xFAD AD mice, the presence of Aβ helped protect against *Caenorhabditis elegans* nematode infection and described how *Salmonella typhimurium* infection in the brain can induce an accelerated Aβ deposition that co-localizes with the bacteria [142]. They describe how amyloid oligomerization mediates the protective capacity of Aβ and the presence of microbial cells within the cerebrum accelerates Aβ deposition in 5xFAD AD mice [142]. The authors, therefore, suggest that Aβ may have dual protective and pathological role during infection [142].

The anti-microbial role of Aβ is also supported by studies where Aβ42-overexpressing cells are shown to be resistant to killing by yeast and bacteria [143]. This presents an important finding in AD development. If as suggested by Frost *et al.* that APP and Aβ are involved in pathogen defence, then excessive Aβ production could be a by-product from innate immune cell activation supporting the hypothesis that infectious pathogens could play a vital role in AD development [19]. This raises the possibility that combination therapies that target the pathogen and the associated proinflammatory cytokine response may be a useful treatment regimen for AD.

Immunotherapy

There have been many studies that have used immunotherapy as a way to specifically target Aβ to prevent plaque formation for effective treatment of AD [144]. These approaches used either synthetic Aβ peptides (AN1792) to stimulate anti-Aβ antibodies [145, 146], or use antibodies that target various regions of Aβ [144]. However, these studies have largely failed due to a lack of efficacy and safety concerns. Further direct entry of antibodies into the brain poses a clinical challenge as well as the timings required to treat an individual recruited into a trial who may already have different levels of Aβ throughout the cohort [47].

There have been more recent proof of concept approaches targeting Aβ using anti-IgG1 antibody therapy (Gantenerumab and Lecanemab) which have been designated 'Breakthrough Therapies' by the US FDA [147, 148]. Both antibodies, (recently through Phase III trials), using between 850 and 2000 patients, showed reduction of Aβ plaques and slowed cognitive decline. Lecanemab is intended for early-stage AD and resulted in a 27% slowing in cognitive decline with reduced plasma Aβ42/40 ratio and reduced amyloid in the brain [149]. Gantenerumab has now failed to reach its key secondary endpoints in Phase III clinical trials and is currently suspended [150]. Donanemab is another anti-IgG1 Aβ antibody that has recently come through Phase III trials with promise [151]. The results of the trial are similar to the effects seen with Lecanemab and provide a 35% slowing of cognitive decline as compared to placebo [151]. Whilst Donanemab is not yet licensed, permissions are being actively sought for approval [151]. Until recently the only approved monoclonal antibody therapy to target Aβ was Aducanumab that lead to a reduction in amyloid; however, the approval of this drug is still debated [152–154]. Also, as mentioned above, due to successful Phase III trials, Lecanemab has recently been licensed for use in human AD patients [6, 155]. However, it is important to consider that it is widely accepted that for the brain to respond to treatment and thus recover, amyloid plaques need to be completely removed from the brain [150]. It is important to note that Lecanemab treatment only results in a 27% slowing in cognitive decline in AD patients with the potential risk of side effects and consider whether any anti-amyloid IgG therapies are effective at removing most if not all, amyloid from human brains.

Based on the mostly failed approaches and more recently the mild benefits of 'breakthrough' drugs that target Aβ, it is, therefore, appropriate to also target the immune system for effective AD treatment utilizing the approaches that target various immune pathways as described throughout.

As described above Tregs can play an important immune-modulatory role that contributes to AD pathology. Recent studies have suggested that Tregs can potentially be neuroprotective and can suppress excessive microglia activation and inflammation seen in AD brains [156, 157]. These studies took an approach that examines what impact the adoptive transfer of *in vitro* expanded Tregs has on AD pathology using AD mice. Tregs were either isolated from mouse splenocyte cultures and expanded using Aβ1-42 peptide to ensure antigen-specific Tregs were expanded [157], or were derived from human PBMC cultures and expanded for 24 days [156]. Expanded mouse Tregs were transferred into 3xTG AD mice where a noted reduction in microglial activation was seen with an associated amelioration of cognitive impairment [157]. Human Tregs were transferred into 5xFAD AD mice that were crossed with Rag2 deficient mice. The immune activity in these mice is, therefore, restricted to the Treg compartment and resulted in a reduction of both amyloid burden and reactive glial cells but was also shown to reduce proinflammatory cytokine release [156]. These studies show promise, however, whilst targeting excessive inflammation may be useful therapeutically, Baruch *et al.* suggest that there is already an observed overall increase in Tregs in both AD patients and mice as compared to non-AD cohorts [45]. Contrastingly, they suggest that Treg depletion is more useful therapeutically in reversing cognitive impairment in mice [45]. They also suggest that activating T-cells in this context may be more useful than increasing the prevalence of Tregs (described above (page 4). There are also studies that are now examining the potential efficacy of chimeric-antigen-receptor (CAR)-Treg-based therapies in neurological disorders [158]. CARs are manufactured receptors that can provide a T-cell with the ability to target a specific surface target and activate the T-cell simultaneously upon target recognition [159]. Due to the different studies suggesting either a pathological or protective role of Tregs in AD, CAR-Treg therapies may potentially have promise yet more studies are needed to understand the mechanisms between modifying Tregs that either protect or exacerbate disease.

