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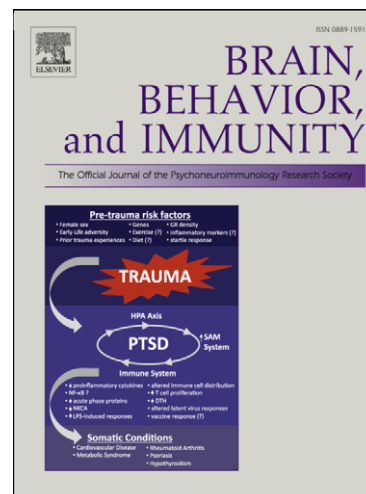
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Immunology meets neuroscience –
opportunities for immune intervention in neurodegenerative diseases

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ABSTRACT

Neuroinflammatory changes are characteristic of many, if not all, neurodegenerative diseases but the extent to which the immune system is involved in the pathogenesis of these diseases is unclear. The findings of several studies during the past decade has established that there is a well-developed communication between the central nervous system (CNS) and the peripheral immune system, but also has revealed that the immune system in the CNS is much more sophisticated than previously acknowledged. In this mini-review, we discuss two major neurodegenerative disorders, Alzheimer's Disease (AD) and multiple sclerosis (MS), and consider whether the therapies most likely to succeed are those that are identified by studying the marriage of neuroscience and immunology.

Keywords: Neuroinflammation, Neurodegeneration, T cells, Alzheimer's Disease, Multiple Sclerosis, Immune therapy.

1. Introduction

Neurodegenerative diseases share common characteristics at the cellular and molecular levels; apart from the cell loss and loss of function, there is evidence of a change in membrane composition, mitochondrial dysfunction and oxidative damage to lipids, proteins and nucleic acids. In parallel, there is overwhelming evidence of glial activation which is responsible for the chronic inflammation that typifies most, if not all, neurodegenerative diseases. The altered activation state of glia, particularly microglia, is an indicator of chronic immune activation and the reduced ability of the brain's immune system to restore homeostasis. Chronic neuroinflammation can lead to cell dysfunction triggering a self-perpetuating cycle of damaging events driving pathogenic processes and consequently neurodegeneration. Degrading cells, particularly neurons, are an integral part of this self-destructive cycle releasing danger-associated molecular patterns (DAMPs), like ATP and high mobility group protein 1 (HMGB-1), and these, by interacting with Toll-like receptors (TLRs) and other pathogen recognition receptors (PRRs), trigger inflammatory changes. Other DAMPs include aggregated, modified or misfolded proteins for instance β -amyloid ($A\beta$), tau and α -synuclein which accumulate in Alzheimer's Disease (AD) and/or Parkinson's Disease (PD).

Inflammatory changes develop with age and in age-related neurodegenerative diseases, like AD, PD and macular degeneration, the likelihood is that the underlying neuroinflammation is a significant factor in the pathogenesis of the disease. Whereas AD, PD and MD are age-related neurodegenerative conditions, others like Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Huntington's Disease are less so, yet neuroinflammation and microglial activation is common to each of these conditions. At this time it is not known whether microglial activation drives the neurodegenerative changes or microglial activation is a response to the neurodegenerative process. Apart from MS, where the role of infiltrating T cells is well-studied, little is known about their contribution to the disease process in most degenerative diseases although their presence has been described in AD (Togo et al., 2002), PD (McGeer et al., 1988; Stone et al., 2009), ALS (Sta et al., 2011) and MD (Ezzat et al., 2008). However sustained neuroinflammation is a pathogenic component in acute, as well as chronic, neurodegenerative disorders.

This mini-review, written by life-long partners and collaborators, Marina Lynch, a neuroscientist, turned neuroimmunologist and Kingston Mills, an immunologist, with a keen interest in neuroinflammation, brings two perspectives to the problems of neuro-inflammation and neurodegeneration and considers how we may be able to tackle these therapeutically by exploiting knowledge from the two different fields.

2. Innate immune system - Role of dendritic cells, macrophages and microglia

The immune system employs a combination of innate and adaptive responses to detect and eliminate pathogens. Cells of the innate immune system include dendritic cells (DC), macrophages and microglia (macrophages of the CNS); these provide the first line of defense but also instruct the T cells in relation to the adaptive immune system. The T and B cells of the adaptive immune system employ T cell receptors (TCR) and B cell receptors (BCR or antibodies) to specifically recognize a wide diversity of foreign antigens. Furthermore, the development of immunological memory is a defining feature of the adaptive immune system, which is exploited during vaccination. The generation of T and B cell responses by immunization with an antigen can be re-called following a subsequent exposure to the antigen or a pathogen containing that antigen. In contrast, the innate immune system lacks specificity, diversity and memory. However, the recent discoveries around a diverse array PRRs expressed

on innate immune cells has revealed that the innate immune system has the capacity to respond to a variety of conserved different structures, termed pathogen-associated molecular patterns (PAMPs) on pathogens. So far, nine families of PRRs have been identified and the most studied are the TLRs, NOD-like receptors (NLRs), RIG-I like receptors (RLR) and C-type lectin receptors (CLR).

A major function of cells of the innate immune system is to provide effector function against microbes. Macrophages, neutrophils and DC phagocytose and kill bacteria and small parasites. NK cells kill virally-infected cells. Finally a variety of innate immune cells, including macrophages, NK cells, NKT cells, $\gamma\delta$ T cells secrete inflammatory chemokines and cytokines that mobilize and mediate immune responses to pathogens. The production of inflammatory cytokines and other functions of innate immune cells are activated through PRRs. Binding of PAMPs to PRRs on DC, macrophages and other cell types results in signaling via nuclear factor kappa B (NF κ B), mitogen-activated protein (MAP) kinase and interferon regulatory factor (IRF) pathways that leads to the activation of genes coding for inflammatory cytokines including IL-6, TNF- α , IL-12 and IL-23. The production of the inflammatory cytokines, IL-1 β and IL-18, is more complex and involves activation of the nucleotide-binding domain, leucine rich containing family (NLR) by TLR-primed DC and macrophages. IL-1 β and IL-18 are produced as immature pro-forms in response to TLR activation, but require cleavage by caspase-1 to generate the mature cytokines IL-1 β and IL-18. Caspase-1 is activated by a variety of exogenous molecules, including bacterial toxins, but can also be induced by endogenous DAMPs including monosodium urate prominent in patients with gout, but also by A β that accumulates in the brains of patients with AD. The pro-inflammatory cytokines, IL-1 α , IL-1 β , IL-6 and TNF- α , are major mediators of inflammation and contribute to tissue damage in a number of diseases, including MS and possibly AD. However, together with IL-12, IL-23 and IL-4, these cytokines also play crucial roles in directing adaptive immune responses (Mills, 2008).

