Received Date : 04-Jun-2013

Revised Date : 17-Jul-2013

Accepted Date : 18-Jul-2013

Article type : Review

The impact of neuroimmune changes on development of amyloid pathology; relevance to Alzheimer's disease

Marina A. Lynch
Trinity College Institute for Neuroscience,
Trinity College,
Dublin 2,
Ireland.
Email: lynchma@tcd.ie
Tel: 353-1-896-8531
Fax: 353-1-896-3545.

Abstract

Neuroinflammatory changes are a characteristic of several, if not all, neurodegenerative diseases including Alzheimer's disease (AD) and are typified by increased microglial activation. Microglia express several receptors making them highly reactive and plastic cells, and, at least in vitro, they adopt different phenotypes in a manner analogous to their peripheral counterparts, macrophages. Microglia also express numerous cell surface proteins enabling them to interact with cells and the evidence indicates that maintenance of microglia in a quiescent state relies, at least to some extent, on an interaction with neurons by means of specific ligand-receptor pairs for example CD200-CD200R. It is clear that microglia also interact with T cells and recent evidence indicates that co-incubation of microglia with Th1 cells markedly increase their activation. Under normal conditions, small numbers of activated T cells gain entry to the brain and are involved in immune surveillance but infiltration of significant numbers of T cells occurs in disease and following injury. The consequences of T cell infiltration appear to depend on the conditions, with descriptions of both neurodestructive and neuroprotective effects in animal models of different diseases. This review will discuss the modulatory effect of T cells on microglia and impact of infiltration of T cells into the brain with a focus on AD and will propose that infiltration of interferon (IFN)- γ -producing cells may be an important factor in triggering inflammation that is pathogenic and destructive.

Introduction

Although the pathological hallmarks of Alzheimer's Disease (AD) were described over a decade ago, the pathogenesis of the late-onset form of the disease remains poorly understood. One theory, the amyloid hypothesis, suggests that the accumulation of β -amyloid ($A\beta$), because of a decrease in $A\beta$ clearance, perhaps accompanied by increased

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1111/imm.12156

This article is protected by copyright. All rights reserved.

Accepted Article

processing of amyloid precursor protein (APP), triggers a cascade of damaging reactions. Another theory proposes that tau hyperphosphorylation is key to the demise of neurons. However the trigger leading to the initial changes has not been identified, and the likelihood is that there is not a single factor but a collection of coincident events which superimpose upon already-existing age-related changes. For some time now it has been recognized that inflammatory changes may be a factor in accelerating disease onset. Indeed many of the risk factors for the disease, for example atherosclerosis, neurotrauma, Type 1 diabetes and infection, are associated with inflammatory changes.

Neuroinflammation and AD

A great deal of evidence indicates that inflammatory changes are a feature of AD and it is agreed that a key change is an increase in microglial activation which was originally described by Alzheimer over 100 years ago. Several reports have confirmed this observation and have shown that activated cells cluster around A β -containing plaques^{1, 2}. An increase in expression of inflammatory cytokines, interleukin (IL)-1 β , IL-6 and tumour necrosis factor (TNF) α has been observed in the AD brain and IL-1-positive microglia co-localize with A β -containing plaques, as do activated astrocytes. These changes are associated with other indicators of inflammatory changes including increased expression of several chemokines and elements of the complement activation pathway³⁻⁵. However it is still debated whether these changes are a consequence of the disease or contribute to its pathogenesis; this is a difficult issue to dissect since the evidence from model systems indicates the existence of a cycle in which inflammatory changes drive A β accumulation while A β stimulates glia to produce inflammatory mediators. A possible resolution to this question was presented when early epidemiological evidence indicated that the incidence or severity of AD was reduced in individuals who were treated with non-steroidal anti-inflammatory drugs (NSAID)⁶⁻⁸. These observations suggested that anti-inflammatory agents might be a useful therapeutic option for the treatment of the disease, but several clinical trials have failed to identify a beneficial effect of anti-inflammatory agents⁹⁻¹¹. It has been argued that, since inflammatory changes occur early in the disease, only very early intervention with anti-inflammatory treatments is likely to be valuable¹² and indeed in a study where participants were ≥ 65 years on enrollment (older than participants in other studies), the use of NSAIDs was detrimental with adjusted hazard ratio of risk for AD of 1.57¹³. Interestingly, postmortem examination of brain tissue from non-demented elderly individuals indicated a correlative decrease in microglial activation and senile plaque number in those treated with NSAIDs but not steroids¹⁴, although other data have not shown this¹⁵.

Microglia and macrophages share certain properties

Microglia are the primary immune cells in the brain and they are often referred to as macrophages of the brain, although we now know that microglia are an ontogenically distinct population of cells derived from primitive haematopoietic cells in the yolk sac¹⁶. Therefore microglia, being confined to the brain, are protected by the blood brain barrier (BBB), from exposure to circulating high molecular weight molecules as well as the vast array of stimuli encountered by macrophages. Morphologically, microglia and macrophages are somewhat distinct. Under resting conditions microglia, unlike macrophages, are multi-processed cells and the processes are constantly motile enabling the cells to sample their microenvironment and react, when necessary, to noxious stimuli. Activation of microglia results in retraction of processes and the cells adopt an amoeboid

morphology. However the cells share many functions and both are phagocytic and function as antigen presenting cells (APC).

Microglia are highly reactive cells and, like macrophages, express a multitude of cell surface receptors¹⁷ including pathogen recognition receptors (PPRs), complement receptor, Fc receptors, chemokine and cytokine receptors, and receptors for numerous neurotransmitters^{17, 18}. While macrophages are regularly exposed to pathogen-associated molecular patterns (PAMPs), whereas brain infections are relatively rare and therefore activation of PPRs on microglia is more likely to be induced by damage-associated molecular patterns (DAMPs); these endogenously-generated molecules include ATP and high mobility group box-1 (HMGB-1), that are released from damaged/dying cells¹⁹. However an association between AD and certain pathogens has been identified²⁰ and infections can accelerate cognitive decline in AD patients^{21, 22}. Evidence has indicated that a significant proportion of AD brains were positive for *Chlamydia pneumoniae*²³ while intranasal inoculation of mice with *C. pneumoniae* induced deposition of fibrillar A β associated with reactive glia²⁴. Peripheral challenge with the TLR agonists, LPS or polyriboinosinic-polyribocytidilic acid (PolyI:C), induced amyloid pathology in some^{25, 26}, but not all²⁷, animal models of AD. Herpes simplex virus DNA has also been found in the cortex of a high proportion of individuals with AD²⁸ and the risk of developing AD is exacerbated by the virus in individuals with the type 4 allele of the apolipoprotein E²⁹.

