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The role of the immune system in driving neuroinflammation

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Abstract

Neuroinflammation is now recognised as an important contributory factor in the progression of Alzheimer's disease and probably also in the early stages of the disease. It is likely that this derives largely from aberrant activation of microglia, the resident mononuclear phagocytes of the brain. These cells are responsible for physiological immune surveillance and clearance of pathogens in the central nervous system, but evidence indicates that in Alzheimer's disease, microglial function is compromised, and this contributes to the pathology. It is unclear what factors cause the inappropriate activation of the microglia in Alzheimer's disease, but one contributor may be infiltrating peripheral immune cells and these include macrophages and T cells. It has been suggested that both cell types modulate the phenotype of microglia, highlighting the importance of crosstalk between the innate and adaptive immune system in Alzheimer's disease. This review outlines our current knowledge of how cells of the peripheral immune system, specifically macrophages and T cells, may modulate microglial phenotype in the context of Alzheimer's disease and considers the impact on their function, especially phagocytic capacity.

Keywords

Microglia, neuroinflammation, Alzheimer's disease, T cells, peripheral immune cells

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Introduction

A role of the innate immune system in the pathogenesis of Alzheimer's disease (AD) is widely acknowledged, but a role for the adaptive immune system remains to be consolidated. Thus, microgliosis is an acknowledged common feature of AD (Hansen et al., 2018), and these cells, with a morphology that reflects activation, cluster around amyloid plaques in humans (Perlmutter et al., 1992) and animal models of AD (Frautschy et al., 1998; McIntosh et al., 2019). Evidence suggests that these cells are hypermotile (Gyoneva et al., 2016) and less phagocytic, although they contain fibrillar material (El Hajj et al., 2019), so they can phagocytose, but not process, amyloid-β (Aβ). It is proposed that microglia may clear Aβ in early disease, but switch to an inflammatory and less phagocytic phenotype as disease progresses (Hickman et al., 2008).

Genome-wide association studies revealed that mutations in genes that confer a significant risk of developing the AD were genes that code for proteins involved in immune function (Jansen et al., 2019; Lambert et al., 2013). These studies provided the first clear evidence that perturbations in immune function and inflammatory changes contribute to the pathogenesis of AD, and this was confirmed by the demonstration that microglial activation preceded Aβ accumulation in the 5XFAD mice model of AD (Boza-Serrano et al., 2018). To make any progress in combating AD, it is imperative to establish how microglial activation is triggered. In this review, the focus will be on assessing whether the infiltrating immune cells may play a part in AD development.

Immune cell populations have been identified in the normal brain

T cells and macrophages locate to the meningeal space, perivascular space and choroid plexus, but limited numbers are found in the parenchyma under resting conditions, indicating that the immune-privileged status of the brain is compromised in the perivascular space and choroid plexus, and more preserved in the parenchyma. However, recent mass cytometry and flow cytometry analysis revealed the presence of dendritic cells, monocytes and macrophages, T cells, B cells, natural killer (NK) cells and granulocytes in the brain of naïve mice. While most were in the meninges and choroid plexus, a small population remained when

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the meninges and choroid plexus were removed (Korin et al., 2017). Using a combination of mass cytometry, 22-colour fluorescence cytometry and immunohistochemistry, another group confirmed these findings (Mrdjen et al., 2018). The presence of $CD11c^+$ dendritic cells in brain parenchyma confirmed an earlier finding (Bulloch et al., 2008) which showed that a population of dendritic cells resides among microglia, especially when neurogenesis is ongoing. More recent findings confirmed the presence of $CD4^+$ and $CD8^+$ T cells in white matter (Smolders et al., 2018). These $CD8^+$ cells expressed cell surface markers and transcription factors consistent with a tissue-resident memory T-cell phenotype, and of these, $CD103^+CD69^+$ cells expressed chemokine receptors, which facilitate their migration (Smolders et al., 2018).

Macrophages infiltrate the brain with age and in AD

Significant infiltration of immune cells, including macrophages, occurs when there is evidence of neuroinflammation, for example, in aged animals and animal models of AD (Becher et al., 2017; Blau et al., 2012; Korin et al., 2017; McManus et al., 2014; Mrdjen et al., 2018; Toly-Ndour et al., 2011; Wolfe et al., 2018). The presence of NK cells (Kelly et al., 2013) and neutrophils (Minogue et al., 2014) has also been reported in the brain of APP/PS1 mice, and a correlation between blood–brain barrier (BBB) permeability and infiltrating cells has been identified (Blau et al., 2012; Denieffe et al., 2013; Kelly et al., 2013; Minogue et al., 2014). This is associated with increased expression of the chemokines CCL2 and IP-10 (Blau et al., 2012), which is consistent with the evidence that infiltration of monocytes relies on CCL2; thus, it was shown that the marked increase in infiltrating $CD11b^+CD45^{hi}$ cells that is identified in Tg2576 (APP) mice was markedly decreased in APP-CCR2$+^{/-}$ mice (El Khoury et al., 2007). These authors reported that deficiency of CCR2 increased Aβ plaque burden and suggested that this was because it decreased microglial accumulation, compromising their role in Aβ clearance. Others have reported that overexpression of CCL2 increased the number of plaque-associated microglia, but amyloid burden was increased because apolipoprotein E–associated Aβ clearance was reduced (Yamamoto et al., 2005).

A specific subgroup of infiltrating macrophages was identified in a study in which microglia were eliminated by PLX5622, the colony-stimulating factor 1 receptor (CSF1R) inhibitor; these phagocytic cells were $CD11b^+Iba1^+TMEM119^-$ macrophages and adjacent to Aβ deposits (Unger et al., 2018b). These authors suggested that the extracellular adhesion molecule CD44, the expression of which was greatest at sites of Aβ plaques, played a significant role in homing of these cells to amyloid deposits. In contrast, although macrophage infiltration was reported in 12-month-old female 5XFAD mice, this was not statistically significant (Shukla et al., 2019).