The cells primarily responsible for driving the innate immune response in the CNS are the microglia. They are highly dynamic, highly motile cells, with processes that constantly sample the parenchyma (Nimmerjahn et al. 2005) and react rapidly to changes in the microenvironment. Microglia express PRR, and therefore respond to PAMPs and endogenously-produced DAMPs and, analogous to the periphery, a fundamental role is played

by TLRs, which are expressed not only on glia, but also on neurons. Microglia, like macrophages, are immune effector cells and have multiple phenotypes; they are responsible for phagocytosing foreign factors, and they are secretory cells, responding to an array of molecules by variously secreting pro- and anti-inflammatory cytokines, chemokines, reactive oxygen and nitrogen species and neurotrophins. Antigen presentation is a key role of microglia and, when activated exhibit enhanced expression of cell surface markers including MHC class II, CD80, CD86, as well as adhesion molecules and complement receptors.

DC are the most efficient antigen-presenting cells and have been identified in the parenchyma, at least in mouse models of some neurodegenerative diseases (Jain et al., 2010; Monsonago and Weiner, 2003). In the healthy brain, until recently these cells were thought, to be confined to the meninges, the area around the choroid plexus and perivascular areas (McMenamin et al., 2003). However it has been reported that there is a resident population of DC in the brain (identified in enhanced yellow fluorescent protein transgenic mice). The number of these cells, as well as the number of DC recruited from the periphery, increases with age in several areas of the brain (Kaunzner et al., 2010). These authors suggested that the increase in recruitment of DC from the periphery may contribute to the development of the inflammatory phenotype and contribute to the processes which endow the increased susceptibility to neurodegenerative disease on the brain of aged individuals.

Bone marrow-derived cells can pass through the blood brain barrier (Simard and Rivest, 2004) and although there are few cells in the normal brain, numbers are increased following insult or injury (Carson et al., 2004). It is not clear whether infiltration of these cells is detrimental or beneficial; depletion of peripheral macrophages in a model of traumatic brain injury to the spinal cord reduced necrosis (Popovich *et al.* 2003) but preventing infiltration of blood-derived cells in a mouse model of AD resulted in increased plaque size. This suggests that they play a significant role in A β clearance and it has been suggested that bone marrow-derived cells are more efficient phagocytes than resident microglia (Simard et al., 2006). However this function may be compromised in AD since macrophages obtained from blood of AD patients were unable to phagocytose A β as effectively as cells from control subjects (Fiala *et al.* 2005).

3. Adaptive immune system - T cells, antibodies and vaccines

The primary function of the adaptive immune system is to clear pathogens from the host and to prevent re-infection. It also plays a major role in controlling the growth of tumors. Cellular immune responses are directed by CD4 Th cells and mediated by a variety of effector cells including CD4 T cells, CD8 cytotoxic T cells, $\gamma\delta$ T cells, NK cells, macrophages and neutrophils. These function either by phagocytosis and killing of microbes (macrophages, neutrophils and microglia), killing host cells infected with viruses, intracellular bacteria or small parasites (CD8 CTL and NK cells) or through the release of cytokines, such as IFN- γ , TNF- α and IL-17 (CD4 Th cells, $\gamma\delta$ T cells and NK cells), which activate other effector cells to take up and kill microorganisms (Mills, 2008). The main function of antibody is to prevent infection with viruses and intracellular bacteria through the process of neutralization that involves blocking the binding of the pathogen to receptors on host cells. Antibodies also help to kill microbes through opsonization, which involves coating of the bacteria or viruses by antibodies and/or complement which facilitates their uptake via Fc or complement receptors expressed on macrophages and neutrophils. Most, if not all, current prophylactic vaccines against infectious diseases work by generating protective antibody responses. CD4 T cells are also induced by vaccination and these are required to provide help for B cell production of antibody. In the case of therapeutic vaccines against infection or tumors, the induction of cell-mediated immunity has a more central role, because the aim here is to eliminate a pathogen or tumor that is already present in the host when the vaccine is administered. In the context of AD, vaccination approaches are directed at clearance of A β or a reduction in plaque burden, and while very different from clearance of viruses or bacteria, lessons can be learned from experiences with infectious disease and cancer.

4. CNS immune system

Although it is fundamentally different from the peripheral immune system in many respects, the immune system of the CNS robustly defends the integrity of the tissue and is vital for the maintenance of homeostasis. Several features set the brain's immune system apart – the presence of the blood brain barrier, a minimal number of T cells, limited numbers of cells which constitutively express MHC class I and MHC class II and therefore have limited ability to trigger T cell responses, and the lack of a lymphatic system. In addition, it is argued that microglia, even when activated, are poor APC (Rivest, 2009). However, the continuous

sampling of the tissue by microglia ensures constant monitoring, and the ability of these cells to respond to any threat to homeostasis, has led to the acceptance that there is a continuing low-level inflammatory activity in the CNS which is primarily concerned with repair. Microglia are aided in this function by astrocytes and perivascular macrophages, and also infiltrating T cells. The key to the beneficial ongoing inflammatory activity in the brain is control, and dysregulation of control mechanisms is the most likely cause of pathological inflammation and the consequent neurodegeneration. What is important to note is that the reparative function of the immune response occurs under non-pathological conditions but also in response to insults, infection, injury and inflammation. The probability is that, with age, this function is compromised as it is in conditions characterized by chronic neuroinflammation or neurodegeneration.