Several factors act to downregulate microglial activation

Under resting conditions, microglia are maintained in a relatively quiescent state and, while the evidence suggests that cell-cell interactions are primarily responsible for this, it is also known that some neurotransmitters particularly noradrenaline and acetylcholine also modulate the activation of microglia³⁰. Other factors which assist in maintaining the 'resting' state of microglia are the low numbers of T cells in the brain and therefore the minimal expression of potent activators like interferon (IFN) γ , the presence of electrically active neurons which suppress glial expression of MHC and co-stimulatory molecules³¹ and the production by neurons and astrocytes of TGF β and IL-10^{32, 33}.

Microglia physically interact with other cells and, in the case of microglia-neuron interactions, several ligand-receptor pairs have been shown to support this interaction. Perhaps the 2 best studied pairs are CD200-CD200R and CX3CL1-CX3CR1. CD200 is expressed on many cell types including neurons whereas CD200 receptor expression is confined to cells of the myeloid lineage^{34, 35}; consequently co-culturing microglia with neurons decreases lipopolysaccharide (LPS)- or amyloid- β (A β)-induced microglial activation in a CD200-dependent manner^{36, 37}. CD200 deficiency increases inflammatory changes in models of multiple sclerosis³⁸, Parkinson's Disease³⁹ and experimental autoimmune uveoretinitis⁴⁰ and these mice also exhibit exaggerated responses to inflammatory challenges^{37, 41}. Perhaps predictably, a fusion protein CD200Fc, which acts on CD200R to induce its signalling, attenuates the inflammatory changes associated with age and A β treatment^{42, 43} and to decrease the symptoms and inflammatory changes in experimental autoimmune encephalomyelitis⁴⁴ and collagen-induced arthritis^{45, 46}. Interestingly CD200 is decreased in tissue from individuals with AD⁴⁷ and in tissue adjacent to the plaques in multiple sclerosis^{48, 49} and CD200R signalling is dysfunctional in macrophages from individuals with Parkinson's disease⁵⁰.

The largely complementary expression of CX3CL1 on neurons and its receptor on microglia suggests an interaction similar to that described for CD200-CD200R, and evidence to support this has been reported⁵¹. Several studies have reported that disruption in CX3CL1-CX3CR1 interaction is associated with microglial activation and increased secretion of inflammatory cytokines⁵². However in the APP/PS1 transgenic mouse model of AD, knockdown of CX3CR1 was associated with increased clearance of A β ⁵³ indicating that the impact of CX3CR1 activation is complex with respect to microglial activation. Interestingly, expression of both ligand and receptor is decreased in hippocampal and cortical tissue in AD⁵⁴.

Other ligand-receptor pairs include CD45 and signal regulatory protein (SIRP)1 α which are expressed predominantly on microglia and interact with neuronally-expressed CD22 and CD47 respectively⁵⁵⁻⁵⁹. These interactions function as 'off' signals, whose role is to keep microglia in a resting state; other 'off' signals include secreted CD22 and fractalkine, secreted neurotrophins and anti-inflammatory cytokines such as IL-10 and IL-4^{55, 60} and several of these factors attenuate IFN γ -, LPS- and A β -induced microglial activation^{60, 61}.

Astrocytes, like neurons, express CD200 and they also have the ability to interact with microglia to downregulate their activation. Indeed incubation of microglia with CD200-bearing astrocytic membrane preparations attenuate the LPS-induced increase in mRNA expression of IL-1 β , TNF α and IL-6 and the LPS-induced increase in release of TNF α and IL-6⁶². However soluble factors secreted by astrocytes also modulate microglial activation⁶³ and it has been shown that conditioned medium obtained from astrocytes decreased hydrogen peroxide (H₂O₂)-induced reactive oxygen species (ROS) production, increased expression and activity of the antioxidant enzyme, haemoxygenase-1, and decreased IFN γ -induced inducible nitrous oxide synthase (iNOS) expression in microglia⁶⁴. The modulatory effect of astrocytes on microglial activation perhaps derives from the fact that astrocytes are GABA-ergic cells which impact on GABA receptors expressed by microglia⁶⁵. However it is clear that astrocytes can also release factors which trigger microglial activation and therefore contribute to the changes that occur as a consequence of chronic inflammation^{66, 67}.

T cells can also interact with microglia to modulate their function (Table 1). It was shown in co-culture experiments that Th1 cells upregulated expression of markers which are typical of APC in microglia, including MHCII and CD40 induced, whereas Th2 cells were unable to do so⁶⁸. Conversely, microglia induced Th1 cells to release IFN γ but were unable to trigger release of IL-4 from Th2 cells⁶⁸. In addition, conditioned medium obtained from Th1 cells, but not Th2 cells, increased expression of CD80, CD86, CD40 and the adhesion molecule CD54 on microglia; these changes were mimicked by IFN γ and inhibited by anti-IFN γ antibody, although only partially, prompting the authors to conclude that the effect of Th1 cells cannot be attributed exclusively to IFN γ release⁶⁹. We have also reported that T cells, specifically Th1 and Th17 cells, interact with microglia and induce their activation *in vitro*^{70, 71}. A β -specific Th1 cells increased production of inflammatory cytokines IL-1 β , IL-6 and TNF α and increased expression of MHCII and CD86 on microglia⁷⁰. Th17 cells exerted similar effects, whereas Th2 cells exerted little effect. However Th2 cells attenuated the effect of Th17 cells on microglia but did not inhibit the effect of Th1 cells. MOG-specific Th1 cells and Th1/Th17 cells also increased microglial production of inflammatory cytokines and expression of MHCII, CD80 and CD86⁷¹. Consistent with these findings, it has also been shown that co-culture of organotypic slices with OVA-specific or myelin basic protein-specific Th1 cells increased

microglial activation whereas Th2 cells exerted no effect⁷². These *in vitro* data all suggest that APC function of microglia is increased when cells interact with Th1 and Th17 cells and interestingly upregulation of APC function induced by Th1 cells appears to be associated with a switch in microglial phenotype away from one that is efficient at phagocytosis⁷³. The evidence from our recent studies suggest that the modulatory effect of T cells on microglial function observed *in vitro* also occurs *in vivo*. Focussing on analysis of the effects in an amyloid-overexpressing model of AD, we found that intravenous administration of A β -specific Th1 cells into APP/PS1 mice, which tracked to the brain, increased microglial activation and enhanced A β pathology and this effect was attenuated in APP/PS1 mice treated with an anti-IFN γ antibody⁷⁴. The effect of Th17 cell administration was less profound whereas injection of Th2 cells was essentially without effect in these mice. The lack of effect of Th2 cells is at variance with an earlier report which suggested a beneficial effect of transfer of A β -specific Th2 cells on behavioural deficits and pathology in APP/PS1 mice⁷⁵. This group also reported that Th2 cells reduced the numbers of activated microglia surrounding A β -containing plaques.

Do microglia adopt the M1 and M2 phenotypes observed in macrophages?