How do infiltrating macrophages impact neuroinflammation

Evidence of a beneficial effect. Whether infiltrating immune cells, including macrophages, are beneficial or detrimental to neuronal function is debatable. It was proposed that macrophages have a greater phagocytic capacity, and engulf Aβ more effectively, than microglia (Simard et al., 2006; Simard and Rivest, 2004; Stalder et al., 2005); this and their role in tissue repair suggest a neuroprotective function. Infiltrating macrophages are considered to be beneficial in the recovery from spinal cord injury (Shechter et al., 2009). These researchers also suggested that the phagocytic ability of macrophages underpins their beneficial effect in the brain in animal models of AD (Schwartz and Shechter, 2010). Consistent with this is the observation that Aβ pathology is exacerbated in CCR2-deficient APP/PS1 mice, in which macrophage infiltration is minimal (El Khoury et al., 2007), while the importance of perivascular macrophages in clearing the Aβ in leptomeningeal and cortical blood vessels was highlighted by depleting perivascular macrophages in TgCRND8 mice (Hawkes and McLaurin, 2009). In addition, adoptive transfer of green fluorescent protein (GFP)-expressing bone marrow cells into irradiated APP/PS1 mice, which migrated to the brain, decreased plaque number and size (Simard et al., 2006).

Evidence of a detrimental effect. While these data support the idea that infiltrating macrophages are beneficial and effective phagocytes, other data indicate that when microglia were replaced by peripheral myeloid cells, amyloid pathology was unchanged (Prokop et al., 2015; Varvel et al., 2015), although $Ly6C^{low}CX3CR1^{high}CCR2^-$ monocytes can engulf Aβ in perivascular spaces (Michaud et al., 2013). Similarly, ablation of microglia in APP/PS1 mice did not change amyloid pathology, even though blood-derived monocytes were spared (Grathwohl et al., 2009), arguing against the participation of peripheral cells in Aβ phagocytosis.

While these data suggest that infiltrating macrophages exert little effect, there are reports indicating that they can cause damage. In organotypic hippocampal slices, macrophages exacerbate oxygen-glucose deprivation–induced damage and cell death (Girard et al., 2013), while the age-related macrophage infiltration increased microglial activation (Barrett et al., 2015a) and decreased synaptic plasticity in aged rats (Blau et al., 2012). Furthermore, macrophages from aged rats are sensitised to inflammatory stimuli and conditioned medium from these cells activates microglia (Barrett et al., 2015a). Thus, the proposal is that, in age, infiltrating macrophages will encounter an inflammatory environment, adopt an inflammatory phenotype and contribute to the ongoing age-related neuroinflammation.

Infiltration of macrophages into the brain of APP/PS1 mice has also been closely linked with neuroinflammation and microglial activation (Cowley et al., 2012; Kelly et al., 2013; McManus et al., 2014; Minogue et al., 2014) and with reduced synaptic plasticity (Blau et al., 2012; Denieffe et al., 2013). However a population of anti-inflammatory $CX3CR1^{high}CCR2^-Ly6C^{low}$ monocytes have been reported in the brain of APP/PS1 mice, and it seems that these cells contribute to the maintenance of homeostasis in brain since, when they are deleted, total and vascular Aβ deposition increases and cognitive function declines (Michaud et al., 2013).

T-cell subsets

T cells, along with B cells, make up the adaptive arm of the immune system, and a small number of T cells are found in the brain even in homeostatic conditions (Hickey, 2001). T cells

comprise $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, which are further subdivided into the well-studied effector $CD4^+$ Th1, Th2, Th17 cells and regulatory T cells (Tregs), and the more recently described Th9, Th22 and follicular helper T cells (Tfh cells) (Golubovskaya and Wu, 2016). The polarisation of $CD4^+$ T cells is guided by cytokines, and each subpopulation further produces a distinct set of cytokines, which modulate other immune cells (Zhu et al., 2010).

T cells in AD

Evidence of T-cell activation in peripheral blood. Changes in peripheral T cells in AD patients have been reported. For example, Aβ-induced T-cell reactivity has been described in peripheral blood mononuclear cells (PBMCs) from AD patients and age-matched controls compared with young individuals; these cells were mainly interleukin (IL)-5^+ and IL-13^+ although smaller numbers of IFNγ^+ and IL-10^+ cells were identified (Monsonego et al., 2003). An AD-related increase in $CD8^+$IFNγ^+ cells, which is indicative of differentiation into Th1 cells, was reported (McManus et al., 2014), while differentiation into Th2 cells was suggested by $CD4^+$GATA-3^+ cells in patients with mild cognitive impairment (MCI) but not AD (Saresella et al., 2011). These authors also reported that there was an MCI- and AD-related bias towards Th17 cell differentiation as indicated by $CD4^+$RORγt^+ cells. In a separate study, increases in $CD4^+$ and $CD8^+$ that were also positive for human leukocyte antigen (HLA)-DR, which suggests cell activation, were observed in blood and cerebrospinal fluid of AD patients compared to age-matched healthy controls (Lueg et al., 2015), and an increase in peripheral T-cell activation has also been described in 3xTg-AD mice, providing support for the findings described in humans (St-Amour et al., 2019). In contrast, others have failed to find changes in circulating $CD4^+$ or $CD8^+$ cells in AD, although assessment of naïve ($CD4^+$ $CD28^+$ $CD27^+$ $CD45RA^+$ $CD45RO^-$) and late-differentiated ($CD4^+$ $CD28^-$ $CD27^-$ $CD45RA^+$ $CD45RO^+$) subsets revealed an AD-related decrease and increase, respectively (Pellicano et al., 2012)

Tregs make up a small proportion (<2%) of peripheral lymphocytes, but they play a role in suppressing immune responses and modulating immune homeostasis and tissue inflammation (Fontenot et al., 2003; Hori et al., 2003). These $CD4^+$ cells are characterised by the expression of transcription factor forkhead box P3 (FoxP3) and IL-2 receptor α-chain (CD25), and they produce the anti-inflammatory cytokines transforming growth factor-β (TGF-β) and IL-10, which alter the function of effector T cells (Fontenot et al., 2003). A recent study reported that resting $CD4^+$ $CD25^{high}CD127^{low/-}$ $CD45RA^+/CD25^{dim}$ resting Tregs were decreased in blood samples prepared from AD patients, providing a potential explanation for attenuated modulation and increased inflammation in AD (Ciccocioppo et al., 2019). Separately, an increase in $CD4^+CD25^+$ cells (Pellicano et al., 2012) but no change in $FoxP3^+CD4^+$ Tregs (Le Page et al., 2017) was noted. In contrast, an earlier study reported an increase $FoxP3^+CD4^+$ Tregs in peripheral blood samples of AD patients, indicating a suppressive phenotype (Rosenkranz et al., 2007) that produced more IL-10 (Torres et al., 2013). Interestingly, $CD4^+CD25^+FoxP3^+$ Tregs that are negative for the surface expression of PD-1 exhibit the strongest suppressive activity and are elevated in patients with MCI; more PD-1^+ Tregs are observed in AD patients, suggesting a protective mechanism in early disease that is lost as pathology progresses (Saresella et al., 2010).