The brain also protects itself by maintenance of an immunosuppressive environment, due to soluble factors released by neurons and astrocytes, but also as a consequence of neuronal expression of immunosuppressive proteins like CD200, CD47, CD22 and fractalkine, which interact with their receptors on microglia and maintain microglia in a quiescent state. Released soluble factors which downregulate immune responses include neurotrophins, anti-inflammatory cytokines like TGF- β (which downregulates endothelial expression of adhesion molecules required to allow entry of peripheral cells into the brain), and anti-inflammatory prostaglandins.

Many of these unique features, which have been identified as a form of 'immune privilege' of the CNS are broken down by chronic inflammation. The blood brain barrier (BBB) plays a key role in modulating entry of solutes and ions into the CNS and, although migration of cells appears to be controlled to a significant extent by expression of chemokines and adhesion molecules and their receptors, infiltration of circulating cells occurs during chronic neuroinflammation when release of inflammatory mediators from activated microglia increases BBB permeability (Popescu et al., 2009). Predictably T cell infiltration has been found in CNS tissues of PD patients (Stone et al., 2009), where evidence of neuroinflammation is accompanied by increased BBB permeability (Desai et al., 2007) and similar correlative changes are found following ischaemic insult and with age (Popescu et al., 2009) and bacterial and viral infections (Stamatovic et al., 2008). BBB permeability is also increased by A β (Mackic et al., 1998) and consequently the presence of T cells in brain as well as increased T

cell reactivity have been reported in patients with AD (Schindowski et al., 2007; Togo et al., 2002). Interestingly T cells obtained from AD patients express increased CXCR2 and MIP-1 α , which enhance T cell migration into brain (Liu et al., 2010; Man et al., 2007). The presence of T cells in the brain has the capacity to profoundly affect glial function and both Th1 and Th17 cells increase microglial activation (McQuillan et al., 2010; Murphy et al., 2010). However part of the CNS defence is that astrocytes can suppress Th1 and Th2 cell activation and are capable of causing T cell apoptosis (Bechmann et al., 2002), whereas neurons can also induce T cell apoptosis (Tian et al., 2009).

5. Two diseases characterized by neuroinflammatory and neurodegenerative changes: Alzheimer's Disease and Multiple Sclerosis

It has been argued that AD is primarily a neurodegenerative disease and that the neurodegenerative processes cause neuroinflammation. In contrast MS is an immune-mediated disease and it is proposed that neuroinflammation is one of the first changes to occur in MS and that this can trigger the neurodegenerative changes.

5.1 Alzheimer's Disease – Immunology perspective

AD is a neurodegenerative disease characterized by neuritic plaques or lesions in the brain with deposits of A β surrounded by reactive astrocytes and activated microglia, and neurofibrillary tangles which are composed predominantly of hyperphosphorylated tau; the role of tau in AD will not be considered in this review. When compared with MS, it is more difficult to ascribe a role for immune cells or molecules in the pathogenesis of AD and it has to be concluded that AD is less clearly an immune-mediated disease. Nevertheless data are emerging to suggest that immunology will provide the clues to the underlying mechanisms and the basis for future therapies. From an immunological perspective, one of the most significant finding has been that A β is a potent activator of the NLRP3 inflammasome (Halle et al., 2008). Activation of caspase-1 as a consequence of assembly of the inflammasome complex mediates processing of pro-IL-1 β into mature IL-1 β , which together with other consequences of microglial activation, may play a crucial role in inflammation and tissue damage in AD. IL-1 β is known to play a central role in the pathology of many inflammatory diseases; there is

convincing evidence that IL-1 β plays a key role in the age-related deterioration of neuronal function (Lynch, 2010) though its role in AD remains to be clarified (Shafteel et al., 2007)

The role of adaptive immunity in the pathogenesis of AD is not entirely clear, with evidence of host protective and damaging roles for antibody and T cells specific for A β . Much of this evidence is based on studies in animal models and early results from clinical trials involving active and passive immunization with A β . However, there have also been some studies on peripheral T cells from AD patients. It was reported that T cell responses to A β ₁₋₄₀ found in healthy individuals were absent in patients with AD, suggesting that normal clearance of A β by T cell may be defective in AD patients (Trieb et al., 1996). It has also been reported that IFN- γ -secreting Th1-type T cells specific for A β ₁₋₄₂ were present in young individuals but decline with age and are lost in patients with AD, where IL-10-producing Treg cells predominate (Loewenbrueck et al., 2010). Our studies in mice have shown that A β -specific Th1 or Th17 cells enhance pro-inflammatory cytokine production and MHC class II and co-stimulatory molecule expression by A β -stimulated microglia. In contrast, A β -specific Th2 cells suppressed cytokine production by A β -specific Th1 cells and Th17 cells and inhibited glial production of IL-1 β and IL-6 (McQuillan et al., 2010). We also have preliminary data showing that transfer of A β -specific Th1 cells enhanced A β plaque development in APP^{swe}/PS1^{dE9} transgenic mice, which was associated with loss of cognitive function. In contrast, transfer of A β -specific Th2 cells had no effect, whereas Th17 cells reduced the concentrations of A β in the hippocampus. Collectively, these findings might predict that Th1 cells may enhance A β burden in AD and that inflammation mediated by this T cell subtype may promote disease progression. In contrast Th2 or Treg cells can suppress Th1 cells and local IL-1 β production by microglia and may therefore be protective against disease progression if indeed this disease has an inflammatory basis.

5.2. Alzheimer's Disease: Neuroscience perspective

The predominant theory relating to AD is the so-called amyloid theory which states that the accumulation of A β initiates a cascade of events resulting in a diverse set of consequences including formation of A β plaques, synapse loss, neuronal loss, inflammation and the signaling events which trigger hyperphosphorylation of tau. Alternative theories have been proposed; for example, it is suggested that AD is triggered by the effects of an initiating injury (which may be

an infection, head trauma, vascular event etc) superimposed on the endogenous ongoing age-related changes which include neuroinflammatory changes and synapse loss. It is suggested that this injury initiates a response designed to be reparative but the age-related loss of sufficient control over homeostatic functions, particularly in glia, renders the brain susceptible to insult, and therefore the precipitating factor results in inappropriate inflammation which is perceived as an additional stress which ultimately leads to major neuronal loss.