It has been known for a few decades that macrophages adopt different activation states, identified by upregulation of specific markers, in response to different signals⁷⁶. These are broadly described as M1, an inflammatory phenotype and M2, an anti-inflammatory phenotype. The Th1 cell-derived cytokine IFN γ induces classical activation (M1), and this phenotype is identified by upregulation of TNF α and iNOS. The term alternative activation (M2a phenotype) was first used to describe a macrophage which adopted a phenotype distinct from that induced by IFN γ and LPS⁷⁷. These cells were not capable of producing NO and so were not cytotoxic and, although MHCII expression was increased, the cells were not efficient APC and prevented proliferation of T cells⁷⁸. This phenotype is induced by the Th2 cell-derived cytokines, IL-4, IL-5 and IL-13 and is identified by upregulation of mRNA expression of arginase I, mannose receptor, chitinase 3-like 3 and found in inflammatory zone-1 (FIZZ1). Because the cells were shown to inhibit inflammatory cytokine production, they were recognized as regulatory macrophages⁷⁹. Acquired deactivation (M2c phenotype) is induced by the immunosuppressive cytokines, IL-10 and TGF β , which are derived from regulatory T cells, and this phenotype is associated with upregulation of anti-inflammatory cytokines like IL-10 and TGF β and downregulation of factors that contribute to APC function like MHCII⁷⁶. Like macrophages, microglia respond to IL-10 and administration of IL-10 to aged rats decreases microglial activation and neuroinflammatory changes⁸⁰ suggesting that microglia can also adopt the acquired deactivated state. It has been shown that this state, which is characterized by an increase in receptors like scavenger receptors, which support their phagocytic function, can also be induced by phagocytosis of apoptotic cells, or TGF β though the data is largely derived from *in vitro* studies⁸¹.

In the past 5 years or so, significant interest has developed in determining whether microglia react to the different stimuli in the same way as macrophages. Although there are data which support this, it remains to be established whether the characteristics of these activation states, and their patterns of stimulation, faithfully translate from the *in vitro* into the *in vivo* situation. It is also not entirely clear that the phenotypic markers which apply to macrophages are relevant in the context of microglia. A further issue relates to the nature of the stimuli which trigger classical and alternative activation states since resident

cells in the brain produce limited IFN γ and IL-4. It must therefore be considered that infiltrating cells are responsible for production of these cytokines and consequently for triggering polarization of microglia into classically- and alternatively-activated phenotypes, or that other polarizing stimuli substitute in the brain. Despite these caveats, it is known that IFN γ potently activates microglia and among the changes observed is increased expression of TNF α and iNOS as well as upregulation of other inflammatory cytokines and markers typical of an APC in vivo^{82, 83} as well as in vitro⁸⁴. A recent very comprehensive study in microglia also identified that COX2 mRNA was markedly increased in IFN γ -treated cells while mannose receptor and arginase-1 mRNA were upregulated by IL-4⁸⁵. Alternatively-activated macrophages have a key role in tissue repair and restructuring of the extracellular matrix⁸¹; whereas alternatively-activated microglia may also play a role in tissue repair, a key role is likely to be re-establishing homeostasis following an inflammatory stimulus.

Identifying factors that enable switching of microglia from an inflammatory to an anti-inflammatory phenotype is an important goal since it is likely to point towards strategies that might prevent chronic inflammation. One potential molecular switch is activation of PPAR γ ⁸⁶; its activation by pioglitazone increased expression of several markers of alternative activation in 12 month-old APP/PS1 mice. This was associated with decreased A β pathology suggesting that alternatively-activated microglia are more phagocytic⁸⁷. Inhibition of NADPH oxidase or functional deletion of p47phox have also been identified as factors which potentially control the polarization of microglia from the classically- to the alternatively-activated state in the brain⁸⁸. Similarly, knockdown of NLRP3 in APP/PS1 mice switches microglia from the classical to the alternative activation state⁸⁹. The tetrapeptide, (threonine-lysine-proline-arginine), tuftsin, also induces an anti-inflammatory phenotype in vitro and in vivo⁹⁰ whereas CD45 which inhibits the interaction between CD40 ligand and receptor appears to switch off the inflammatory M1 state in vivo⁹¹. In contrast, age induces microglia to adopt an inflammatory phenotype⁹². Recent evidence has revealed that specific microRNAs may be key factors in polarization of microglia, and it has been suggested that miR-155 skews microglia towards an M1 phenotype, at least in cultured cells⁹³. However changes in upregulation of other miRNAs including miR-101 and miR-125b, together with downregulation of miR-92, also appear to be characteristics of the M1 phenotype⁹⁴.

What microglial phenotype is observed in AD and is this linked with A β accumulation?

With the focus on the amyloid hypothesis of AD, the question of which microglial phenotype is associated with A β accumulation and/or with greater phagocytic capability has been the subject of intense interest. In the context of AD in particular, it is important to unravel the factors that contribute to the apparent inability of microglia to phagocytose A β despite the proximity of activated cells to the A β -containing plaques. The consensus suggests that an inflammatory milieu inhibits the phagocytic function of microglia. Thus it has been reported that Th1 cytokines inhibit microglial phagocytosis of A β , whereas IL-4 and IL-10 have the opposite effect⁷³. Jimenez and colleagues demonstrated that the microglial phenotype changed with age in APP/PS1 mice, shifting from an alternative activation state which was associated with phagocytic capability to a classically-activated phenotype which was associated with proinflammatory cytokine production. A β -immunoreactivity was observed in tomato lectin-stained microglia that surrounded plaques

in 6 month-old APP/PS1 mice and the evidence indicated that these cells were alternatively-activated microglia because they stained positively for YM-1. By 18 months of age, microglia had adopted a classically-activated phenotype and these cells appeared not to be phagocytic⁹². It was also shown that knocking out IFN γ R1 in APP mice was associated with reduced A β deposition in cortex and hippocampus and this correlated with decreased gliosis⁹⁵. Additionally, alternative activation of microglia in APP/PS1 mice, which was induced by the PPAR γ activator pioglitazone⁸⁷ or NLRP3 knockdown⁸⁹ was associated with an increase in A β clearance. We have found that adoptive transfer of A β -specific Th1 cells markedly increased microglial activation, inflammatory changes and A β pathology but Th2 cells were without effect⁷⁴. This contrasts with the findings of others which suggested that injection of Th2 cells decreased plaque burden⁷⁵. This finding followed up a previous report from this group which demonstrated that injection of a mixed population of A β -specific T cells decreased A β pathology in 8.5 month-old APP/PS1 mice though this effect was not evident if an enriched Th1 preparation was injected⁹⁶. Our evidence has indicated that, even in 6-7 month-old APP/PS1 mice, there was evidence of an inflammatory phenotype^{97,98}, and in a recent study we were unable to detect any evidence of alternatively-activated microglia in 12 month-old APP/PS1 mice (Minogue et al. unpublished). This may vary between models of AD since increased mRNA expression of TNF α (although not iNOS), as well as mannose receptor and arginase-1, was observed in cortical tissue prepared from 60 week-old Tg2576 mice suggesting a heterogeneity in microglial phenotypes in at least this model of AD⁷⁹. This heterogeneity was also observed in transgenic mice that overexpressed APP only but was more marked in APP mice with a deficiency in NOS2⁹⁹. However this group have suggested that amyloid deposition is greater in circumstances in which there is upregulation of markers of alternatively-activated microglia which is at variance with most of the literature.