It is clear that the use of different markers in identifying cell populations prevents a consensus being reached, and at this time, there is significant controversy relating to AD-associated changes in cells that express different markers of T cells including Treg cells.

T cells are present in the post-mortem AD brain. Thirty years ago, T cells were first identified in the brain of AD patients (Rogers et al., 1988), and a number of reports have substantiated this claim (McGeer et al., 1989; Parachikova et al., 2007; Pirttila et al., 1992; Togo et al., 2002), with a recent report suggesting an important contributory role for T cells in disease pathogenesis (McManus et al., 2014). It is not known why T cells infiltrate the brain during disease, but it may be facilitated by the reported increase in BBB permeability, which has been reported in APP/PS1 mice (Minogue et al., 2014). The underlying cause of this remains unclear, but one possibility is an increase in circulating inflammatory cytokines (Brosseron et al., 2014). Significantly, serum from APP/PS1 mice markedly reduces the expression of tight junction proteins, including claudin-5, occludin and zonula occludens, indicating that circulating factors impact BBB (Barrett et al., 2015b), effects that are caused by Aβ peptides (Wan et al., 2015) and also by inflammatory cytokines (Camire et al., 2015).

Evidence of T-cell involvement in models of AD. An increase in $CD4^+$ and $CD8^+$ cells has been observed in the brain of APP/PS1 and 5XFAD mice (Browne et al., 2013; Ferretti et al., 2016; McManus et al., 2014; MacPherson et al., 2017), in particular female 5XFAD mice (Shukla et al., 2019), and in APP/PS1 mice, this is accompanied by gliosis and amyloid pathology. It was shown that FTY720, which decreased T-cell infiltration in APP/PS1 mice, also decreased gliosis and Aβ pathology, providing circumstantial evidence that T cells may increase Aβ accumulation (McManus et al., 2017). Consistently, adoptive transfer of Aβ-specific Th1 cells increased $CD4^+$IFNγ^+ cells in the brain and increased Aβ deposition (Browne et al., 2013). In contrast, it was reported that intracerebroventricular injection of Aβ-specific T cells to 5-month-old APP/PS1 mice reduced plaque load (Fisher et al., 2014), and a similar effect of Aβ-specific Th1 cells was observed in 9-month-old female 5XFAD mice (Mittal et al., 2019).

Treatment also altered the morphology of $MHCII^+Iba1^+$ cells, which co-localised with Aβ, suggesting phagocytosis by the cells (Mittal et al., 2019). The complete contradiction between these findings is difficult to explain. Clearly, the mouse model, the preparation and delivery of T cells and the age of the mice differ, but these do not provide a satisfactory explanation for such contrary findings. However, Mittal and colleagues indicated that the injected Th1 cells had reduced IFNγ messenger RNA (mRNA) expression, contrasting with the IFNγ-producing Th1 cells transferred by Browne and colleagues. This may also feed into the current debate surrounding whether or not IFNγ impacts the phagocytic function of microglia (Chakrabarty et al., 2010; McIntosh et al., 2019; Townsend et al., 2005).

Age- and genotype-related increases in $CD3^+$ cells were reported in the brain of another AD model, ArcAβ mice, and in

this case, $CD8^+$ cells predominated but the infiltrating cells did not proliferate and expressed low IFNγ (Ferretti et al., 2016). These authors also reported that the absence of B and T cells in RAG2-deficient APP/PS1 mice was associated with decreased Aβ and increased phagocytosis (Spani et al., 2015), and on the basis of these two studies, it was suggested that the lack of IFNγ was indicative of a regulatory role for infiltrating T cells.

A recent study suggested that infiltration of $CD3^+CD8^+$ T cells was markedly increased in APP/PS1 mice when microglia were ablated by PLX5622, suggesting that microglia influence T-cell infiltration. Deletion of microglia also reduced the expression of anti-inflammatory MRC1 and TGFβ, suggesting that microglia might help to maintain an anti-inflammatory milieu, although inflammatory markers, IL-6 and H2-Aa, were also reduced (Unger et al., 2018b).

Infiltration of T cells also occurs with age and with infection

Infiltration of peripheral immune cells including $CD11c^+$ dendritic cells and $CD3^+$ T cells has also been described with age, and T-cell infiltration is a common denominator in conditions that are characterised by neuroinflammatory changes. With respect to age, increased infiltration of both $CD8^+$ and $CD4^+$ T cells (MacPherson et al., 2017) or only $CD8^+$ T cells has been reported (Dulken et al., 2019). In the latter study, $CD8^+$ cells were IFNγ-secreting and adjacent to neural stem cells, and this is significant for two reasons. First, these cells decreased proliferation of neural stem cells, potentially explaining the age-related decrease in neurogenesis; this was mediated by IFNγ. Second, the authors suggest that this $CD8^+$ cell population may adopt their particular phenotype because of exposure to brain-specific antigens.

Increased T-cell infiltration occurs with injury and infection (McManus et al., 2014) and this is often linked with BBB permeability (Kelly et al., 2013; Minogue et al., 2014). Thus, infection with murine cytomegalovirus induced significant and rapid infiltration of macrophages, neutrophils and also IFNγ-producing $CD4^+$ and $CD8^+$ cells, which are probably responsible for the persistent microglial activation (Mutnal et al., 2011). Similarly, *Bordetella pertussis* infection in APP/PS1 mice triggered a persistent age-related increase in Th1 and Th17 cells, which was accompanied by marked microglial activation and amyloidosis (McManus et al., 2014). Infection in early life is known to exert a long-lasting susceptibility to subsequent insults, and a recent study revealed that viral infection in young mice induced a population of $CCL5^+$ memory T cells in the brain of mice that were in close apposition to activated microglia and led to persistent inflammation (Steinbach et al., 2019).

How do T cells access the brain?