The possibility that inflammation is a precipitating factor in the pathogenesis of AD is supported by the epidemiological evidence that long-term non-steroidal anti-inflammatory (NSAID) treatment reduced the risk of developing the disease (McGeer et al., 1996) in a manner which is dependent on the duration of treatment (Stewart et al., 1997) and the age at which treatment began (Breitner et al., 2009). It has also been shown that chronic treatment with ibuprofen (Yan et al., 2003) or indomethacin (Sung et al., 2004) decreased pathology and improved cognitive function in transgenic mouse models of AD and that these effects were linked with decreased microglial activation. On the contrary, A β generation was increased by overexpression of cyclooxygenase-2 (Qin et al., 2003) and the increase in A β accumulation in APP/PS1 mice is accompanied by upregulation of cyclooxygenase-2 (Xiang et al., 2002); in both cases, microglial activation correlated with increased cyclooxygenase-2 activity. A key role for microglial activation in the pathogenic processes leading to AD-like symptomatology is the observation that minocycline improved cognition and decreased inflammatory cytokine production in a mouse model characterized by accumulation of cerebral microvascular fibrillar amyloid deposits and overt inflammation (Fan et al., 2007).

Despite the consistent and reproducible findings that neuroinflammatory changes are fundamentally linked to AD pathology, there is no evidence that NSAIDs offers a useful therapeutic strategy for the *treatment* of AD (Walker and Lue, 2007) implying that inflammation precedes overt neuronal loss. However, it is likely that there are at least two waves of neuroinflammation – the initial changes which are targeted by NSAID, and a second wave triggered by degenerating neurons which release DAMPs that trigger microglial activation and cause further neuroinflammation. Modulating release of DAMPs or targeting PRRs on which they act may provide a strategy for slowing cognitive decline. Indeed it has been suggested that activation of TLRs is primarily responsible for the neuroinflammatory changes which accompany the accumulation of A β in AD; although the precise role of TLRs is

unclear, plaque burden in mouse models of AD is enhanced when TLR4 signalling is defective (Tahara et al., 2006) and decreased in TLR2- and CD14-deficient mice (Reed-Geaghan et al., 2010; Richard et al., 2008). At present, there is no simple explanation for these apparently contradictory results, but it is possible that they reflect the role of CD14 in binding of ligands to TLR2 as well as TLR4; TLR2 signaling has been associated with anti-inflammatory as well as pro-inflammatory responses. Furthermore, soluble CD14 can suppress responses to LPS by preventing its binding to membrane CD14 and therefore TLR4 signalling.

Immune cells invade the brain in AD and probably contribute to the profound inflammation but resident glia also proliferate and synthesize inflammatory mediators. The evidence suggests that A β -containing plaques are decorated, not only by microglia but also by peripherally-derived monocytes and that chemotaxis of these cells is dependent on interaction between CCL2 which is upregulated in AD and its receptor CCR2 (Hickman and El Khoury, 2010). Similarly, exogenously-administered A β leads to migration of blood-derived cells to the site of injection and subsequently to microgliosis (Simard *et al.* 2006); although initial data suggested that the microgliosis was mainly due to bone-marrow-derived cells (Simard and Rivest 2004), recent findings suggest that it may result from proliferation of resident cells (Ajami et al., 2007; Milder, 2006; Neumann et al., 2009).

There is considerable debate surrounding the effect of the microenvironment on A β clearance; it is suggested by some that clearance relies on a local inflammatory response, involving microglia, macrophages or both, and failure of this system is responsible for A β accumulation (Weiner and Frenkel, 2006). In contrast, others have suggested that an inflammatory environment attenuates phagocytosis (Koenigsknecht-Talboo and Landreth, 2005). An age-related decrease in the phagocytosis of myelin following demyelination injury has been reported (Zhao et al., 2006) and it has been shown that phagocytic function of microglia is decreased in aged, compared with young, APP/PS1 mice correlating with A β accumulation (Hickman et al., 2008). Interestingly, phagocytosis of A β is decreased in macrophages prepared from AD patients (Fiala et al. 2005) and it is suggested that microglia in AD exhibit a deficit in phagocytosis enabling accumulation (Koenigsknecht-Talboo and Landreth, 2005). These and other findings have led to the proposal that microglia, like other cells, become senescent and are unable to perform their reparative and neuroprotective functions, and that this is ultimately responsible for neurodegeneration (Streit et al., 2008).

Consistent with this, microscopic examination has identified dystrophic microglia in the brain with age, and also in post-mortem AD brains where they are associated with neurodegenerative changes (Streit et al., 2009).

It is known that T cells interact with microglia and alter their activation state (McQuillan et al., 2010; Murphy et al., 2010); recent evidence has indicated that they can specifically modulate phagocytic function. Thus immunization of APP mice which were crossed with mice expressing IFN- γ , with A β resulted in recruitment of CD4 T cells to A β -containing plaques which were also decorated with CD11b⁺ microglia. The evidence suggested T cells increased microglial expression of MHC class II, CD86, triggering receptor expressed on myeloid cells-2 (TREM2) and signal regulatory protein- β 1 (SIRP β 1) and, in parallel, their ability to clear A β (Fisher et al., 2010).

In the post-mortem AD brain, there is evidence of increased numbers of CD3⁺ T cells but numbers do not correlate with Braak stage, nor with the occurrence of A β -containing plaques or neurofibrillary tangles. Accumulation of T cells was greatest in hippocampus, the area in which most neuronal damage was evident (Togo et al., 2002) but neuronal damage is evident in non-AD dementias where there is little T cell infiltration; this indicates that damaged cells are not the sole signal to initiate cell infiltration. The mechanism by which T cells enter the brain remains to be clarified. In AD, one possibility is that it is dependent on the expression of MIP-1 α , which interacts with CCR5 on brain endothelial cells enabling transendothelial migration (Man et al., 2007). Interestingly A β increases CCR5 expression in endothelial cells and so transendothelial migration of T cells is increased in AD patients (Li et al., 2009).