It has been suggested that macrophages rather than microglia are the primary phagocytes in the brain¹⁰⁰ and that these infiltrating cells are key to reparative processes¹⁰¹. However the evidence suggests that alternatively-activated macrophages, like microglia, have enhanced phagocytic capability¹⁰² and the possibility exists that the inflammatory microenvironment in the AD brain, which inhibits efficient phagocytosis¹⁰³, prevents the macrophages from adopting the alternatively-activated state. This may explain the finding that macrophages which infiltrate the brain in AD patients fail to phagocytose A β efficiently¹⁰⁴. Therefore, a therapeutic value of anti-inflammatory therapies given at the appropriate time in the disease, may be a reduction on A β pathology.

Does infiltration of peripheral cells contribute to the onset or progression of AD?

In AD and amyloid-based transgenic models of AD, microglia adopt an inflammatory phenotype^{97,98}, and increased expression TNF α and iNOS, which are markers of classical activation, have been reported in the brain of mouse models of AD and in postmortem tissue from AD patients^{89,99,105}. A link between microglial activation and tau hyperphosphorylation has also been reported¹⁰⁶, though accumulating tau in a mouse model in which tau is overexpressed, leads to an LPS-induced upregulation of markers of alternative activation¹⁰⁷. If it is accepted that IFN γ is required for inducing classical activation of microglia, then it follows that there must be infiltration of IFN γ -producing cells, for example Th1 cells, since IFN γ is generally not produced to any significant degree by resident cells in the brain. However it must be considered that factors other than IFN γ

can induce changes that mimic classical activation and, in this context it is known that several of the changes induced by IFN γ R activation including upregulation of TNF α and iNOS, as well as cell surface markers of activation like MHCII and CD40, are also triggered by A β □□□TLR agonists^{42, 108}.

It is widely accepted that T cell entry into the CNS under normal circumstances is very limited and the evidence suggests that their role is immuno-surveillance^{109, 110}; it has been proposed that cells gain entry at the choroid plexus under these conditions when there is no evidence of neuroinflammation¹¹¹. However significant infiltration of immune cells occurs in neuroinflammatory conditions¹¹¹. The role of these cells in the pathogenesis of multiple sclerosis is well rehearsed^{112, 113}, but a recent study revealed that T cell infiltration also occurs in Parkinson's disease¹¹⁴ and the evidence from animal studies suggests that the presence in the brain of CD4⁺ cells significantly contributes to the demise of dopaminergic cells.

The first evidence that T cells were present in the brain of AD patients was presented 25 years ago^{115, 116} and similar findings have been sporadically reported since^{12, 117-122}. These cells were found to be in close apposition with plaques and activated glia¹¹⁹. CD8⁺ cells have been found in the post-mortem brain of individuals with mild-moderate AD but also in non-demented controls, though some evidence suggests that their numbers were decreased in AD brains^{12, 121}. We have recently shown that there is significant infiltration of T cells, particularly IFN γ -positive and IL-17-positive T cells, into the brain of 6-8 month-old APP/PS1 mice⁷⁴ and this infiltration increases with age so that infiltration in 12 month-old animals was significantly greater (McManus et al., unpublished). T cell infiltration has also been shown in 18 month-old, but not 6 month-old, APP/PS1 mice⁹².

Infiltration of immune cells may result from the creation of a chemotactic gradient as a consequence of increased expression of chemokines in brain; CCL3, CXCL10 and CCL5 have established lymphocyte chemotactic properties¹²³⁻¹²⁵ and increased expression of these chemokines has been reported in AD¹²⁶⁻¹²⁸. Interestingly, expression of CCR5 and CXCR3 on T cells obtained from AD patients has been reported¹²⁹⁻¹³¹. A loss of BBB integrity, which will also enable cell infiltration, has been described in AD; increased fibrinogen immunoreactivity, altered immunohistochemical staining for von Willebrand's factor, and dystrophic vessels have been reported¹³². This was accompanied by marked glial activation; activated microglia were co-located with fibrinogen immunoreactivity, suggesting that fibrinogen induce cell activation¹³³. Interestingly intrahippocampal injection of A β induced BBB permeability in the rat hippocampus, as revealed by fibrinogen immunoreactivity, whereas we have recently found that the age-related accumulation of endogenous A β in APP/PS1 mice was accompanied by increased BBB permeability, infiltration of CD4⁺IFN γ ⁺ cells and increased expression of markers of classical activation of microglia. (Minogue et al., unpublished).

Summary

A proposed sequence of events presented in Figure 1 suggests that BBB permeability, which is increased in AD, together with the creation of a chemotactic gradient, leads to infiltration of IFN γ -producing T cells. Inflammatory T cells together with IFN γ , produced by these cells, induces classical activation of microglia which leads to inflammatory cytokine and chemokine production. These changes act to increase APP processing and A β accumulation and also induce BBB permeability with further infiltration of cells, and

so a cycle of damaging events ensues. It is proposed that interrupting this cycle is key to limiting disease progression in AD. Validation (or otherwise) of this hypothesis requires significant investigation. For example, it predicts that preventing BBB permeability or infiltration of IFN γ -producing T cells will reduce inflammation and pathology. It also predicts that IFN γ -induced changes in microglia, and upregulation of chemokines, induce further BBB permeability whereas the effects of microglia which have an anti-inflammatory phenotype are not. It remains to be established whether these changes impact in the predicted way on neuronal and cognitive function.