The mechanism by which T cells enter the brain is still not clear, but neuroinflammatory changes, which trigger cell infiltration, increase the expression of cell adhesion molecules and this is likely to be an important contributory factor. In models of AD, there is evidence that cell infiltration may be regulated by chemotactic signals from the brain. For example, in APP/PS1 mice, cell infiltration was associated with an increase in the expression of CCL3 and CXCL10 (McManus et al., 2014), while in 5XFAD mice, a role for CCL2 has been described. Thus, it has been shown that XPro1595, an inhibitor of soluble tumour necrosis factor (TNF), decreased CCL2 in the brain of 5XFAD mice and also decreased $CD4^+$ Th1 cells. Consistent with a role for Th1 cells in microglial activation, XPro1595 reduced microglial activation as indicated by the number of $MHCII^+CD11b^+CD45^{low}$ cells, while it decreased amyloid pathology and inflammatory changes and improved long-term potentiation (LTP) (MacPherson et al., 2017), and similar neuroinflammatory changes have been described in APP/PS1 mice (McManus et al., 2014). In the ArcAβ mouse model of AD, the genotype-related increase in $CD8^+$ cells was associated with increased expression of intercellular adhesion molecules (ICAM) and vascular cell adhesion molecule (VCAM) (Ferretti et al., 2016). The BBB becomes more leaky with age (Minogue et al., 2014) and, as indicated above, a correlation between BBB permeability and infiltrating immune cells has been established. Thus, in aged and APP/PS1 mice, where BBB permeability was indicated by magnetic resonance imaging (MRI) analysis of gadolinium, macrophage infiltration (Blau et al., 2012; Denieffe et al., 2013) and T-cell infiltration have been described (Browne et al., 2013; McManus et al., 2014).

In short, BBB permeability, reactive astrocytes and the associated inflammatory changes, as well as altered expression of cell adhesion molecules and chemokines may all contribute to T-cell infiltration, but the mechanism by which these factors act alone or in concert to modulate cell infiltration remains to be determined.

Infiltrating T cells modulate microglial activation

T cells can interact with microglia and modulate their phagocytic and secretory phenotype. For example, it has been shown that incubation of Aβ-specific T cells with microglia treated with Aβ and CD40L increased the release of T-cell-derived IFNγ and IL-2 and microglia-derived TNFα and IL-6 and caused the microglia to shift from a phagocytic to an antigen presentation phenotype (Townsend et al., 2005). In broad agreement with this, incubation of Aβ-stimulated mixed glia with Aβ-specific Th1 or Th17 cells increased the release of IL-1β, IL-6 and TNFα, while fluorescence-activated cell sorting (FACS) analysis revealed that microglial expression of MHCII and CD86 was increased (McQuillan et al., 2010). While both Th1 and Th17 cells induced microglial activation, incubation of microglia with Th2 cells exerted no effect on cytokine production (McQuillan et al., 2010). Myelin oligodendrocyte glycoprotein (MOG)-specific Th1 and Th17 exerted similar effects, but synergised to increase cytokine release (Murphy et al., 2010). This is relevant because both $CD4^+IFN\gamma^+$ and $CD4^+IL\text{-}17^+$ T cells are present in the brain of APP/PS1 mice where they may combine to increase microglial activation and drive inflammation (Browne et al., 2013).

Although activated $CD4^+$ T cells can enhance the antigen-presenting cell (APC) phenotype of microglia, it has been proposed that modest activation of T cells in the brain actually reduces their APC capacity. Ferretti and colleagues reported that, in APP/PS1 and other transgenic mouse models of amyloidosis, infiltrating T cells are increased but do not co-localise with Aβ plaques and display low proliferation and IFNγ production

(Ferretti et al., 2016). This contrasts with other reports, which demonstrated that T cells co-located to Aβ plaques in APP/PS1 mice (Fisher et al., 2010; Unger et al., 2018a).

The complex and often contradictory interaction between peripheral immune cells and microglia, and the subsequent impact on Aβ pathology were examined in Rag-5XFAD mice that lacked T, B and NK cells (Marsh et al., 2016). In these mice, microglial activation and inflammatory cytokine expression were increased, but the phagocytic capacity of the microglia was impaired and therefore soluble and insoluble Aβ, as well as Aβ-containing plaques, were increased. The authors suggested that these findings point to a protective role for the adaptive immune system in AD, and this was attributed to IgG–microglial association since the function was restored by injection of preimmune IgG into the brain. At least on a superficial level, these observations are at variance with those described above, but B and NK cells, as well as T cells, are absent in Rag-5XFAD mice, and their contribution to microglial activation remains to be clarified. Furthermore, the absence of T cells includes all T-cell subsets, and at present, the increase in Aβ pathology and enhanced microglial activation are identified as effects of Th1 and Th17 cells.

Regulatory T cells in AD

Tregs can infiltrate the brain and, because of the secreted IL-10, suppress effector T-cell activation and the microglial response to lipopolysaccharide stimulation in rats (Xie et al., 2015). These infiltrating Tregs displayed an activated/memory phenotype, supporting reports that T cells are activated peripherally and reactivated in the central nervous system (CNS) (McManus et al., 2014; Xie et al., 2015).

The effect of Tregs in mouse models of AD remains to be determined. Dansokho and colleagues showed that transient depletion of Tregs by administering an anti-CD25 antibody to APP/PS1 mice leads to accelerated cognitive decline, with onset occurring 1 month earlier than in APP/PS1 mice that did not receive antibody treatment (Dansokho et al., 2016). These authors also showed that the number of microglia co-localising with Aβ deposits was reduced. Consistently, amplifying peripheral Tregs by IL-2 administration improved cognitive function in APP/PS1 mice. This also enhanced recruitment of activated microglia to Aβ deposits, although plaque burden was not affected. The authors concluded that Tregs induce microglia to adopt a protective microglial phenotype that does not alter phagocytosis. In the 3xTg-AD transgenic mouse model, adoptive transfer of Tregs ameliorated cognitive decline, reduced Aβ burden and reduced the expression of proinflammatory cytokines and increased the expression of IL-10 in splenocytes (Baek et al., 2016). However, it has been reported that Tregs can modulate Aβ-induced $CD4^+$ T-cell responses in APP/PS1 mice, and this may also impact the observed neuroinflammation (Toly-Ndour et al., 2011).