5.3. Multiple Sclerosis: Immunology perspective

Multiple sclerosis is an autoimmune disease caused by uncontrolled inflammatory T cell responses to self antigens (myelin) in the brain and spinal cord, leading to demyelination and neurodegeneration. The disease is characterized by the presence of inflammatory plaques, which are detected by magnetic resonance imaging (MRI) and by the presence of inflammatory cells in the brain lesions (Frohman et al., 2006). Much of our underlying of mechanism leading to the dysregulated immune responses and consequent neuroinflammation has come from studies in the mouse model of the disease, experimental autoimmune encephalomyelitis (EAE) (Fletcher et al., 2010). Although by no means a perfect model, many of the immunological and

inflammatory features of EAE are similar to that seen in MS and it has been used for pre-clinical evaluation of many, if not all, of the current drugs used to treat MS. Several reviews have considered the many factors that contribute to the pathogenesis of the disease and the current treatments (Siffrin et al., 2010) (Hohlfeld et al., 2011) and these details will not be repeated here. Instead we will focus on the role of T cells, particularly Th17 cells.

From an immunological perspective, MS and EAE are classic T cell mediated autoimmune diseases. Until recently, it was considered that IFN- γ -secreting Th1 cells mediate pathology in the CNS. However, following the discovery of IL-17-secreting CD4 T cells (Th17 cells), many immunologists now believe that these are the primary pathogenic T cell in the CNS of mice with EAE and in humans with MS. Indeed much of the new generation drugs in development for MS have focused on the IL-17 pathway. The swing from a Th1- to a Th17-mediated disease took place following some seminal observations in MS patients and in the EAE model. In fact one of the first description of IL-17 in any diseases setting was made in MS patients over 12 years ago, when it was reported that IL-17 mRNA was elevated in the CSF and blood of patients with MS (Matusevicius et al., 1999). In 1995 it reported that IL-17 could be secreted by human CD4⁺ T cells (Yao et al., 1995). A few years later, studies in mice showed that IL-17-secreting Th17 cells were a distinct population from Th1 and other Th cell subtypes and that these cells played a central role in autoimmune inflammation. It was shown that mice defective in IL-23, a critical innate cytokine involved in induction of expansion of Th17 cells had reduced susceptibility to EAE and that IL-17^{-/-} mice had reduced susceptibility to EAE (Komiyama et al., 2006), though not as pronounced as that observed in IL-23^{-/-} mice. In contrast, IL-12p35^{-/-} mice had exacerbated disease (Cua et al., 2003). Furthermore, myelin-specific Th17 from mice with EAE expanded in vitro with IL-23 transferred EAE to naïve mice (Langrish et al., 2005). More recently it has been shown that IL-23 synergizes with IL-1 β , IL-1 α or IL-18 to promote IL-17 production by CD4 T cells and by $\gamma\delta$ T cells and that both of these cell types contribute to CNS inflammation seen in EAE (Brereton et al., 2009; Kapsenberg, 2009; Lalor et al., 2011; Sutton et al., 2006; Sutton et al., 2009a, b). Studies in MS patients, showed enhanced IL-17 production by CD4⁺ T cells and enhanced IL-23 production by LPS-activated DC, when compared with corresponding cells from healthy individuals (Vaknin-Dembinsky et al., 2006).

Following the initial discovery of Th17 cells, Th1 cells were dismissed as pathogenic T cell in EAE. Indeed there was evidence that IFN- γ suppressed IL-17 production by Th17 cells (Harrington et al., 2005; Park et al., 2005). These studies provide an explanation for the failure of anti-IFN- γ and for the observations that mice deficient in IFN- γ or IFN- γ receptors had increased susceptibility to EAE (Krakowski and Owens, 1996). However, recent reports have suggested that Th1 cells do play a pathogenic role in the CNS inflammation, perhaps acting at a different stage of disease or recruiting different effector cells. Furthermore, T cells from TCR Tg mice that recognized MBP Ac1-11 expanded *in vitro* with antigen and IL-12, secreted IFN- γ , but not IL-17 or IL-4, and were capable of inducing EAE in naïve mice (Gocke et al., 2007). Transfer experiments with IL-12 or IL-23 activated myelin-specific T cells showed that they could both induce EAE in naive mice, with Th1 cells promoting macrophage dominated pathology and Th1 cells recruiting neutrophils (Kroenke et al., 2008). It has also been reported that mice deficient in a key Th1 transcriptional factor T-bet are resistant to EAE, despite having stronger Th17 responses (Bettelli et al., 2004). Therefore, the precise roles of Th1 and Th17 cells in EAE and MS are still not fully resolved.

5.4. Multiple Sclerosis: Neuroscience perspective

The traditional, and immunologists', view is that MS is an autoimmune disease that targets the CNS and is characterized by neuroinflammatory changes which drive the progressive destruction of myelin and lead to axonal dysfunction. However, recent evidence points to degenerative changes in grey matter, as well as white matter (Rudick and Trapp, 2009; Vercellino et al., 2009). Despite years of research, the etiology of the disease is not understood, with several factors apparently contributing to its pathogenesis including exposure to different viruses, environmental factors and genetic factors (with 30% concordance between monozygotic twins). The question is whether multiple sclerosis is triggered by an inappropriate immune response directed at CNS antigens which leads sequentially to inflammation and progressive axo-glial degeneration. If this is the case, then it might be predicted that interruption of the sequence of events, for example, by intervention with anti-inflammatory agents, would limit the degenerative changes. This is not the case and therefore the premise on which this hypothesis is based appears to be flawed.

Examination of lesions in early disease suggested that oligodendrocyte loss was in process around lesions where cell debris was apparently cleared by phagocytosing macrophages, but there was no evidence of T or B cells. These cells were, however, evident in areas where complete demyelination occurred (Henderson et al., 2009). These findings are inconsistent with the view that destructive cell-mediated immunity directed against myelin is a key event in initiating the pathology. An alternative proposal is that the initiating event is a primary change in oligodendrocyte function (rather than an autoimmune insult) and this is supported by the observation that changes in myelin proximal to axons, as opposed to its external face, preceded total demyelination (Rodriguez and Scheithauer, 1994).