REFERENCES

1. McGeer PL, Itagaki S, Tago H, McGeer EG. Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci Lett* 1987; 79:195-200.
2. Guillot-Sestier MV, Town T. Innate Immunity in Alzheimer's Disease: A Complex Affair. *CNS Neurol Disord Drug Targets* 2013.
3. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000; 21:383-421.
4. Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. *ScientificWorldJournal* 2012; 2012:756357.
5. Solito E, Sastre M. Microglia function in Alzheimer's disease. *Front Pharmacol* 2012; 3:14.
6. Launer L. Nonsteroidal anti-inflammatory drug use and the risk for Alzheimer's disease: dissecting the epidemiological evidence. *Drugs* 2003; 63:731-9.
7. Rich JB, Rasmusson DX, Folstein MF, Carson KA, Kawas C, Brandt J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. *Neurology* 1995; 45:51-5.
8. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; 48:626-32.
9. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003; 289:2819-26.
10. Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology* 2004; 62:66-71.
11. Imbimbo BP, Solfrizzi V, Panza F. Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? *Front Aging Neurosci* 2010; 2.
12. Parachikova A, Agadjanyan MG, Cribbs DH, Blurton-Jones M, Perreau V, Rogers J, et al. Inflammatory changes parallel the early stages of Alzheimer disease. *Neurobiol Aging* 2007; 28:1821-33.
13. Breitner JC, Haneuse SJ, Walker R, Dublin S, Crane PK, Gray SL, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. *Neurology* 2009; 72:1899-905.
14. Mackenzie IR. Postmortem studies of the effect of anti-inflammatory drugs on Alzheimer-type pathology and associated inflammation. *Neurobiol Aging* 2001; 22:819-22.
15. Halliday GM, Shepherd CE, McCann H, Reid WG, Grayson DA, Broe GA, et al. Effect of anti-inflammatory medications on neuropathological findings in Alzheimer disease. *Arch Neurol* 2000; 57:831-6.
16. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 2010; 330:841-5.
17. Lucin KM, Wyss-Coray T. Immune activation in brain aging and neurodegeneration: too much or too little? *Neuron* 2009; 64:110-22.

18. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. *Trends Neurosci* 2007; 30:527-35.
19. Savage CD, Lopez-Castejon G, Denes A, Brough D. NLRP3-Inflammasome Activating DAMPs Stimulate an Inflammatory Response in Glia in the Absence of Priming Which Contributes to Brain Inflammation after Injury. *Front Immunol* 2012; 3:288.
20. Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? *Alzheimers Dement* 2009; 5:348-60.
21. Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003; 74:788-9.
22. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 2009; 73:768-74.
23. Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. *BMC Neurosci* 2010; 11:121.
24. Little CS, Hammond CJ, MacIntyre A, Balin BJ, Appelt DM. Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiol Aging* 2004; 25:419-29.
25. Krstic D, Madhusudan A, Doehner J, Vogel P, Notter T, Imhof C, et al. Systemic immune challenges trigger and drive Alzheimer-like neuropathology in mice. *J Neuroinflammation* 2012; 9:151.
26. Sheng JG, Bora SH, Xu G, Borchelt DR, Price DL, Koliatsos VE. Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APPswe transgenic mice. *Neurobiol Dis* 2003; 14:133-45.
27. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. *J Neurosci* 2005; 25:8843-53.
28. Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. *J Pathol* 2009; 217:131-8.
29. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* 1997; 349:241-4.
30. Carnevale D, De Simone R, Minghetti L. Microglia-neuron interaction in inflammatory and degenerative diseases: role of cholinergic and noradrenergic systems. *CNS Neurol Disord Drug Targets* 2007; 6:388-97.
31. Neumann H. Control of glial immune function by neurons. *Glia* 2001; 36:191-9.
32. Lacmann A, Hess D, Gohla G, Roussa E, Kriegelstein K. Activity-dependent release of transforming growth factor-beta in a neuronal network in vitro. *Neuroscience* 2007; 150:647-57.
33. Fernandez AM, Fernandez S, Carrero P, Garcia-Garcia M, Torres-Aleman I. Calcineurin in reactive astrocytes plays a key role in the interplay between proinflammatory and anti-inflammatory signals. *J Neurosci* 2007; 27:8745-56.
34. Wright GJ, Cherwinski H, Foster-Cuevas M, Brooke G, Puklavec MJ, Bigler M, et al. Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. *J Immunol* 2003; 171:3034-46.
35. Wright GJ, Puklavec MJ, Willis AC, Hoek RM, Sedgwick JD, Brown MH, et al. Lymphoid/neuronal cell surface OX2 glycoprotein recognizes a novel receptor on macrophages implicated in the control of their function. *Immunity* 2000; 13:233-42.
36. Lyons A, McQuillan K, Deighan BF, O'Reilly JA, Downer EJ, Murphy AC, et al. Decreased neuronal CD200 expression in IL-4-deficient mice results in increased neuroinflammation in response to lipopolysaccharide. *Brain Behav Immun* 2009.

37. Lyons A, Downer EJ, Crotty S, Nolan YM, Mills KH, Lynch MA. CD200 ligand receptor interaction modulates microglial activation in vivo and in vitro: a role for IL-4. *J Neurosci* 2007; 27:8309-13.
38. Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, et al. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science* 2000; 290:1768-71.
39. Wang XJ, Ye M, Zhang YH, Chen SD. CD200-CD200R regulation of microglia activation in the pathogenesis of Parkinson's disease. *J Neuroimmune Pharmacol* 2007; 2:259-64.
40. Broderick C, Hoek RM, Forrester JV, Liversidge J, Sedgwick JD, Dick AD. Constitutive retinal CD200 expression regulates resident microglia and activation state of inflammatory cells during experimental autoimmune uveoretinitis. *Am J Pathol* 2002; 161:1669-77.
41. Lyons A, McQuillan K, Deighan BF, O'Reilly JA, Downer EJ, Murphy AC, et al. Decreased neuronal CD200 expression in IL-4-deficient mice results in increased neuroinflammation in response to lipopolysaccharide. *Brain Behav Immun* 2009; 23:1020-7.
42. Lyons A, Downer EJ, Costello DA, Murphy N, Lynch MA. Dok2 mediates the CD200Fc attenuation of A β -induced changes in glia. *J Neuroinflammation* 2012; 9:107.
43. Cox FF, Carney D, Miller AM, Lynch MA. CD200 fusion protein decreases microglial activation in the hippocampus of aged rats. *Brain Behav Immun* 2012; 26:789-96.
44. Liu Y, Bando Y, Vargas-Lowry D, Elyaman W, Khoury SJ, Huang T, et al. CD200R1 agonist attenuates mechanisms of chronic disease in a murine model of multiple sclerosis. *J Neurosci* 2010; 30:2025-38.
45. Gorczynski RM, Chen Z, Lee L, Yu K, Hu J. Anti-CD200R ameliorates collagen-induced arthritis in mice. *Clin Immunol* 2002; 104:256-64.
46. Gorczynski RM, Chen Z, Yu K, Hu J. CD200 immunoadhesin suppresses collagen-induced arthritis in mice. *Clin Immunol* 2001; 101:328-34.
47. Walker DG, Dalsing-Hernandez JE, Campbell NA, Lue LF. Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: a potential mechanism leading to chronic inflammation. *Exp Neurol* 2009; 215:5-19.
48. Koning N, Bo L, Hoek RM, Huitinga I. Downregulation of macrophage inhibitory molecules in multiple sclerosis lesions. *Ann Neurol* 2007; 62:504-14.
49. Koning N, Swaab DF, Hoek RM, Huitinga I. Distribution of the immune inhibitory molecules CD200 and CD200R in the normal central nervous system and multiple sclerosis lesions suggests neuron-glia and glia-glia interactions. *J Neuropathol Exp Neurol* 2009; 68:159-67.
50. Luo XG, Zhang JJ, Zhang CD, Liu R, Zheng L, Wang XJ, et al. Altered regulation of CD200 receptor in monocyte-derived macrophages from individuals with Parkinson's disease. *Neurochem Res* 2010; 35:540-7.
51. Lyons A, Lynch AM, Downer EJ, Hanley R, O'Sullivan JB, Smith A, et al. Fractalkine-induced activation of the phosphatidylinositol-3 kinase pathway attenuates microglial activation in vivo and in vitro. *J Neurochem* 2009; 110:1547-56.
52. Wolf Y, Yona S, Kim KW, Jung S. Microglia, seen from the CX3CR1 angle. *Front Cell Neurosci* 2013; 7:26.
53. Lee S, Varvel NH, Konerth ME, Xu G, Cardona AE, Ransohoff RM, et al. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. *Am J Pathol* 2010; 177:2549-62.
54. Cho SH, Sun B, Zhou Y, Kauppinen TM, Halabisky B, Wes P, et al. CX3CR1 protein signaling modulates microglial activation and protects against plaque-independent cognitive deficits in a mouse model of Alzheimer disease. *J Biol Chem* 2011; 286:32713-22.
55. Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal 'On' and 'Off' signals control microglia. *Trends Neurosci* 2007; 30:596-602.