In contrast with these findings, a study by Baruch and colleagues, in which Tregs were transiently depleted systemically in 5XFAD mice, indicated that cognitive function improved and Aβ plaque burden, inflammatory cytokine expression and gliosis in the hippocampus were reduced (Baruch et al., 2015). Interestingly, although these results appear to be at odds with the Dansokho study, transient depletion of Tregs peripherally enhanced cerebral recruitment of Tregs and regulatory monocyte–derived macrophages, with IL-10- and FoxP3-expressing T cells co-localising with microglia at Aβ plaques (Baruch et al., 2015). On the face of it, the results of the Dansokho and Baruch studies appear to be contradictory, but the different models and, more importantly, the disease stage at which Tregs were depleted, 4–5 months of age in 5XFAD mice compared with 5–6 weeks in APP/PS1 mice, may be significant factors.

A recent paper reported that depletion of Tregs enhanced T-cell infiltration and reactive astrogliosis in a model of traumatic brain injury, suggesting that Tregs play a role in modulating the damage induced by tissue injury (Kramer et al., 2019). Consistently, it was suggested that the infiltration of Tregs into the brain following ischaemic injury reduced astrogliosis and did so by increasing the production of amphiregulin (Ito et al., 2019). This was determined by decreasing Treg infiltration using FTY720 or by depleting Tregs using depletion of regulatory T-cell (DEREG) mice in which diphtheria toxin receptor is expressed exclusively on Tregs and which is eliminated when the animals are treated with diphtheria toxin; in both models, recovery was delayed and astrogliosis was increased. Both these studies reveal that injury-associated astrocytosis can be modulated by Tregs and the detrimental effects that follow can be reduced. Separately a protective effect of Tregs has been described in a model of Parkinson's disease, and in this case, adoptive transfer of $CD4^+CD25^+$ Tregs attenuated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced microglial activation and reduced neuronal death (Reynolds et al., 2007). This neuroprotective effect of Tregs, mediated by microglia, was confirmed in a co-culture experiment. A beneficial effect of Tregs has also been described in a model of optic nerve injury since depleting Tregs using DEREG mice exacerbated the deleterious effect of the injury on neuronal survival (Walsh et al., 2014). These collective findings indicate that there is no consensus regarding the effects of Tregs and some indication that the effects may differ in different models, and significant work is necessary to provide clarity.

The T-cell response to Aβ immunisation

To date, clinical trials aimed at resolving Aβ pathology have generated underwhelming results despite the initial promise. Early preclinical studies in mouse models demonstrated that immunisation with the $A\beta_{42}$ peptide cleared Aβ burden and improved cognitive function without causing immunopathology (Janus et al., 2000; Morgan et al., 2000; Schenk et al., 1999). Based on these studies, the first human trial of an active vaccine against a self-antigen, containing full-length $A\beta_{42}$ peptide, along with the QS-21 adjuvant was undertaken, but the Phase 2 trial was terminated because 18 of the 298 participants developed meningoencephalitis (Orgogozo et al., 2003). In long-term follow-up studies, post-mortem examinations provided evidence of Aβ plaque clearance, whereas tau and cerebral amyloid angiopathy (CAA) pathologies did not decrease and time to onset of severe dementia was not increased (Ferrer et al., 2004; Holmes et al., 2008; Nicoll et al., 2003, 2006). The meningoencephalitis has been attributed to $CD4^+$ T cells, specifically to a Th1 cell response, likely caused by the full-length $A\beta_{42}$ and a strong Th1 adjuvant (Marciani, 2014). This is consistent with the findings in the APP/PS1 mouse model, in which adoptive transfer of Th1 cells induces significant inflammation (Browne et al., 2013), although it also causes increased pathology.

Several recent clinical trials have attempted to circumvent a T-cell response by using passive immunisation with Aβ-specific

monoclonal antibodies. Two of these trials that assessed solanezumab and bapineuzumab did not meet primary end points in improving clinical outcomes (Doody et al., 2014; Salloway et al., 2014; Vandenberghe et al., 2016). Meanwhile, second-generation active Aβ vaccines are currently in trials, such as CAD106 and UBI-311, solely B-cell vaccines and combined B cell–T cell (Th2 epitope) vaccines, respectively (Vandenberghe et al., 2017; Wang et al., 2007), and while evidence indicates a good safety profile, their efficacy remains to be determined.

It is clear that the Aβ-specific T cells can contribute to neuroinflammation and neurodegeneration if proinflammatory subpopulations are too strongly induced. Therefore, fine-tuning of the T-cell response is key in the search for safer and more effective treatments for AD. At present, our knowledge of the impact of different infiltrating T-cell populations is deficient, and at the very least, it is necessary to determine how they impact microglia, and indeed astrocytes, with a view to understanding how neuroinflammation might be modulated. Thereafter questions relating to how Aβ vaccination affects T-cell function and T cell–glial interaction will need to be asked, and answers to these will help to refine Aβ vaccine–based therapy design so that it is safe and effective at clearing Aβ.

Conclusion

There can be little debate about the involvement of the innate and adaptive immune systems in the pathogenesis of AD, but despite the vast literature that has accumulated over the past years, there is little progress in identifying the key events in triggering pathology, nor charting the chronology of changes that occur early in the disease. These are the fundamental issues that impede progress in the search for treatments. However, with the benefit of the findings from the genome-wide association study (GWAS) and the clear knowledge that the innate immune system must be now a specific target, some momentum might be anticipated. The growing realisation that infiltrating immune cells, particularly T cells, impact pathology will propel efforts to examine the role of the adaptive more extensively and potentially open a relatively unexplored area to scrutiny that might ultimately proffer additional hope of a treatment breakthrough.

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References

Baek H, Ye M, Kang GH, et al. (2016) Neuroprotective effects of CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells in a 3xTg-AD Alzheimer's disease model. *Oncotarget* 7(43): 69347–69357.

Barrett JP, Costello DA, O'Sullivan J, et al. (2015a) Bone marrow-derived macrophages from aged rats are more responsive to inflammatory stimuli. *Journal of Neuroinflammation* 12(1): 67.

Barrett JP, Minogue AM, Jones RS, et al. (2015b) Bone marrow-derived macrophages from AbetaPP/PS1 mice are sensitized to the effects of inflammatory stimuli. *Journal of Alzheimer's Disease* 44(3): 949–962.

Baruch K, Rosenzweig N, Kertser A, et al. (2015) Breaking immune tolerance by targeting Foxp3$^+$ regulatory T cells mitigates Alzheimer's disease pathology. *Nature Communications* 6: 7967.

Becher B, Spath S and Goverman J (2017) Cytokine networks in neuroinflammation. *Nature Reviews Immunology* 17(1): 49–59.