The presence of peripheral cells in the CNS in certain conditions, and the certain knowledge that there is significant cross talk between the immune system and the CNS, has highlighted the need to address the effects of interactions between cells on the microenvironment. It is known that myelin-specific Th1 cells are encephalitogenic and suggested by some to trigger the symptomatology since EAE can be induced by adoptive transfer of encephalitogenic myelin basic protein-specific Th1 cells (Khoruts et al., 1995). Th2 cells do not have this capability. Indeed a shift from Th1 to Th2 phenotype is associated with remission (Chen et al. 1998) and, in a cultured slice model, polarized Th1 cells induced microglial activation which was attenuated by Th2 cells, although both Th1 and Th2 cells induced CD40 expression (Chen et al. 1998). Consistent with this, it was observed that supernatants from myelin basic protein-specific Th1 cell lines, but not Th2 cells, increased cell surface expression of MHC class II, CD80, CD86, CD40, and CD54 on microglia as well as increasing production of TNF α , IL-6, and IP-10 (Seguin et al., 2003). A role for Th17-producing cells in EAE has also been described (Kroenke *et al.* 2008) and it has been shown that T cells which produce both IFN- γ and IL-17, as well as Th1 cells, increase cell surface markers of microglial activation and also inflammatory cytokine production by microglia (Murphy et al., 2010). It is worth noting that prior to development of symptoms in EAE, the presence of T cells in brain is accompanied by activated microglia (Murphy et al., 2010) and, in a recent study, the evidence suggested that microglial activation may even precede T cell entry (Deighan and Lynch unpublished).

6. Therapeutic options

6.1 Immune interventions for AD

From an immunologist's perspective the most exciting and promising therapeutic intervention for AD is centered around active and passive immunization with A β -based vaccine or anti-A β antibodies with the aim of preventing an increase or even reducing the burden of A β plaques. There are a number of clinical trials, some already in Phase III, in which the effects of both monoclonal and polyclonal antibodies are being assessed (Pul et al., 2011). This approach is of course based on the premise that the amyloid hypothesis of AD is correct. The first studies carried out in a mouse model over a decade ago, showed that immunization of young APP transgenic (Tg) mice with A β ₄₂ in complete Freund's adjuvant (CFA) prevented the development of A β plaques, neuritic dystrophy and astrogliosis and reduced the development of AD-like neuropathologies in older APP Tg mice (Schenk et al., 1999). Immunization of TgCRND8 mice reduced cognitive dysfunction as well as deposition of cerebral fibrillar A β (Janus et al., 2000). The vaccine-induced protection was linked to the induction of A β -specific antibody production. Direct evidence for a role for antibody was provided by the demonstration that passive transfer of A β -specific antibodies reduced clearance of A β through Fc receptor mediated uptake by macrophages or microglia (Bard et al., 2000); although other mechanisms of antibody-mediated A β clearance have also been proposed. The successful mouse studies were translated to the clinic, where active immunization with A β ₄₂ and the adjuvant QS21 (AN 1792) was assessed in phase I and phase II clinical trials (Schenk, 2002). Although there was subsequent evidence of a reduction in plaque burden, a number of patients developed meningoencephalitis and the trial was halted. It has also been suggested that the meningoencephalitis observed following immunization with A β ₄₂ may be mediated by enhanced inflammatory T cell responses promoted by release of antigenic peptides from A β processing (Ferrer et al., 2004). Since QS-21 promotes Th1 responses to co-administered antigen, this might be interpreted as suggesting that A β -specific Th1 cells mediated the meningoencephalitis. Strategies to circumvent these adverse effects include preparation of antibodies directed at C-terminally truncated A β fragments thereby avoiding T cell activation (Petrushina et al., 2007), vaccination with A β in virus-like-particles (Bach et al., 2009) and passive immunotherapy; these strategies have been reviewed recently (Lemere, 2009).

Post-mortem analysis of the brains of AD patients who enrolled in the phase I AN1792 trial revealed that A β load was decreased but was not coupled with improved cognition (Holmes et al., 2008). In a phase 2a study, 25 of 129 AN1792-treated patients were classified as ‘responders’, based on sustained anti-AN1792 titres and, in this cohort, cognitive decline was reduced compared with a placebo group 4.6 years after immunization (Vellas et al., 2009). Results from preclinical studies also suggested that the reduction in plaque burden resulting from immunotherapy was associated with some functional recovery (DeMattos et al., 2001; Morgan et al., 2000; Schenk et al., 1999; Wilcock et al., 2004). Proposed mechanisms include antibody-mediated phagocytosis (Schenk et al., 1999), chemical modification of A β so that formation of fibrils is curtailed (Morgan, 2006), and promotion of A β efflux from the CNS (DeMattos et al., 2001). Analysis using multiphoton microscopy has revealed that administration of A β antibodies to APP-overexpressing mice rapidly induces microgliosis, that this requires recognition of aggregated A β and that microglia cluster around A β -containing plaques (Koenigsknecht-Talboo et al., 2008). Increasing or decreasing microglial activity by IFN- γ or minocycline respectively, did not markedly affect antibody-mediated A β clearance (Garcia-Alloza et al., 2007). This is of interest in the context of the debate that combination therapy may be useful for plaque clearance. Despite these proposals, the role of T cells and antibodies in plaque clearance and reversal of cognitive decline is far from clear. Although immunization with A β clearly has potential in preventing the development of plaques in AD, further studies are required to define the protective versus possible damaging roles of Th1, Th2, Th17 and Treg cells. Once we have a clearer picture on the respective roles of distinct T cell subtypes, it should then be possible to apply vaccine approaches with novel adjuvants for selective induction of the protective T cell subtype. For example, if AD can be clearly identified as an inflammatory disease, then therapies based on Th2 or Treg cells may be beneficial. Th2 cells can readily be induced with alum as the adjuvant, whereas selective induction of Treg cells will require adjuvants that selectively promote IL-10 and/or TGF- β production by innate immune cells.