56. Adams S, van der Laan LJ, Vernon-Wilson E, Renardel de Lavalette C, Dopp EA, Dijkstra CD, et al. Signal-regulatory protein is selectively expressed by myeloid and neuronal cells. *J Immunol* 1998; 161:1853-9.
57. Reinhold MI, Lindberg FP, Plas D, Reynolds S, Peters MG, Brown EJ. In vivo expression of alternatively spliced forms of integrin-associated protein (CD47). *J Cell Sci* 1995; 108 (Pt 11):3419-25.
58. van Beek EM, Cochrane F, Barclay AN, van den Berg TK. Signal regulatory proteins in the immune system. *J Immunol* 2005; 175:7781-7.
59. Mott RT, Ait-Ghezala G, Town T, Mori T, Vendrame M, Zeng J, et al. Neuronal expression of CD22: novel mechanism for inhibiting microglial proinflammatory cytokine production. *Glia* 2004; 46:369-79.
60. Lyons A, Griffin RJ, Costelloe CE, Clarke RM, Lynch MA. IL-4 attenuates the neuroinflammation induced by amyloid-beta in vivo and in vitro. *J Neurochem* 2007; 101:771-81.
61. Clarke RM, Lyons A, O'Connell F, Deighan BF, Barry CE, Anyakoha NG, et al. A pivotal role for interleukin-4 in atorvastatin-associated neuroprotection in rat brain. *J Biol Chem* 2008; 283:1808-17.
62. Cox FF, Berezin V, Bock E, Lynch MA. The neural cell adhesion molecule-derived peptide, FGL, attenuates lipopolysaccharide-induced changes in glia in a CD200-dependent manner. *Neuroscience* 2013; 235:141-8.
63. Eng LF, Ghirnikar RS, Lee YL. Glial fibrillary acidic protein: GFAP-thirty-one years (1969-2000). *Neurochem Res* 2000; 25:1439-51.
64. Min KJ, Yang MS, Kim SU, Jou I, Joe EH. Astrocytes induce hemeoxygenase-1 expression in microglia: a feasible mechanism for preventing excessive brain inflammation. *J Neurosci* 2006; 26:1880-7.
65. Lee M, Schwab C, McGeer PL. Astrocytes are GABAergic cells that modulate microglial activity. *Glia* 2011; 59:152-65.
66. Pascual O, Ben Achour S, Rostaing P, Triller A, Bessis A. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proc Natl Acad Sci U S A* 2012; 109:E197-205.
67. von Bernhardi R, Ramirez G. Microglia-astrocyte interaction in Alzheimer's disease: friends or foes for the nervous system? *Biol Res* 2001; 34:123-8.
68. Aloisi F, De Simone R, Columba-Cabezas S, Penna G, Adorini L. Functional maturation of adult mouse resting microglia into an APC is promoted by granulocyte-macrophage colony-stimulating factor and interaction with Th1 cells. *J Immunol* 2000; 164:1705-12.
69. Seguin R, Biernacki K, Prat A, Wosik K, Kim HJ, Blain M, et al. Differential effects of Th1 and Th2 lymphocyte supernatants on human microglia. *Glia* 2003; 42:36-45.
70. McQuillan K, Lynch MA, Mills KH. Activation of mixed glia by Abeta-specific Th1 and Th17 cells and its regulation by Th2 cells. *Brain Behav Immun* 2010; 24:598-607.
71. Murphy AC, Lalor SJ, Lynch MA, Mills KH. Infiltration of Th1 and Th17 cells and activation of microglia in the CNS during the course of experimental autoimmune encephalomyelitis. *Brain Behav Immun* 2010; 24:641-51.
72. Wolf SA, Gimsa U, Bechmann I, Nitsch R. Differential expression of costimulatory molecules B7-1 and B7-2 on microglial cells induced by Th1 and Th2 cells in organotypic brain tissue. *Glia* 2001; 36:414-20.
73. Townsend KP, Town T, Mori T, Lue LF, Shytle D, Sanberg PR, et al. CD40 signaling regulates innate and adaptive activation of microglia in response to amyloid beta-peptide. *Eur J Immunol* 2005; 35:901-10.
74. Browne TC, McQuillan K, McManus RM, O'Reilly JA, Mills KH, Lynch MA. IFN-gamma Production by amyloid beta-specific Th1 cells promotes microglial activation and increases plaque burden in a mouse model of Alzheimer's disease. *J Immunol* 2013; 190:2241-51.

