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 (Perlmuter 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...
the meninges and choroid plexus were removed (Korin et al., 2017). Using a combination of mass cytometry, 22-colour fluo-
rescence 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 neuro-
genesis 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 tran-
scription 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 exam-
ple, 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 con-
istent with the evidence that infiltration of monocytes relies on
CCL2; thus, it was shown that the marked increase in infiltrating
CD11b+CD45hi cells that is identified in Tg2576 (APP)
mouse was markedly increased in APP-CCR2−/− mouse (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 amy-
loid 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 sig-
nificant (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 effec-
tively, than microglia (Simard et al., 2006; Simard and Rivest,
2004; Stalder et al., 2005); this and their role in tissue repair sug-
gest 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 bene-
ficial 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 trans-
fer 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
Ly6CloCX3CR1hiCCR2- monocytes can engulf Aβ in perivas-
cular spaces (Michaud et al., 2013). Similarly, ablation of microg-
lia 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 infiltra-
tion 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 inflam-
matory environment, adopt an inflammatory phenotype and con-
tribute to the ongoing age-related neuroinflammation.

Infiltration of macrophages into the brain of APP/PS1 mice has also been closely linked with neuroinflammation and microg-
rial 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 CX3CR1hiCCR2-Ly6Clo
monocytes have been reported in the brain of APP/PS1 mice, and
it seems that these cells contribute to the maintenance of homeo-
estasis 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 (Thf 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 (Monson et al., 2003). An AD-related increase in CD4+ 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., 2013). 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; Horii 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+ CD25highCD127low/− CD45RA+/CD25dim 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; Pirritalla 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., 2015), 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 MHCIId1+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).

**Infiltiration of T cells also occurs with age and with infection**

Infiltiration 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-secretting 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 increased 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 chemoattractant 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+ 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 increased 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.

**Infiltirating 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+IFNγ+ and CD4+IL-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.
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.

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 Aβ1–42 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 Aβ1–42 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 (Ferré 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 Aβ1–42 and a strong Th1 adjuvant (Marchi et al., 2014). This is consistent with the findings in the APP/PS1 mouse model, in which adoptive transfer of Th1 cells induces significant inflammation (Brown 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 neuro-inflammation and neurodegeneration if proinflammatory sub-populations 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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