6.2 Immune interventions for MS

The current first line immunomodulatory therapies for MS, IFN- β and glatiramer acetate are only modestly effective and many patients are either non-responders or develop neutralizing

antibodies to IFN- β . Non-responder patients are often treated with natalizumab (Tysabri), a humanised monoclonal antibody that targets the $\alpha 4$ -chain of $\alpha 4\beta 1$ integrin (VLA-4) and inhibits leukocyte traffic across the BBB. Natalizumab improves outcomes for patients with relapsing MS who do not respond to IFN- $\beta 1a$ (Polman et al., 2006). Furthermore, treatment with natalizumab and IFN- β was more effective than IFN- β alone. However, natalizumab therapy is associated with a risk of developing potentially fatal progressive multifocal leukoencephalopathy (Langer-Gould et al., 2005). The first orally effective drug for treating MS, Fingolimod, was licensed for use in patients with relapsing remitting MS late last year. Fingolimod prevents lymphocyte egress from lymph nodes and therefore prevents lymphocyte recruitment from lymph nodes to sites of inflammation by inhibiting sphingosine-1-phosphate (S1P) binding to its receptor. Clinical trials have also shown that an anti-CD52 antibody (Alemtuzumab; CAMPATH-1H), which depletes T cells, B cells and monocytes, reduced the rate of sustained accumulation of disability in a significantly higher proportion of patients with relapsing remitting MS than those treated with IFN- β (Coles et al., 2008).

In addition to inhibition of T cell migration across the BBB, strategies to specifically inhibit IL-17, or cytokines like IL-23, IL-6 and IL-1 that promote the development of Th17 cells, have become a major focus for many pharmaceutical companies. Antibodies against IL-12/IL-23 (IL-12p40) have been shown to be highly effective against rheumatoid arthritis and have already been licensed for psoriasis (Kurzeja et al., 2011). However, an IL-12/IL-23 p40 monoclonal antibody was not effective in preventing lesion formation in MS patients (Segal et al., 2008). Although the literature may not reflect all the clinical trials carried out to date, there are no reports of success with IL-1 targeted therapies in MS. One problem here is that it may be necessary to block IL-1 α and/or IL-18 as well as IL-1 β , since each of these cytokines can synergize with IL-23 to promote IL-17 production (Lalor et al., 2011). Therefore, blocking the inflammasome may be more effective than inhibiting IL-1 β . Alternatively blockade of Th1 and Th17 responses by the anti-IL-12p40 MoAb has the risk of increased susceptibility to infection and cancer. The antibodies that specifically block IL-17 or the p19 chain of IL-23, and therefore Th17 but not Th1 cells, may carry less risk. Clinical trials in other autoimmune diseases suggest that IL-17 targeted immunotherapies may also be effective in some but not all autoimmune diseases. An alternative approach which may have greater specificity with reduced risks of infection and cancer, involves activation of the patients own anti-inflammatory

responses; for example induction of host IL-10, TGF- β or IL-27. We have recently shown that IFN- β therapy in MS may function by inducing IL-27, and the high frequency of patients that fail to respond to IFN- β do not produce IL-27 (Sweeney et al., 2011). This suggests that IL-27 or agents that induce its production in vivo may be more effective than IFN- β in treating MS. Alternatively, approaches that specifically target the diseased tissue (the CNS in the case of MS), or the antigenic target (e.g. myelin) may have reduced risks of global immunosuppression. One possible approach to achieve this objective may be through the induction of myelin-specific Treg cells. Studies in mice have shown that transfer of MBP-specific CD4⁺CD25⁺ Treg cells prevented disease induction and progression in the EAE model (Stephens et al., 2009). Interestingly protection was only achieved with myelin antigen-specific Treg cells and not with polyclonal Treg cells. While this has the advantage of confining the suppression to the site of inflammation, its success may be dependent on identifying the antigen of the Treg and pathogenic T cells

Alemtuzumab, which depletes lymphocytes and has anti-inflammatory effects, reduces relapse and retards progression of relapsing-remitting MS (Jones and Coles, 2009) although disability progressed in patients with secondary progressive MS (Coles et al., 1999). Rituximab, which depletes CD20⁺ B lymphocytes, was associated with a decreased relapse rate and a reduction in gadolinium-enhanced brain lesions in patients with relapsing-remitting MS (Hauser et al., 2008), but over a 96 week period, there was no evidence of a delay in progression of disease in patients with primary progressive MS, although T2 lesion volumes were decreased. Subgroup analysis suggested that Rituximab may affect progression of the disease in younger patients, where inflammatory changes were evident (Hawker et al., 2009). It has to be concluded from these studies that targeting inflammation may alter characteristics of the disease but not its progression. These and other studies have led to the proposal that the primary event in triggering the disease is neither inflammatory nor immunogenic in origin but rather results from a cell injury which leads to progressive degeneration of oligodendrocytes and therefore impacts on myelinogenesis. Among the consequences are demyelination-induced immunogenic and inflammatory changes which sets up a damaging positive feedback cascade and which impacts negatively on the process of remyelination (Stys, 2010).

Concluding remarks

It is likely that the best therapeutic approaches to the treatment of neurodegenerative diseases are those that target the immune responses that appear to precipitate the disease. Figure 1 identifies some of the elements of the immune system which probably contribute to the pathogenesis of AD and MS and highlight the need to ensure that the marriage between neuroscience and immunology is enduring.