Blau CW, Cowley TR, O'Sullivan J, et al. (2012) The age-related deficit in LTP is associated with changes in perfusion and blood-brain barrier permeability. *Neurobiology of Aging* 33(5): 1005.e23–35.

Boza-Serrano A, Yang Y, Paulus A, et al. (2018) Innate immune alterations are elicited in microglial cells before plaque deposition in the Alzheimer's disease mouse model 5xFAD. *Scientific Reports* 8(1): 1550.

Brosseron F, Krauthausen M, Kummer M, et al. (2014) Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: A comparative overview. *Molecular Neurobiology* 50(2): 534–544.

Browne TC, McQuillan K, McManus RM, et al. (2013) IFN-gamma production by amyloid beta-specific Th1 cells promotes microglial activation and increases plaque burden in a mouse model of Alzheimer's disease. *Journal of Immunology* 190(5): 2241–2251.

Bulloch K, Miller MM, Gal-Toth J, et al. (2008) CD11c/EYFP transgene illuminates a discrete network of dendritic cells within the embryonic, neonatal, adult, and injured mouse brain. *Journal of Comparative Neurology* 508(5): 687–710.

Camire RB, Beaulac HJ and Willis CL (2015) Transitory loss of glia and the subsequent modulation in inflammatory cytokines/chemokines regulate paracellular claudin-5 expression in endothelial cells. *Journal of Neuroimmunology* 284: 57–66.

Chakrabarty P, Ceballos-Diaz C, Beccard A, et al. (2010) IFN-gamma promotes complement expression and attenuates amyloid plaque deposition in amyloid beta precursor protein transgenic mice. *Journal of Immunology* 184(9): 5333–5343.

Ciccocioppo F, Lanuti P, Pierdomenico L, et al. (2019) The characterization of regulatory T-cell profiles in Alzheimer's disease and multiple sclerosis. *Scientific Reports* 9(1): 8788.

Cowley TR, O'Sullivan J, Blau C, et al. (2012) Rosiglitazone attenuates the age-related changes in astrocytosis and the deficit in LTP. *Neurobiology of Aging* 33(1): 162–175.

Dansokho C, Ait Ahmed D, Aid S, et al. (2016) Regulatory T cells delay disease progression in Alzheimer-like pathology. *Brain* 139(4): 1237–1251.

Denieffe S, Kelly RJ, McDonald C, et al. (2013) Classical activation of microglia in CD200-deficient mice is a consequence of blood brain barrier permeability and infiltration of peripheral cells. *Brain, Behavior, and Immunity* 34: 86–97.

Doody RS, Thomas RG, Farlow M, et al. (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *New England Journal of Medicine* 370(4): 311–321.

Dulken BW, Buckley MT, Navarro Negredo P, et al. (2019) Single-cell analysis reveals T cell infiltration in old neurogenic niches. *Nature* 571(Suppl. 2): 205–210.

El Hajj H, Savage JC, Bisht K, et al. (2019) Ultrastructural evidence of microglial heterogeneity in Alzheimer's disease amyloid pathology. *Journal of Neuroinflammation* 16(1): 87.

El Khoury J, Toft M, Hickman SE, et al. (2007) Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer's disease. *Nature Medicine* 13(4): 432–438.

Ferrer I, Boada Rovira M, Sanchez Guerra ML, et al. (2004) Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. *Brain Pathology* 14(1): 11–20.

Ferretti MT, Merlini M, Spani C, et al. (2016) T-cell brain infiltration and immature antigen-presenting cells in transgenic models of Alzheimer's disease-like cerebral amyloidosis. *Brain, Behavior, and Immunity* 54: 211–225.

Fisher Y, Nemirovsky A, Baron R, et al. (2010) T cells specifically targeted to amyloid plaques enhance plaque clearance in a mouse model of Alzheimer's disease. *PLoS ONE* 5(5): e10830.

Fisher Y, Strominger I, Biton S, et al. (2014) Th1 polarization of T cells injected into the cerebrospinal fluid induces brain immunosurveillance. *Journal of Immunology* 192(1): 92–102.

Fontenot JD, Gavin MA and Rudensky AY (2003) Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. *Nature Immunology* 4(4): 330–336.

Frautschy SA, Yang F, Irrizarry M, et al. (1998) Microglial response to amyloid plaques in APPsw transgenic mice. *American Journal of Pathology* 152(1): 307–317.

Girard S, Brough D, Lopez-Castejon G, et al. (2013) Microglia and macrophages differentially modulate cell death after brain injury caused by oxygen-glucose deprivation in organotypic brain slices. *GLIA* 61(5): 813–824.

Golubovskaya V and Wu L (2016) Different subsets of T cells, memory, effector functions, and CAR-T immunotherapy. *Cancers* 8(3): 36.

Grathwohl SA, Kalin RE, Bolmont T, et al. (2009) Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *Nature Neuroscience* 12(11): 1361–1363.

Gyoneva S, Swanger SA, Zhang J, et al. (2016) Altered motility of plaque-associated microglia in a model of Alzheimer's disease. *Neuroscience* 330: 410–420.

Hansen DV, Hanson JE and Sheng M (2018) Microglia in Alzheimer's disease. *Journal of Cell Biology* 217(2): 459–472.

Hawkes CA and McLaurin J (2009) Selective targeting of perivascular macrophages for clearance of beta-amyloid in cerebral amyloid angiopathy. *Proceedings of the National Academy of Sciences of the United States of America* 106(4): 1261–1266.

Hickey WF (2001) Basic principles of immunological surveillance of the normal central nervous system. *GLIA* 36(2): 118–124.

Hickman SE, Allison EK and El Khoury J (2008) Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *Journal of Neuroscience* 28(33): 8354–8360.

Holmes C, Boche D, Wilkinson D, et al. (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled Phase 1 trial. *Lancet* 372(9634): 216–223.

Hori S, Nomura T and Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. *Science* 299(5609): 1057–1061.

Ito M, Komai K, Mise-Omata S, et al. (2019) Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. *Nature* 565(7738): 246–250.

Jansen IE, Savage JE, Watanabe K, et al. (2019) Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature Genetics* 51(3): 404–413.

Janus C, Pearson J, McLaurin J, et al. (2000) A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature* 408(6815): 979–982.