75. Cao C, Arendash GW, Dickson A, Mamcarz MB, Lin X, Ethell DW. Abeta-specific Th2 cells provide cognitive and pathological benefits to Alzheimer's mice without infiltrating the CNS. *Neurobiol Dis* 2009; 34:63-70.
76. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol* 2003; 3:23-35.
77. Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. *J Exp Med* 1992; 176:287-92.
78. Mosser DM. The many faces of macrophage activation. *J Leukoc Biol* 2003; 73:209-12.
79. Colton CA, Mott RT, Sharpe H, Xu Q, Van Nostrand WE, Vitek MP. Expression profiles for macrophage alternative activation genes in AD and in mouse models of AD. *J Neuroinflammation* 2006; 3:27.
80. Moore ME, Piazza A, McCartney Y, Lynch MA. Evidence that vitamin D3 reverses age-related inflammatory changes in the rat hippocampus. *Biochem Soc Trans* 2005; 33:573-7.
81. Colton CA, Wilcock DM. Assessing activation states in microglia. *CNS Neurol Disord Drug Targets* 2010; 9:174-91.
82. Maher FO, Clarke RM, Kelly A, Nally RE, Lynch MA. Interaction between interferon gamma and insulin-like growth factor-1 in hippocampus impacts on the ability of rats to sustain long-term potentiation. *J Neurochem* 2006; 96:1560-71.
83. Downer EJ, Cowley TR, Cox F, Maher FO, Berezin V, Bock E, et al. A synthetic NCAM-derived mimetic peptide, FGL, exerts anti-inflammatory properties via IGF-1 and interferon-gamma modulation. *J Neurochem* 2009; 109:1516-25.
84. Kim HS, Whang SY, Woo MS, Park JS, Kim WK, Han IO. Sodium butyrate suppresses interferon-gamma-, but not lipopolysaccharide-mediated induction of nitric oxide and tumor necrosis factor-alpha in microglia. *J Neuroimmunol* 2004; 151:85-93.
85. Chhor V, Le Charpentier T, Lebon S, Ore MV, Celador IL, Josserand J, et al. Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. *Brain Behav Immun* 2013.
86. Chawla A. Control of macrophage activation and function by PPARs. *Circ Res* 2010; 106:1559-69.
87. Mandrekar-Colucci S, Karlo JC, Landreth GE. Mechanisms Underlying the Rapid Peroxisome Proliferator-Activated Receptor-gamma-Mediated Amyloid Clearance and Reversal of Cognitive Deficits in a Murine Model of Alzheimer's Disease. *J Neurosci* 2012; 32:10117-28.
88. Choi SH, Aid S, Kim HW, Jackson SH, Bosetti F. Inhibition of NADPH oxidase promotes alternative and anti-inflammatory microglial activation during neuroinflammation. *J Neurochem* 2012; 120:292-301.
89. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 2013; 493:674-8.
90. Wu M, Nissen JC, Chen EI, Tsirka SE. Tuftsin promotes an anti-inflammatory switch and attenuates symptoms in experimental autoimmune encephalomyelitis. *PLoS One* 2012; 7:e34933.
91. Salemi J, Obregon DF, Cobb A, Reed S, Sadic E, Jin J, et al. Flipping the switches: CD40 and CD45 modulation of microglial activation states in HIV associated dementia (HAD). *Mol Neurodegener* 2011; 6:3.
92. Jimenez S, Baglietto-Vargas D, Caballero C, Moreno-Gonzalez I, Torres M, Sanchez-Varo R, et al. Inflammatory response in the hippocampus of PS1M146L/APP751SL mouse model of Alzheimer's disease: age-dependent switch in the microglial phenotype from alternative to classic. *J Neurosci* 2008; 28:11650-61.
93. Cardoso AL, Guedes JR, Pereira de Almeida L, Pedroso de Lima MC. miR-155 modulates microglia-mediated immune response by down-regulating SOCS-1 and promoting cytokine and nitric oxide production. *Immunology* 2012; 135:73-88.

94. Guedes J, Cardoso AL, Pedrosa de Lima MC. Involvement of MicroRNA in Microglia-Mediated Immune Response. *Clin Dev Immunol* 2013; 2013:186872.
95. Yamamoto M, Kiyota T, Horiba M, Buescher JL, Walsh SM, Gendelman HE, et al. Interferon-gamma and tumor necrosis factor-alpha regulate amyloid-beta plaque deposition and beta-secretase expression in Swedish mutant APP transgenic mice. *Am J Pathol* 2007; 170:680-92.
96. Ethell DW, Shippy D, Cao C, Cracchiolo JR, Runfeldt M, Blake B, et al. Abeta-specific T-cells reverse cognitive decline and synaptic loss in Alzheimer's mice. *Neurobiol Dis* 2006; 23:351-61.
97. Gallagher JJ, Finnegan ME, Grehan B, Dobson J, Collingwood JF, Lynch MA. Modest Amyloid Deposition is Associated with Iron Dysregulation, Microglial Activation, and Oxidative Stress. *J Alzheimers Dis* 2012; 28:147-61.
98. Gallagher JJ, Minogue AM, Lynch MA. Impaired Performance of Female APP/PS1 Mice in the Morris Water Maze Is Coupled with Increased Abeta Accumulation and Microglial Activation. *Neurodegener Dis* 2013; 11:33-41.
99. Wilcock DM, Zhao Q, Morgan D, Gordon MN, Everhart A, Wilson JG, et al. Diverse inflammatory responses in transgenic mouse models of Alzheimer's disease and the effect of immunotherapy on these responses. *ASN Neuro* 2011; 3.
100. Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* 2006; 49:489-502.
101. Shechter R, Schwartz M. Harnessing monocyte-derived macrophages to control central nervous system pathologies: no longer 'if' but 'how'. *J Pathol* 2013; 229:332-46.
102. Chinetti-Gbaguidi G, Baron M, Bouhrel MA, Vanhoutte J, Copin C, Sebti Y, et al. Human atherosclerotic plaque alternative macrophages display low cholesterol handling but high phagocytosis because of distinct activities of the PPARgamma and LXRAalpha pathways. *Circ Res* 2011; 108:985-95.
103. Koenigsknecht-Talboo J, Landreth GE. Microglial phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines. *J Neurosci* 2005; 25:8240-9.
104. Fiala M, Lin J, Ringman J, Kermani-Arab V, Tsao G, Patel A, et al. Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease patients. *J Alzheimers Dis* 2005; 7:221-32; discussion 55-62.
105. Rao JS, Rapoport SI, Kim HW. Altered neuroinflammatory, arachidonic acid cascade and synaptic markers in postmortem Alzheimer's disease brain. *Transl Psychiatry* 2011; 1:e31.
106. Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. *Neuron* 2010; 68:19-31.
107. Lee DC, Rizer J, Selenica ML, Reid P, Kraft C, Johnson A, et al. LPS- induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. *J Neuroinflammation* 2010; 7:56.
108. Downer EJ, Johnston DG, Lynch MA. Differential role of Dok1 and Dok2 in TLR2-induced inflammatory signaling in glia. *Mol Cell Neurosci* 2013; 56C:148-58.
109. Hickey WF. Migration of hematogenous cells through the blood-brain barrier and the initiation of CNS inflammation. *Brain Pathol* 1991; 1:97-105.
110. Hickey WF. Basic principles of immunological surveillance of the normal central nervous system. *Glia* 2001; 36:118-24.
111. Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood-brain barriers. *Trends Immunol* 2012; 33:579-89.
112. Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Exp Immunol* 2010; 162:1-11.
113. Weissert R. The Immune Pathogenesis of Multiple Sclerosis. *J Neuroimmune Pharmacol* 2013.