Other CAR T-cell-based therapies could therefore pose an exciting prospect for treating AD based on the theory suggested by Baruch *et al* [45]. CAR T-cells are undergoing rapid development and have mostly been investigated to improve T-cell function in cancer [159]. For effective CAR T-cell therapy the antigen or target needs to be defined and as stated above this remains complicated in AD. Studies have investigated whether commonly expressed proteins associated with AD pathology, such as Aβ and tau, could serve as T-cell antigens, but although strong T-cell responses against these antigens are detectable, there are no differences seen between AD patients and healthy controls [160]. In this study, the authors went on to describe that they believe there is not a key role for neuronal antigen-specific T-cells in AD [160]. However, this may be due to the antigens chosen within their study which may not be specific enough to result in observable change. More in-depth GWAS studies have discovered other specific antigens that could potentially serve as CAR targets. Here, novel-specific tau peptides have been shown to aggregate within AD patient cohorts that are dominant towards a specific patient's MHC restriction [161]. These have not been investigated using CAR T-cell therapy to date, but could serve as a more specific target.

There are risks associated with activating T-cells in the brain using CAR T-cell therapy for AD. The neuronal toxicity associated with CAR T-cell therapy has been well described and can include encephalopathy, headaches, and tremors among others [159]. Depending on the CAR T-cell approach taken, those that would intend to induce activated T-cells, albeit to specific neuronal targets, could pose a serious danger to the patient. Those that intend to suppress immune activity to reduce inflammation, including CAR Tregs, could also pose risk as activated Tregs also produce perforins, granzyme B and IL-2 that could damage cells within the brain further exacerbating pathology [158]. These approaches, therefore, suggest that activating T-cells to harness their ability to differentiate or activate to various degrees could be useful for therapy. However, a more recent study went further to state that T-cells are the predominant drivers of AD pathology [35]. Here, the authors found that T-cells (notably $CD8^+$ T-cells) are markedly increased in areas of the brain with increased tau pathology but not amyloid deposition in AD mice. They suggest that the T-cell infiltrate that contributes to tauopathy is driven by T-cell microglia interactions and that T-cell and microglia depletion blocks tau-mediated neurodegeneration [35]. This suggests that enhancing T-cell function may not be useful therapeutically but would point to therapies that reduce T-cell function may be more important.

Based on the immunotherapy approaches discussed above, it may be useful to design studies that target both Aβ in combination with immune modulator/s to maximize any potential success of an immunotherapeutic approach for AD. It is also important to consider the timing of these treatments and to determine whether the efficacy of treatment changes during early, mid, or late disease. These approaches may significantly impact disease progression and pose an exciting avenue for treatment moving forward.

Closing remarks

AD represents one of the greatest risks to global public health as humans now live longer. Without any highly effective therapies to appropriately treat the disease with strong efficacy, it is clear that the healthcare and economic burdens will become overwhelming. The studies that have been discussed here highlight the link between immune system-mediated inflammation in response to microbial infections with AD pathology and neurodegeneration. While therapeutic studies have mostly focused on targeting Aβ, these results have only elicited partial improvements and thus an effective treatment remains elusive. The highly influential role that the immune system plays in AD has been well described throughout and research surrounding this area is gathering pace. However, the key mechanisms behind these observations still require further study and indeed whether these mechanisms are influenced by an individual's increased genetic risk of disease. Whether the adaptive immune system is eliciting its effect via direct interactions with brain-resident cells altering their function to drive pathology, or whether this is due to neuroinflammation released as a result of an increased antimicrobial response, or whether it is a combination of both, has still not been comprehensively addressed. However, the data discussed here strongly highlights the significant contribution that the adaptive immune system, particularly T-cells, plays in AD pathology. Together, identifying new prognostic markers of disease, related to and derived from the immune system, will be crucial in developing novel therapies that will alleviate the symptoms of this debilitating disease and prevent neurodegeneration in AD.

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Ethical approval

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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