Kelly RJ, Minogue AM, Lyons A, et al. (2013) Glial activation in A beta PP/PS1 mice is associated with infiltration of IFN gamma-producing cells. *Journal of Alzheimer's Disease* 37(1): 63–75.

Korin B, Ben-Shaanan TL, Schiller M, et al. (2017) High-dimensional, single-cell characterization of the brain's immune compartment. *Nature Neuroscience* 20: 1300–1309.

Kramer TJ, Hack N, Bruhl TJ, et al. (2019) Depletion of regulatory T cells increases T cell brain infiltration, reactive astrogliosis, and interferon-gamma gene expression in acute experimental traumatic brain injury. *Journal of Neuroinflammation* 16(1): 163.

Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics* 45: 1452–1458.

Le Page A, Garneau H, Dupuis G, et al. (2017) Differential phenotypes of myeloid-derived suppressor and T regulatory cells and cytokine levels in amnestic mild cognitive impairment subjects compared to mild Alzheimer diseased patients. *Frontiers in Immunology* 8: 783.

Lueg G, Gross CC, Lohmann H, et al. (2015) Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. *Neurobiology of Aging* 36(1): 81–89.

McGeer PL, Akiyama H, Itagaki S, et al. (1989) Immune system response in Alzheimer's disease. *Canadian Journal of Neurological Sciences* 16(Suppl. 1): 516–527.

McIntosh A, Mela V, Harty C, et al. (2019) Iron accumulation in microglia triggers a cascade of events that leads to altered metabolism and compromised function in APP/PS1 mice. *Brain Pathology* 29(5): 606–621.

McManus RM, Finucane OM, Wilk MM, et al. (2017) FTY720 attenuates infection-induced enhancement of Aβ accumulation in APP/PS1 mice by modulating astrocytic activation. *Journal of Neuroimmune Pharmacology* 12(4): 670–681.

McManus RM, Higgins SC, Mills KH, et al. (2014) Respiratory infection promotes T cell infiltration and amyloid-beta deposition in APP/PS1 mice. *Neurobiology of Aging* 35(1): 109–121.

MacPherson KP, Sompol P, Kannarkat GT, et al. (2017) Peripheral administration of the soluble TNF inhibitor XPro1595 modifies brain immune cell profiles, decreases beta-amyloid plaque load, and rescues impaired long-term potentiation in 5xFAD mice. *Neurobiology of Disease* 102: 81–95.

McQuillan K, Lynch MA and Mills KH (2010) Activation of mixed glia by Abeta-specific Th1 and Th17 cells and its regulation by Th2 cells. *Brain, Behavior, and Immunity* 24(4): 598–607.

Marciani DJ (2014) New Th2 adjuvants for preventive and active immunotherapy of neurodegenerative proteinopathies. *Drug Discovery Today* 19(7): 912–920.

Marsh SE, Abud EM, Lakatos A, et al. (2016) The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. *Proceedings of the National Academy of Sciences of the United States of America* 113(9): E1316–E1325.

Michaud JP, Bellavance MA, Prefontaine P, et al. (2013) Real-time in vivo imaging reveals the ability of monocytes to clear vascular amyloid beta. *Cell Reports* 5(3): 646–653.

Minogue AM, Jones RS, Kelly RJ, et al. (2014) Age-associated dysregulation of microglial activation is coupled with enhanced blood-brain barrier permeability and pathology in APP/PS1 mice. *Neurobiology of Aging* 35(6): 1442–1452.

Mittal K, Eremenko E, Berner O, et al. (2019) CD4 T cells induce a subset of MHCII-expressing microglia that attenuates Alzheimer pathology. *Iscience* 16: 298–311.

Monsonego A, Zota V, Karni A, et al. (2003) Increased T cell reactivity to amyloid beta protein in older humans and patients with Alzheimer disease. *Journal of Clinical Investigation* 112(3): 415–422.

Morgan D, Diamond DM, Gottschall PE, et al. (2000) A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature* 408(6815): 982–985.

Mrdjen D, Pavlovic A, Hartmann FJ, et al. (2018) High-dimensional single-cell mapping of central nervous system immune cells reveals distinct myeloid subsets in health, aging, and disease. *Immunity* 48(2): 380–395.e6.

Murphy AC, Lalor SJ, Lynch MA, et al. (2010) Infiltration of Th1 and Th17 cells and activation of microglia in the CNS during the course of experimental autoimmune encephalomyelitis. *Brain, Behavior, and Immunity* 24(4): 641–651.

Mutnal MB, Hu S, Little MR, et al. (2011) Memory T cells persisting in the brain following MCMV infection induce long-term microglial