- Accepted Article
114. Brochard V, Combadiere B, Prigent A, Laouar Y, Perrin A, Beray-Berthet V, et al. Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest* 2009; 119:182-92.
 115. Rogers J, Luber-Narod J, Styren SD, Civin WH. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. *Neurobiol Aging* 1988; 9:339-49.
 116. Itagaki S, McGeer PL, Akiyama H. Presence of T-cytotoxic suppressor and leucocyte common antigen positive cells in Alzheimer's disease brain tissue. *Neurosci Lett* 1988; 91:259-64.
 117. McGeer PL, Akiyama H, Itagaki S, McGeer EG. Immune system response in Alzheimer's disease. *Can J Neurol Sci* 1989; 16:516-27.
 118. Hartwig M. Immune ageing and Alzheimer's disease. *Neuroreport* 1995; 6:1274-6.
 119. Togo T, Akiyama H, Iseki E, Kondo H, Ikeda K, Kato M, et al. Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. *J Neuroimmunol* 2002; 124:83-92.
 120. Town T, Tan J, Flavell RA, Mullan M. T-cells in Alzheimer's disease. *Neuromolecular Med* 2005; 7:255-64.
 121. Pirttila T, Mattinen S, Frey H. The decrease of CD8-positive lymphocytes in Alzheimer's disease. *J Neurol Sci* 1992; 107:160-5.
 122. Monson A, Zota V, Karni A, Krieger JI, Bar-Or A, Bitan G, et al. Increased T cell reactivity to amyloid beta protein in older humans and patients with Alzheimer disease. *J Clin Invest* 2003; 112:415-22.
 123. Murooka TT, Rahbar R, Platanias LC, Fish EN. CCL5-mediated T-cell chemotaxis involves the initiation of mRNA translation through mTOR/4E-BP1. *Blood* 2008; 111:4892-901.
 124. Agostini C, Faccio M, Siviero M, Carollo D, Galvan S, Cattelan AM, et al. CXC chemokines IP-10 and mig expression and direct migration of pulmonary CD8+/CXCR3+ T cells in the lungs of patients with HIV infection and T-cell alveolitis. *Am J Respir Crit Care Med* 2000; 162:1466-73.
 125. Schall TJ, Bacon K, Camp RD, Kaspari JW, Goeddel DV. Human macrophage inflammatory protein alpha (MIP-1 alpha) and MIP-1 beta chemokines attract distinct populations of lymphocytes. *J Exp Med* 1993; 177:1821-6.
 126. Tripathy D, Thirumangalakudi L, Grammas P. Expression of macrophage inflammatory protein 1-alpha is elevated in Alzheimer's vessels and is regulated by oxidative stress. *J Alzheimers Dis* 2007; 11:447-55.
 127. Tripathy D, Thirumangalakudi L, Grammas P. RANTES upregulation in the Alzheimer's disease brain: a possible neuroprotective role. *Neurobiol Aging* 2010; 31:8-16.
 128. Xia MQ, Bacskaí BJ, Knowles RB, Qin SX, Hyman BT. Expression of the chemokine receptor CXCR3 on neurons and the elevated expression of its ligand IP-10 in reactive astrocytes: in vitro ERK1/2 activation and role in Alzheimer's disease. *J Neuroimmunol* 2000; 108:227-35.
 129. Man SM, Ma YR, Shang DS, Zhao WD, Li B, Guo DW, et al. Peripheral T cells overexpress MIP-1alpha to enhance its transendothelial migration in Alzheimer's disease. *Neurobiol Aging* 2007; 28:485-96.
 130. Liu YJ, Guo DW, Tian L, Shang DS, Zhao WD, Li B, et al. Peripheral T cells derived from Alzheimer's disease patients overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF-alpha-dependent. *Neurobiol Aging* 2010; 31:175-88.
 131. Reale M, Iarlori C, Feliciani C, Gambi D. Peripheral chemokine receptors, their ligands, cytokines and Alzheimer's disease. *J Alzheimers Dis* 2008; 14:147-59.
 132. Ryu JK, McLarnon JG. A leaky blood-brain barrier, fibrinogen infiltration and microglial reactivity in inflamed Alzheimer's disease brain. *J Cell Mol Med* 2009; 13:2911-25.
 133. Adams RA, Bauer J, Flick MJ, Sikorski SL, Nuriel T, Lassmann H, et al. The fibrin-derived gamma377-395 peptide inhibits microglia activation and suppresses relapsing paralysis in central nervous system autoimmune disease. *J Exp Med* 2007; 204:571-82.

Table 1. Effect of T cells on microglial activation

Main finding	Preparation	Reference
OVA-specific Th1 cells increased expression of MHCII, CD40 and CD54 on microglia. Th2 cells had little effect.	Microglia from BALB/c mice. T cells prepared from transgenic mice carrying a TCR DO11.10 for cOVA ₃₂₃₋₃₃₉ peptide mouse.	⁶⁸
Conditioned medium from Th1 cells increased expression of CD80, CD86, CD40 and CD54 and release of TNF α , IL-6 and CXCL10. Medium from Th2 cells had no significant effect.	Microglia from human tissue obtained following surgery. T cells from healthy volunteers.	⁶⁹
A β -specific Th1 cells increased expression of MHCII and CD86 and release of IL-1 β , TNF α and IL-6. A β -specific Th17 cells exerted a similar effect. Th2 cells had little effect	Mixed glia and T cells from C57BL/6 mouse.	⁷⁰
MOG-specific Th1 cells increased expression of MHCII, CD80, CD86 and CD40 and release of IL-1 β , TNF α . MOG-specific Th1/Th17 cells exerted a similar effect.	Mixed glia and T cells from C57BL/6 mouse.	⁷¹
MBP-specific and OVA-specific Th1 cells increased CD80 expression (with or without cell contact) but decreased CD86 expression (slices already expressed CD86).	Organotypic entorhinal-hippocampal slice cultures prepared from 11 day-old mice. Th1 and Th2 cell lines from transgenic mice carrying a T-cells receptor (TCR) for MBP peptide Ac1-11 or transgenic mice carrying a TCR DO11.10 for cOVA ₃₂₃₋₃₃₉ peptide.	⁷²
Adoptive transfer of A β -specific Th1 cells increased CD11b immunoreactivity and A β accumulation in APP/PS1 transgenic mice. Th2 cells had little effect.	T cells from C57BL/6 mice adoptively transferred into APP/PS1 mice.	⁷⁴
Adoptive transfer of A β -specific Th2 cells decreased plaque-associated microglial numbers	Th2 cells from congenic mice adoptively transferred into APP/PS1 mice.	⁷⁵
T cell infusion reduced area covered by microglia surrounding A β deposits. Th1 cell-enriched infusion was less effective.	T cell- enriched infusate prepared from Tg2576 mice. Adoptively transferred into 8.5 month-old Tg2576 mice.	⁹⁶