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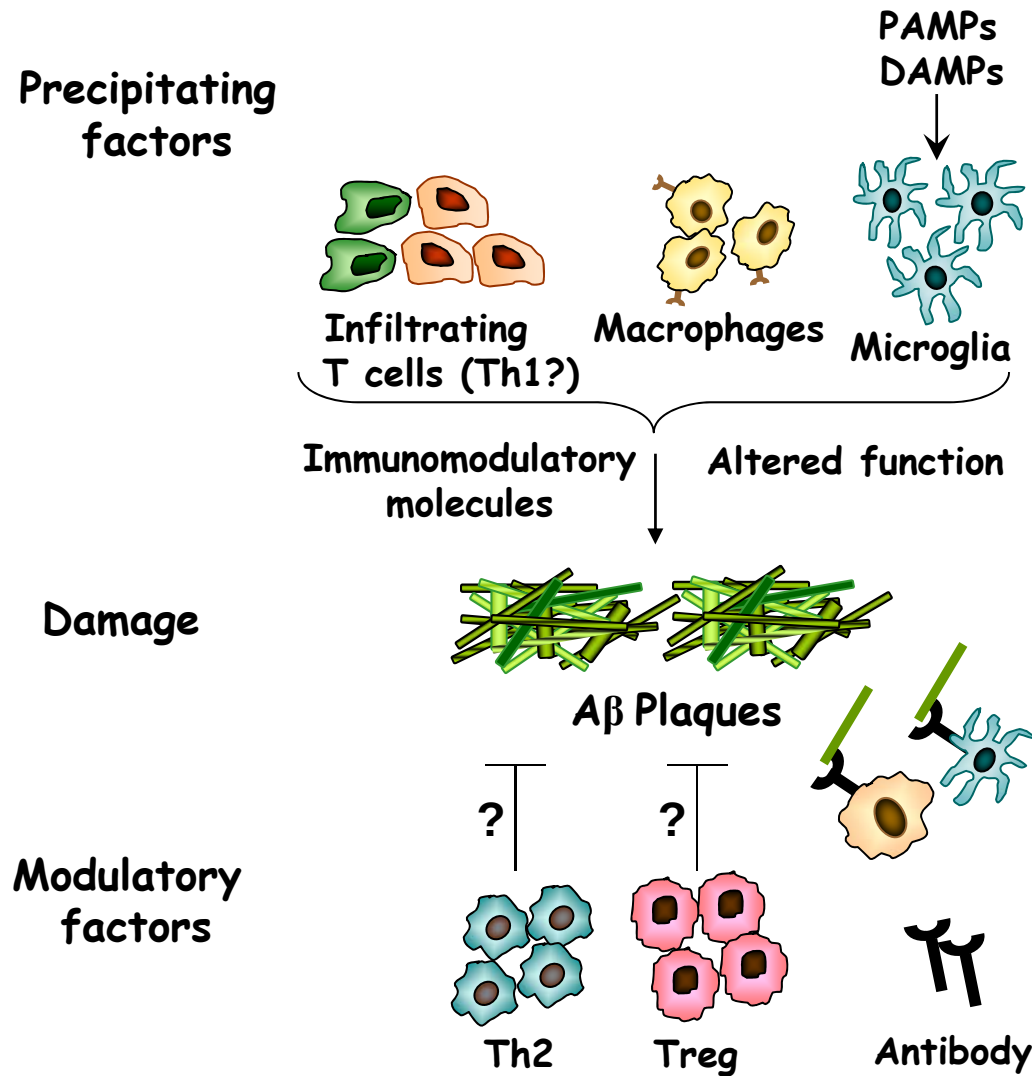
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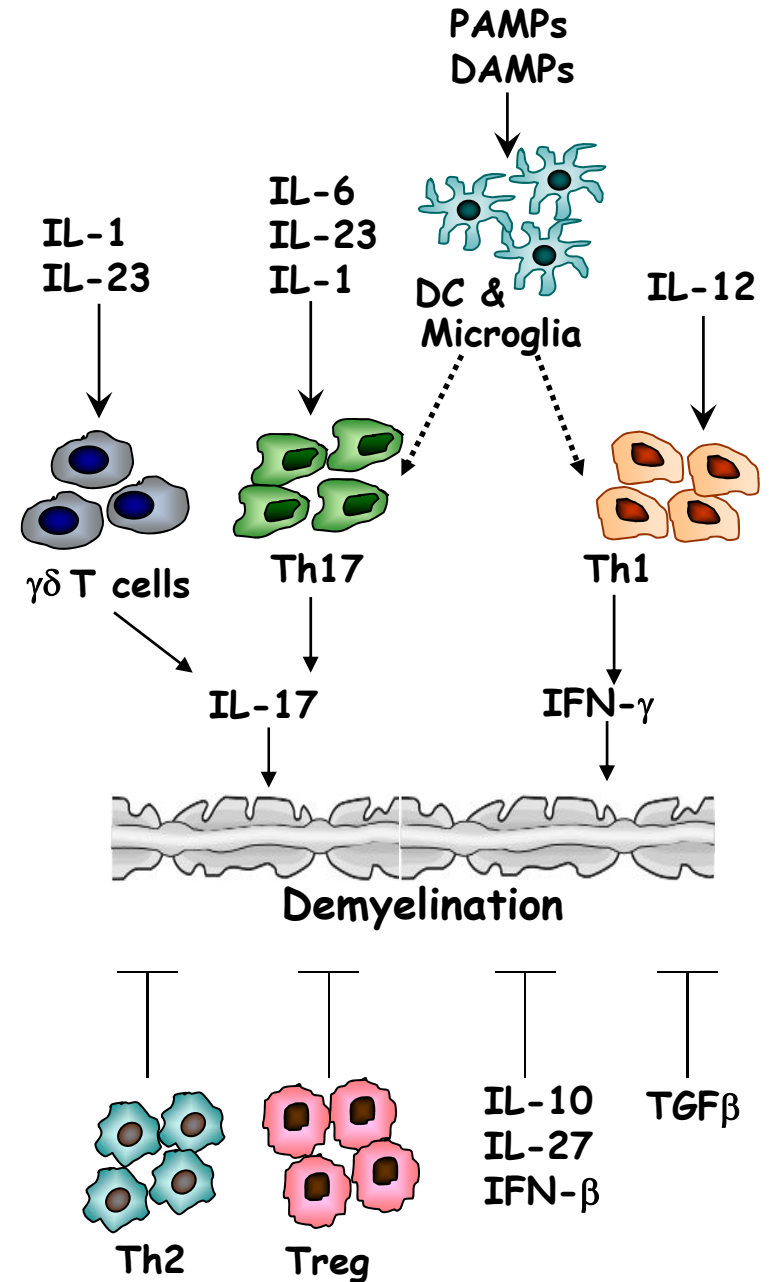
Figure legend

Fig 1. The role of the innate and adaptive immune systems in the inflammatory process in the pathogenesis of multiple sclerosis and Alzheimer's disease.

Alzheimer's Disease



Multiple Sclerosis



Highlights

Perspectives from an Immunologist and a Neuroscientist on inflammatory versus neurodegenerative basis of multiple sclerosis and Alzheimer's disease