activation via interferon-gamma. *Journal of NeuroVirology* 17(5): 424–437.
Nicoll JA, Barton E, Boche D, et al. (2006) Abeta species removal after abeta42 immunization. *Journal of Neuropathology & Experimental Neurology* 65(11): 1040–1048.
Nicoll JA, Wilkinson D, Holmes C, et al. (2003) Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: A case report. *Nature Medicine* 9(4): 448–452.
Orgogozo JM, Gilman S, Dartigues JF, et al. (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* 61(1): 46–54.
Parachikova A, Agadjanyan MG, Cribbs DH, et al. (2007) Inflammatory changes parallel the early stages of Alzheimer disease. *Neurobiology of Aging* 28(12): 1821–1833.
Pellicano M, Larbi A, Goldeck D, et al. (2012) Immune profiling of Alzheimer patients. *Journal of Neuroimmunology* 242(1–2): 52–59.
Perlmutter LS, Scott SA, Barron E, et al. (1992) MHC class II-positive microglia in human brain: Association with Alzheimer lesions. *Journal of Neuroscience Research* 33(4): 549–558.
Pirttila T, Mattinen S and Frey H (1992) The decrease of CD8-positive lymphocytes in Alzheimer's disease. *Journal of the Neurological Sciences* 107(2): 160–165.
Prokop S, Miller KR, Drost N, et al. (2015) Impact of peripheral myeloid cells on amyloid-beta pathology in Alzheimer's disease-like mice. *Journal of Experimental Medicine* 212(11): 1811–1818.
Reynolds AD, Banerjee R, Liu J, et al. (2007) Neuroprotective activities of CD4+CD25+ regulatory T cells in an animal model of Parkinson's disease. *Journal of Leukocyte Biology* 82(5): 1083–1094.
Rogers J, Luber-Narod J, Styren SD, et al. (1988) Expression of immune system-associated antigens by cells of the human central nervous system: Relationship to the pathology of Alzheimer's disease. *Neurobiology of Aging* 9(4): 339–349.
Rosenkranz D, Weyer S, Tolosa E, et al. (2007) Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration. *Journal of Neuroimmunology* 188(1–2): 117–127.
Salloway S, Sperling R, Fox NC, et al. (2014) Two Phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *New England Journal of Medicine* 370(4): 322–333.
Saresella M, Calabrese E, Marventano I, et al. (2010) PD1 negative and PD1 positive CD4+ T regulatory cells in mild cognitive impairment and Alzheimer's disease. *Journal of Alzheimer's Disease* 21(3): 927–938.
Saresella M, Calabrese E, Marventano I, et al. (2011) Increased activity of Th-17 and Th-9 lymphocytes and a skewing of the post-thymic differentiation pathway are seen in Alzheimer's disease. *Brain, Behavior, and Immunity* 25(3): 539–547.
Schenk D, Barbour R, Dunn W, et al. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 400(6740): 173–177.
Schwartz M and Shechter R (2010) Systemic inflammatory cells fight off neurodegenerative disease. *Nature Reviews Neurology* 6(7): 405–410.
Shechter R, London A, Varol C, et al. (2009) Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Medicine* 6(7): e1000113.
Shukla AK, McIntyre LL, Marsh SE, et al. (2019) CD11a expression distinguishes infiltrating myeloid cells from plaque-associated microglia in Alzheimer's disease. *GLIA* 67(5): 844–856.
Simard AR and Rivest S (2004) Bone marrow stem cells have the ability to populate the entire central nervous system into fully differentiated parenchymal microglia. *FASEB Journal* 18(9): 998–1000.
Simard AR, Soulet D, Gowing G, et al. (2006) Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* 49(4): 489–502.
Smolders J, Heutinck KM, Fransen NL, et al. (2018) Tissue-resident memory T cells populate the human brain. *Nature Communications* 9(1): 4593.
Spani C, Suter T, Derungs R, et al. (2015) Reduced beta-amyloid pathology in an APP transgenic mouse model of Alzheimer's disease lacking functional B and T cells. *Acta Neuropathologica Communications* 3: 71.
Stalder AK, Ermini F, Bondolfi L, et al. (2005) Invasion of hematopoietic cells into the brain of amyloid precursor protein transgenic mice. *Journal of Neuroscience* 25(48): 11125–11132.
St-Amour I, Bosoi CR, Pare I, et al. (2019) Peripheral adaptive immunity of the triple transgenic mouse model of Alzheimer's disease. *Journal of Neuroinflammation* 16(1): 3.
Steinbach K, Vincenti I, Egervari K, et al. (2019) Brain-resident memory T cells generated early in life predispose to autoimmune disease in mice. *Science Translational Medicine* 11(498): eaav5519.
Togo T, Akiyama H, Iseki E, et al. (2002) Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. *Journal of Neuroimmunology* 124(1–2): 83–92.
Toly-Ndour C, Lui G, Nunes MM, et al. (2011) MHC-independent genetic factors control the magnitude of CD4+ T cell responses to amyloid-beta peptide in mice through regulatory T cell-mediated inhibition. *Journal of Immunology* 187(9): 4492–4500.
Torres KC, Araujo Pereira P, Lima GS, et al. (2013) Increased frequency of T cells expressing IL-10 in Alzheimer disease but not in late-onset depression patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 47: 40–45.
Townsend KP, Town T, Mori T, et al. (2005) CD40 signaling regulates innate and adaptive activation of microglia in response to amyloid beta-peptide. *European Journal of Immunology* 35(3): 901–910.
Unger MS, Marschallinger J, Kaindl J, et al. (2018a) Doublecortin expression in CD8+ T-cells and microglia at sites of amyloid-beta plaques: A potential role in shaping plaque pathology? *Alzheimer's & Dementia* 14(8): 1022–1037.
Unger MS, Schernthaner P, Marschallinger J, et al. (2018b) Microglia prevent peripheral immune cell invasion and promote an anti-inflammatory environment in the brain of APP-PS1 transgenic mice. *Journal of Neuroinflammation* 15(1): 274.
Vandenberghe R, Rinne JO, Boada M, et al. (2016) Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, Phase 3 trials. *Alzheimer's Research & Therapy* 8(1): 18.
Vandenberghe R, Riviere ME, Caputo A, et al. (2017) Active Abeta immunotherapy CAD106 in Alzheimer's disease: A Phase 2b study. *Alzheimer's & Dementia* 3(1): 10–22.
Varvel NH, Grathwohl SA, Degenhardt K, et al. (2015) Replacement of brain-resident myeloid cells does not alter cerebral amyloid-beta deposition in mouse models of Alzheimer's disease. *Journal of Experimental Medicine* 212(11): 1803–1809.
Walsh JT, Zheng J, Smirnov I, et al. (2014) Regulatory T cells in central nervous system injury: A double-edged sword. *Journal of Immunology* 193(10): 5013–5022.
Wan W, Cao L, Liu L, et al. (2015) Abeta(1–42) oligomer-induced leakage in an in vitro blood-brain barrier model is associated with up-regulation of RAGE and metalloproteinases, and down-regulation of tight junction scaffold proteins. *Journal of Neurochemistry* 134(2): 382–393.
Wang CY, Finstad CL, Walfield AM, et al. (2007) Site-specific UBITh amyloid-beta vaccine for immunotherapy of Alzheimer's disease. *Vaccine* 25(16): 3041–3052.
Wolfe H, Minogue AM, Rooney S, et al. (2018) Infiltrating macrophages contribute to age-related neuroinflammation in C57/BL6 mice. *Mechanisms of Ageing and Development* 173: 84–91.
Xie L, Choudhury GR, Winters A, et al. (2015) Cerebral regulatory T cells restrain microglia/macrophage-mediated inflammatory responses via IL-10. *European Journal of Immunology* 45(1): 180–191.
Yamamoto M, Horiba M, Buescher JL, et al. (2005) Overexpression of monocyte chemotactic protein-1/CCL2 in beta-amyloid precursor protein transgenic mice show accelerated diffuse beta-amyloid deposition. *American Journal of Pathology* 166(5): 1475–1485.
Zhu J, Yamane H and Paul WE (2010) Differentiation of effector CD4 T cell populations (*).*Annual Review of Immunology* 28: 445–489.